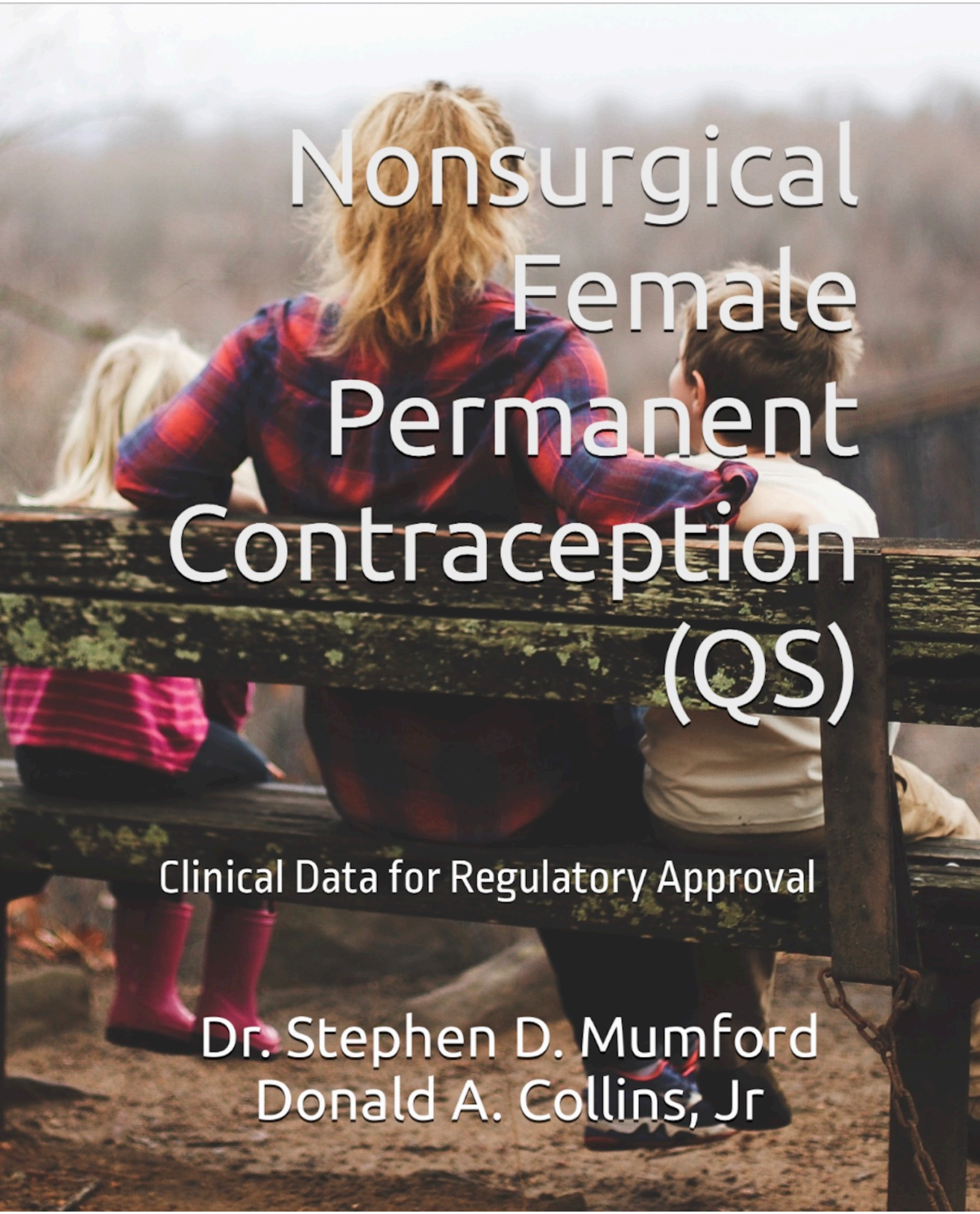


Nonsurgical Female Permanent Contraception (QS)

Clinical Data for Regulatory Approval

Dr. Stephen D. Mumford
Donald A. Collins, Jr

Nonsurgical Female Permanent Contraception (QS)

Clinical Data for Regulatory Approval

Dr. Stephen D. Mumford

Donald A. Collins, Jr.

Donald A Collins Publishing
P.O. Box 7132
Van Nuys, CA, 91409
Phone: (202) 656-6421

Published by Donald A Collins Publishing 12/3/2023

ISBN: 9798869839183

Print information available on the last page.

Because of the dynamic nature of the Internet, any web addresses or links contained in this book may have changed since publication and may no longer be valid. The views expressed in this work are solely those of the author and do not necessarily reflect the views of the publisher, and the publisher hereby disclaims any responsibility for them.

This book is a work of non-fiction. Unless otherwise noted, the author and the publisher make no explicit guarantees as to the accuracy of the information contained in this book and in some cases, names of people and places have been altered to protect their privacy.

Dedication

This book is dedicated to pioneers Dr. Elton Kessel, Dr. Jaime Zipper, Dr. Jack Lippes, and Dr. Do Trong Hieu, for their inspiration to bring the best contraception method to women who no longer wished to have children. Each pursued this endeavor for many decades relentlessly until the end of their lives so that millions more women might live longer happier lives.

Acknowledgements

Thank you to hundreds of unnamed healthcare providers, advisors, friends, funders, family, and colleagues for making this effort possible with your years of research and dedication to women through QS.

Rashidah Abdullah, S. Afsal, Tina Agoestina, Shamim Akram, H. A. Albano, Tim E. Aldrich, L. A. Alfonso, Susan A. Allah, F. Alpizar, Bruse N. Ames, Beth Anderson, P. T. Anh, Renzo Antonini, M. Anwar, A. Aparicio, Hamid Arshat, A. K. Awan, A. M. Azzidani, Ton That Bach, N. R. Bairagi, Barbara Barnett, M. Barr, Altaf Bashir, M. Bashir, Lee R. Beck, Rokeya Begum, Alphonse Benoit, Alfonzo Bernales, Catrina Best, S. Bhateja, S. Bhattacharyya, Rohit V. Bhatt, Pouru Bhiwandi, Pouru Bhiwandiwala, Syeda Nurjahan Bhuiyan, Elizabeth Bianchi, M. Bilgrami, Sven Bjorkman, David A. Blake, Dean Bloch, Lee Bolduc, M. K. Brar, Marc Andre Cagnon, Herbert O. Calvary, Arnoldo Fernando Camargos, Bonnie L. Carson, William Caspary, Ward Cates, Finis L. Cavendar, Sakhrup Chakravarty, A. Giugni Chalbaud, Harish Chandra, P. Chandra, Muhammed Asghar Chcema, Tran Thi Trung Chien, Lynda Painter Cole, Donald A. Collins, Carol Connell, Jay M. Copper, Philip A. Corfman, Donald R. Cowsar, Carolyn F. Craft, Alfredo Dabancens, Carol Danielson, Djaswadi Dasuki, Oscar W. Davidson, Kristin Davenport, Deborah Randazzo Barbosa de Magalhaes, George Denniston, Maria C. Diblasi, James Dingfelder, Rachael DiSantostefano, V. M. Doctor, Rosalie Dominik, L. Dorflinger, Claude Drobnes, Norman H. Dubin, Nguyen Ba Duc, PhamThi Minh Duc, Richard L. Dunn, L. Q. Duong, Carlton A. Eddy, Lindsay Edouard, S. Edwards, Lars Ove Elisson, M. El Faham, A. A. El Kady, M. S. El Mahaishi, I. El Makhzangy, S. El Sahwi, Amy D. Engineer, Sarah G. Epstein, Patricia A. Fail, Paul J. D. Feldblum, Claudia Ramos de Carvalho Ferreira, Diana Carvalho Ferreira, Philip Ferro, Marie Terese Feuerstein, Garth Fitzhugh, Henry Foster, Johan Gabrielsson, V. Garabedian, P. Gerbracht, Ramesh B. Ghodgaonkar, A. K. Ghosh, S. S. Gill, Philippe Girerd, Jerome M. Glassman, Lucinda Glover, Lois Swirsky Golden, Alfredo Goldsmith, Myron Gordon, V. Goyal, Jack Griffith, Richard Grossman, Margaret Miller Growe, Roger Growe, Liu Guanghua, Anibal Guerrero, Enrique Guiloff, Sergio Guzman, Rene Guzman-Serani, Herman Haller, Vera Halpern, M. Z. Hanan, Karen E. Haneke, Robert Hanenberg, Marilee Hanson, Mildred Hanson, Joseph K. Haseman, Sue Haskell, Mark Heller, R. Heywood. Do Trong Hieu, R. Hasan, M. Hoesni, David Hubacher, Douglas Huber, S. Insunza, Charanpat Israngkun, K. Jadwani, J. K. Jain, Barbara Janowitz, Kokila M. Jariwala, J. T. Jensen, L. Jhaveri, Zhu Jiang, Mohammed T. M. Jiffry, Judith K. Jones, Mat-la K. Jones, A. A. Joseph, Sharmila Kamani, M. Kamel, Amiya Kar, Sharon Kardia, Karen R. Katz, Elton Kessel, Kwa Siew Kim, Fred A. Kincl, Theodore M. King, P. Kini, Michael Klitsch, S. Kokkinakis, I.

Kusuma, Miriam H. Labbok, Leonard E. Laufe, Ronald Levin, Danny H. Lewis, JoAnn Lewis, Jie Li, Jack Lippes, Nguyen Dinh Loan, T. T. Luong, Michael I. Luster, Estefania Barbosa Magalhaes, Brajesh Malaviya, M. M. Mansy, Barry H. Margolin, Parthena Martin, Virginia Mason, April Mayberry, Margaret F. McCann, Ernest E. McConnell, Arlene McKay, James McMahan, Mario Medel, Shirin Mehtaji, Jacques Melancon, Rohinee N. Merchant, Leslie Miller, Robert Minor, Sheitaneh Soroodi Moghaddam, A. Mohindroo, Ellen Montgomery, G. Plaza Mora, Nargesh D. Motashaw, Biral C. Mullick, Stephen D. Mumford, Muhammed Mustansar, H. S. Nagib, Razia Naheed, Kavita Nanda, S. Neff, Arthur A. Nelson, Robert S. Neuwirth, D. H. Ngoc, Pham Thi Nguyet, B. M. Ogilvie, S. K. Pal, Timothy Parmley, Eva Patek, Carl J. Pauerstein, Brenda H. Perkins, John C. Pezzullo, Sukhit Phaosavadi, B. Pharm, Cheri Pies, Valerie D. Pope, Amelia G. Potter, Malcolm Potts, S. R. Prabha, Ruth Prager, Martha Pruyas, Benny Hasan Purwara, Pai-Li Qian, Arch Raj, K. Rajgopal, Ljiljana Randic, Leslie Recio, Michael Resnick, Ralph M. Richart, Marilyn Richardson, Susan Richman, Mirta Rivera, E. Robinson, Mana Rochanawutanon, M. I. Rodriquez, A. Rosca, Margie Rose, Irene Rosenfeld, O. Rotaru, A. Samsulhadi, Budi Imam Santoso, Freddy Santschi, S. Raj Sarin, Ashi R. Sarin, Eric A. Schaff, Robert S. Schenkens, John J. Sciarra, I. G. Scott, L. Shah, Michael D. Shelby, James D. Shelton, Xiao Shiwen, Donna Shoupe, M. Sinha, Padjar Siswanto, Irving Sivin, Ariawan Soejoenoes, Silva Sojat, David C. Sokal, Judson Spalding, Stanley Stasiewicz, Gail Stetten, John D. Strandberg, Ang Eng Suan, A. Suhadi, Agung Suhadp, Zou Suping, I. V. Surcel, Gede Puta Surya, Donald F. Swartz, D. N. Tan, T. T. Tan, Arlene Tave, Raymond W. Tennant, Partha Sarathi Thakur, S. S. Thaku, pham Than, Amy S. Thurmond, Raymond R. Tice, Shueh Ping Tien, S. Toader, Nguyen Kim Tong, Pham Trinh, Valentin Trujillo, Nguyen Van Tuong, Fakhar un-Nisa Trinh, Huu Vach, B. Viel, Dao Quang Vinh, Cynthia S. Waszak, Debra H. Weiner, Lu Weiqun, An Wenshi, R. G. Wheeler, Angie Wheeless, Randall Whitney, Carolyn Wilkins, Nancy Williamson, E. W. Wilson, Yu-Hau Wu, John Yeh, Lillian Yin, Tian Yingmei, Hou Yonghua, Bethany Young, J. Liechtenstein Zabrak, S. Zalanyi, Lourens J. D. Zaneveld, Gerald Imam Zatuchni, Errol Zeiger, Y. Zhao, H. G. Zheng, Yang Zhengpin, C. Zhong, Itic Zighelboim, Jaime Zipper

Contents

Introduction

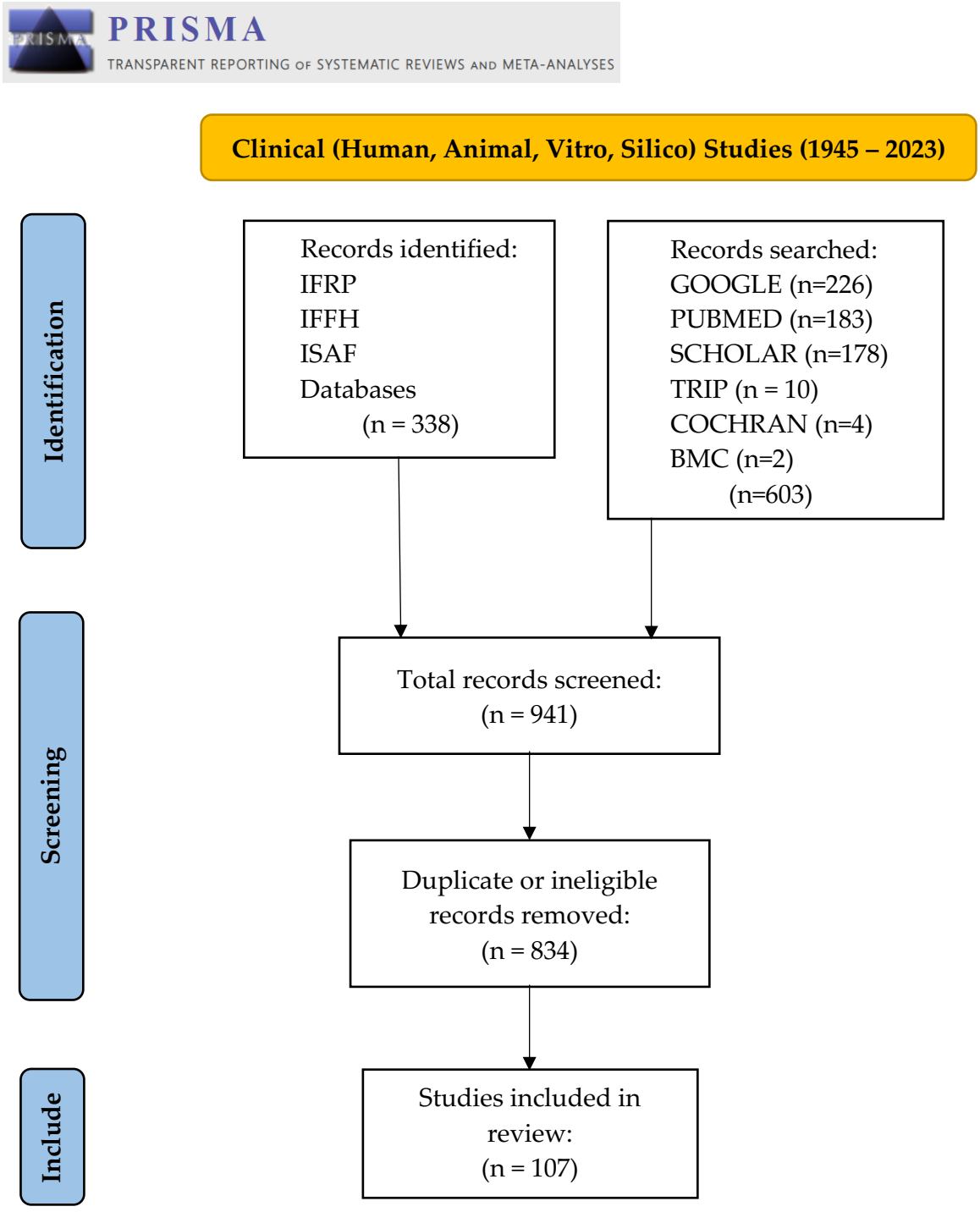
QS is a nonsurgical permanent contraceptive (NSPC) method only for women who wish to have no more children. Following counselling and uncoerced written consent of and by candidates, followed by a prescribed waiting period, QS is given in two doses of quinacrine as seven pellets each 36 mg (total dose 252 mg), during the proliferative phase of the menstrual cycle (days 6 to 12 after the onset of menstruation), 28 days apart, using a modified Copper-T intrauterine device (IUD) inserter which is advanced to the fundus, then using the Hieu method, the inserter is withdrawn 0.5 cm, and the plunger is advanced so that the pellets are all expelled at the top of the uterus "blind." Alternate contraception must continue for 3 months following the first insertion allowing time for a woman's immune system to respond and occlude both of her fallopian tubes.

This systematic literature review was conducted to provide regulators with concise clinical data to support the approval process of QS. All human clinical studies addressing quinacrine sterilization were considered for inclusion, both prospective and retrospective. Studies included successful placement rates, efficacy, safety, and/or risk factors for failure of quinacrine sterilization. There are quite a few longitudinal studies included which attest to the long-term safety of QS. In-vivo (animal), in-vitro (test tube), and in-silico (computer) studies are listed so viewers can see the extensive decades of research.

Only original studies with > 5 consecutively included participants were selected, to allow pooling of data. Descriptive articles, case-series (with non-consecutively included participants), reviews, surveys, technical reports were excluded.

Since 1976, approximately 200,000 cases have been performed in 53 countries, including the U.S.. This literature review of 164 studies (shown in the flowchart below) consolidates 107 unbiased peer reviewed and published studies (summarized in tables) to support that QS is safe (no increase in ectopic pregnancy, hysterectomy, or cancer) and better than 97% effective when women follow the prescribed QS 2-insertion pellet method based upon 47,101 women in 42 studies from 1977 to 2010 including 107,548 women years of follow-up.

Unlike FDA approved, withdrawn, substantially equivalent modes of action devices Essure (CDRH granted "an expedited review because it offers significant advantages over existing approved alternatives for permanent birth control") and Adiana, QS is deliverable by well-trained nonphysicians in low-resource settings, is the least expensive of all contraceptive methods ($1, and is preferred by women. Moreover, QS is safer (0 deaths in 200,000 pellet procedures) than surgical tubal ligation (TL) (CDC reported (3.6 deaths in 100,000 TL procedures), does not require hospitalization or anesthesia, and requires little or no recovery time.



*Search terms, "quinacrine sterilization", quinacrine and women and [non-surgical or nonsurgical]

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71. Visit: http://www.prisma-statement.org/

Since 1977, in addition to more than 1600 healthcare providers, QS was championed by three research organizations IFRP (became FHI, then FHI360), IFFH, and finally ISAF starting in 1994, spending approximately $20 million in total. A lot has been learned. Here are a few lessons that should be noted regarding QS from the last decade below:

1) There are many more deaths from pregnancy or tubal ligation than occur with QS.
2) Multiple long-term human studies in Chile and Vietnam have proven quinacrine does not increase the likelihood of cancer, ectopic pregnancy, or hysterectomy.
3) Multiple animal studies have proven QS is not a carcinogen when given in doses twice those seen in women.
4) With proper training including physical exams and sonography to identify mal-formed uteri (occurring in >5% of women) and in-utero blood at the time of quinacrine insertion, and confirmation of bilateral tubal occlusion by sonography after two insertions and 12 weeks, studies show QS is comparable in effectiveness to tubal ligation with lower risk. Various adjuvants have not improved effectiveness.
5) The most often quoted Sokal et al., clinical trials in Chile and Vietnam, long-term effectiveness data fail to mention that in those studies there was no recommendation that alternative contraception be used for 3 months. Many women did not use contraception to begin with during that time in those places.

Comments regarding QS from the last decade are listed below.

Oregon Health & Science University (OHSU 2023 website);

> "In the 70s and 80s, several groups devoted considerable research effort to this area. One method, quinacrine sterilization (QS), was introduced in several developing nations prior to sufficient testing of safety and efficacy or regulatory approval in the US or Europe. The absence of strong regulatory approval and broad acceptance of the approach in more-developed regions left QS vulnerable to criticism from both human rights advocates and policymakers opposed to contraception. Although the extensive clinical data accumulated with QS strongly supports the safety of the approach, its efficacy, particularly among younger women, is unacceptably poor. While improving the efficacy of QS is possible, concerns about safety have hampered efforts to restart this research."

Chapter 11, (2020) Female Tubal Sterilization, Traditional and Research Methods, Charles M. March

> "With the exception of some recently developed methods and the newer versions of quinacrine administration, many of the following methods are of historical significance and included here to demonstrate the variety of problems encountered. . .

Quinacrine sterilization remains the safest, most effective, and the most widely used (>125,000 cases) non-surgical method. . .
Although the ease of administration and very low cost of quinacrine ($1 per procedure in Asia) have contributed to ongoing interest in this procedure, concern regarding carcinogenicity caused it to be banned by the World Health Organization in 2006, a decision challenged by Lippes."

Women's Health Movements pp 191–229, Sexual and Reproductive Health and Rights, Meredeth Turshen, September 6, 2019

"For these reasons, and because quinacrine is in the public domain and researchers cannot patent it, quinacrine sterilization is less expensive than tubal ligation—in other words, ideal …

This chapter follows the arguments of women's health movements surrounding the conflicts between the sexual and reproductive rights of individual women and the social groups to which they belong, on the one hand, and religious dogma and national and international population policies, on the other hand. Provocative aspects discussed are population dynamics, birth control and contraception, and sterilization and abortion. The second part of the chapter takes up issues of infertility and surrogacy. With the advent of new reproductive technologies, women's groups are questioning the commercialization of the field and their rights in relation to gender and biology and the commodification of body parts. These conflicts are playing out against a backdrop of dramatic economic, social, political, climatic, and demographic changes worldwide."

Veersema, S. (2014). Hysteroscopic Sterilization. [, Vrije Universiteit Amsterdam].

"Quinacrine sterilization is used in many developing countries because of good results and low costs. The technique requires two insertions of quinacrine into the uterine cavity. This can be done "blind" or by hysteroscopic guidance and direct tubal instillation by a specially developed catheter (21). The procedure is reported to have a 1-2% failure rate, although the rates for ectopic pregnancy and serious complications are equal to or less than those for transabdominal sterilization. Drawbacks from the procedure include the need for multiple applications and the problem of reliably confirming tubal occlusion. An HSG is not recommended, because of the risk to blow out the delicate occluding scars. The need to make this procedure simple, safe, inexpensive and thereby more acceptable, even in countries with limited surgical facilities is well recognized. Use of quinacrine pellets has become the most widely adopted method of non-surgical female sterilization. The Family Health International has recently decided not to pursue further research on quinacrine, partly because of the relatively high pregnancy rates after quinacrine compared to other contraceptive methods. The 10-year pregnancy probability is

approximately four times higher than after laparoscopic tubal sterilization (bipolar coagulation) as reported by CREST."

COMMENTARY: ACTIONS IN THE PIPELINE AND THE WAY FORWARD TO REDUCE MATERNAL AND PERINATAL MORTALITY IN ETHIOPIA, Ethiop J Health Sci. Special Issue September 2014, Berhan et al

> "On the other hand, the quinacrine non-surgical sterilization may be the future hope for the majority of the women. Unlike the worldwide report, sterilization is not adequately practiced in Ethiopia probably because of fear of the surgery, unavailability of the service, lack of awareness, religious or cultural factors. Because of the non-invasive nature of the procedure, and application not requiring a highly skilled person, quinacrine sterilization is probably the best option for developing countries including Ethiopia. . . .
>
> Therefore, the issue of FDA approval should not be a limitation to use quinacrine sterilization as an option for permanent female contraceptive methods. Particularly, in the rural areas of Ethiopia where the total fertility rate is high and highly skilled health professionals are very scarce, the benefit of quinacrine sterilization is indispensable.
>
> In short, availing the preferred contraceptive methods (particularly injectable, transdermal patch and quinacrine sterilization) is an important intervention to increase the temporary and permanent contraceptive use prevalence rate and reduce maternal and perinatal mortality related to unplanned pregnancies and high fertility."

All questions posed by the FDA and WHO were answered years ago so QS clinical trials in the U.S. should be complete. This book documents almost 50 years of data supporting the safety and efficacy of the QS method. WHO reported, "About 287,000 women died during and following pregnancy and childbirth in 2020." Guttmacher reported, "In 2011, nearly half (45%, or 2.8 million) of the 6.1 million pregnancies in the United States were unintended. Specifically, 27% of all pregnancies were "wanted later" and 18% of pregnancies were "unwanted." Perhaps (287,000 x 18% x 30 years) or more than a million and a half women have died during and following pregnancy and childbirth for children they did not want since Dr. Webb of WHO sent his 1993 letter to United Nations Population Fund director Linda Demers in Hanoi, stating (with no evidence) "WHO experts and FDA officials have said that they would be very surprised if quinacrine did not turn out to be carcinogenic" halting QS clinical studies in Vietnam for what appeared to be ideological rather than scientific reasons. Please review the scientific evidence in this book.

Thank you,
Don Collins, Jr.
President ISAF

QS Brochure

Quinacrine Sterilization

What is Quinacrine Sterilization (QS)?

Quinacrine Sterilization (QS) is a permanent method of contraception. There is no surgery. Instead, a drug called quinacrine (originally taken orally to treat malaria) is inserted into the uterus. Researchers began to study quinacrine sterilization in humans in the 1970s. Since then, over 125,000 women in 30 countries have used QS as a method of sterilization.

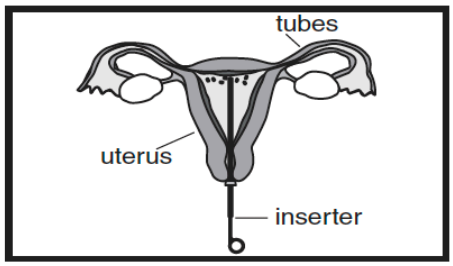
Because it is a relatively new method and many women do not know much about QS, this brochure is provided to answer some questions.

How safe is QS?

Research has been done around the world to find out how safe quinacrine is. What is known is that QS is safer in terms of complications than surgical sterilization especially in parts of the world where hospitals and clinics are poorly equipped.

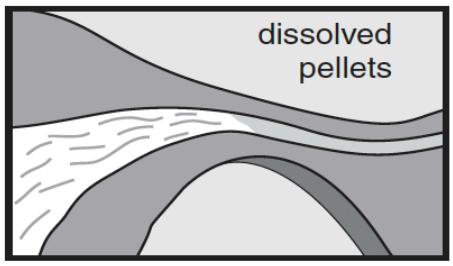
What happens during an insertion?

1



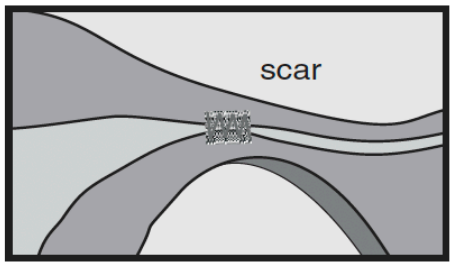
Using a modified IUD inserter, the healthcare provider (a midwife, nurse or doctor) places 7 small pellets (pills) of quinacrine in the uterus on two separate visits.

2



In half an hour, the pellets dissolve and the liquid quinacrine flows into the tubes. The quinacrine causes inflammation of the lining of the fallopian tubes.

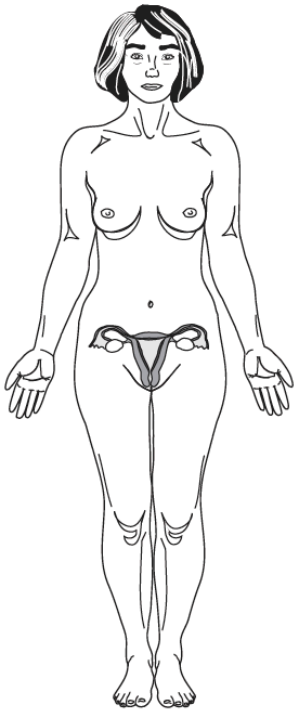
3



Over the next 6-12 weeks, the quinacrine causes plugs of scar tissue to form at the first part of the tubes. These plugs close the tubes and block the egg's path to the uterus.

How many insertions are necessary?

Two insertions greatly increase the chance that the quinacrine sterilization will be successful and are therefore always part of a QS insertion.



What happens after the first insertion?

Because it takes 6-12 weeks for the scar tissue to form, you must use another contraceptive method in addition to QS, starting the day of the first insertion. Examples of contraceptives to use are condoms, foam, pills, IUDs or injectables. To make sure that the scar tissue has formed and that the patient will not become pregnant, she must return for a second insertion one month later. She must continue using the other method for 2 more months after the second insertion.

Does QS ever fail?

Yes. QS fails if the tubes are not blocked completely after two insertions. However, it is becoming more effective with improved technique. Studies conducted 10-20 years ago reported higher failure rates than we see today. Since the adoption of a new insertion technique in 1993, the failure rates reported have been less than 2 out of 100 women after 2 years. Because of improvements in the technique, it is estimated that after ten years, fewer than 5 of 100 women will be become pregnant.

When must the insertions be done?

QS must be done 6-12 days after the onset of the woman's period. (To increase chances of success, there must be no blood in the uterus during the first or second insertion.)

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

days of menstrual period
days to have QS

What are the side effects of QS?

Nearly half of all women report experiencing at least one side effect. If there is a side effect, it usually goes away within a few hours to a few days. Here is a list of the most common side effects, and the number of women out of every 100 who get them:

Symptoms	Number of Women
menstrual pattern changes	20 to 29
lower abdominal pain	9 to 25
headache and dizziness	9 to 20
backache	1 to 21
vaginal itching or irritation	1 to 23
discharge	5 to 16
fever	9 to 10
pain during urination	≤ 1
pain during sex	≤ 1

Some women have menstrual changes after the insertions. This means that they either do not have their period or there is a change in the amount of flow of their period or the number of days it lasts. This usually lasts no more than a few months. In rare cases, it may last a year or more.

What are the advantages of QS?

The main advantages of QS are:

- no surgery, which means less risk of infection, injury or death
- no hospitalization
- less pain than surgical sterilization
- many types of trained healthcare providers, not just doctors, can perform the method
- requires no anesthetic

What are the disadvantages of QS?

The main disadvantages of QS are:

- it has never been successfully reversed (QS may be much less reversible than surgical methods)
- some women may still get pregnant even after they have a QS
- QS is still a new method; there may be risks which are not yet known
- it requires two visits to the clinic
- it does not completely protect against tubal pregnancy
- It does not protect against sexually transmitted diseases (STD's)

Is tubal pregnancy possible?

As with other methods of contraception, tubal pregnancy (a pregnancy which occurs outside of the uterus), though rare, can still occur. Tubal pregnancy may still occur after QS, but it is not caused by this method. The tubal pregnancy rate with this method is lower than the rate in women who use no contraceptive method. Tubal pregnancies are very dangerous. In some countries, 1 out of 20 women with a tubal pregnancy dies. If a woman believes she is pregnant and has any of these signs, she should call or go to her healthcare provider right away:

- a missed period
- severe pain in the lower abdominal area
- dizziness, fainting or weakness
- vaginal bleeding other than a normal menstrual period

A potential QS client should be encouraged to consider the following:

1 Some questions to ask your healthcare provider

- Can I change my mind after the first insertion?
- Are there women in my community who have had QS? Can I contact them?
- What do I do if my side effects last longer than a few days?
- Can I return to all my normal activities right after QS?
- What kind of contraception do you suggest I use for the first 3 months?
- When can I start having sexual relations after QS?
- What happens if I find out I am pregnant?

2 Some questions to ask yourself

- Why am I having this procedure?
- Are there other methods of contraception I can use that will work better for me and my husband at this time?
- Most importantly, am I certain that I never want any more children?

3 Tell your healthcare provider

- if you know or think you might be pregnant
- if you have seizures (fits), cancer or any vaginal infections
- how long it has been since your last child's birth
- if you have doubts about being sterilized
- about any other concerns you have

QUESTIONS FREQUENTLY ASKED BY WOMEN

Q. Will I be sterile immediately?

A. No. It takes 6-12 weeks for the scar tissue to develop. You should use another method of contraception for 12 weeks.

Q. Will I be sterile after one insertion?

A. Maybe. Research has shown that women who have two insertions are half as likely to become pregnant as women who have only one.

Q. What will happen if I cannot or do not return for my second insertion after one month?

A. If you cannot return for the second insertion, go to the clinic as soon as possible to find out what to do next. Until you return, continue to use another contraceptive method. If you do not return, your QS procedure is not complete and there is a higher chance you may become pregnant.

For more information on QS see:
http://quinacrine.org
Questions can be directed to:
info@quinacrine.org
or
Quinacrine Information
P.O. Box 13067
Research Triangle Park, NC 27709 USA
Phone - (919) 933-7491
Fax - (919) 933-0348

ISAF

QS

Permanent Contraception for Women ®

Female Voluntary Non-surgical Sterilization:

The Quinacrine Sterilization Method

Crude Pregnancy Rate

Case #	Investigator Publish (date)	Country	Study Dates	QS Insertion Method	# of Cases	Follow up Cases	Follow up (%)	# Pregnant	Fail Rate (%)	Women Years
1	Lu et al (2012)	China	3/07 - 7/10	(7) 36mg pellets of quinacrine inserted 3 to 7 days after menses repeated 4 weeks later	5917	5780	98%	88	1.5%	9726
2	de Magalhaes et al (2009)	Brazil	2/05 - 8/06	(7) 36mg pellets of quinacrine inserted during the follicular phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	258	258	100%	2	0.8%	229
3	Lu et al (2008)	China	5/95 - 1/00	(7) 36mg pellets of quinacrine inserted 5 days after menses repeated 4 weeks later	3789	3466	91%	72	1.9%	13533
4	Seifi et al. (2008)	Iran	5/05 - 8/06	(7) 36mg pellets of quinacrine inserted during the final days of menstrual bleeding repeated 4 weeks later	100	100	100%	0	0.0%	300
5	Sokal et al. (2008)*	Vietnam	1/89 - 10/82	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	9461	1335	14%	156	1.6%	14294
6	Ferreira et al (2003)	Brazil	3/99 - 3/03	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	128	128	100%	2	1.6%	384
7	Lippes et al (2003)	United States	10/00 - 4/03	(7) 36mg pellets of quinacrine inserted within three days of the end of menses repeated 4 weeks later	10	10	100%	1	10.0%	23
8	Alfonso et al (2003)	Philippines	1/00 - 4/03	(7) 36mg pellets of quinacrine inserted three to five days after menses ended repeated 4 weeks later	36	36	100%	0	0.0%	43
9	Whitney (2003)	United States	10/00 - 4/03	(7) 36mg pellets of quinacrine inserted in the week following a menses repeated 4 weeks later	7	7	100%	0	0.0%	7
10	Garabedian (2003)	Syria	7/01 - 12/02	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	297	297	100%	1	0.3%	297
11	El Mahaishi et al (2003)	Lybia	10/98 - 12/02	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	200	200	100%	0	0.0%	412
12	Bashir et al (2003)	Pakistan	1/97 - 12/01	(7) 36mg pellets of quinacrine inserted in the proliferative phase of the menstrual cycle repeated 4 weeks later	885	885	100%	10	1.1%	4425
13	Roy (2003)	India	11/97 - 3/99	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	122	118	97%	1	0.8%	354

Crude Pregnancy Rate

Case #	Investigator Publish (date)	Country	Study Dates	QS Insertion Method	# of Cases	Follow up Cases	Follow up (%)	# Pregnant	Fail Rate (%)	Women Years
14	Sarin et al (2003)	India	12/93 - 7/99	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	134	134	100%	0	0.0%	965
15	Zipper et al (2003)*	Chile	1/77 - 12/98	(7) 36mg pellets of quinacrine inserted in the proliferative phase of the menstrual cycle repeated 4 weeks later	1,708	1,708	100%	118	6.9%	17080
16	Zipper et al (2003)*	Chile	1/77 - 12/98	(7) 36mg pellets of quinacrine inserted in the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	884	881	100%	46	5.2%	8810
17	Bilgrami et al (2003)	Pakistan	1/94 - 12/97	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	1000	1000	100%	20	2.0%	2230
18	Lu et al (2003)	China	7/95 - 9/97	(7) 36mg pellets of quinacrine inserted from 3 to 7 days after menstruation ended repeated 4 weeks later	265	265	100%	3	1.1%	459
19	Agoestina (2003)	Indonsia	4/93 - 9/95	(7) 36mg pellets of quinacrine inserted in the proliferative phase of the menstrual cycle repeated 4 weeks later	30	29	97%	0	0.0%	203
20	Alpizar (2003)	Costa Rica	1/89 - 8/93	(6) 36mg pellets of quinacrine inserted in the first 14 days of the menstrual cycle repeated 4 weeks later	653	653	100%	16	2.5%	1337
21	Suhadi et al (2003)	Indonsia	8/92 - 10/93	(7) 36mg pellets of quinacrine and 55.5 mg of ibuprofen inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	197	183	93%	8	4.1%	1830
22	Bhatt (2003)	India	6/79 - 1/80	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	84	84	100%	3	3.6%	1932
23	Bhuiyan et al (2001)	Bangladesh	10/89 - 4/99	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	160	160	100%	3	1.9%	80
24	Randit et al (2001)	Croatia	2/88 - 9/92	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	150	109	73%	9	6.0%	872
25	Sokal et al. (2000)* Retrospective	Vietnam	1/89 - 10/92	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	2709	1329	49%	352	13.0%	6645

Crude Pregnancy Rate

Case #	Investigator Publish (date)	Country	Study Dates	QS Insertion Method	# of Cases	Follow up Cases	Follow up (%)	# Pregnant	Fail Rate (%)	Women Years
26	Bhateja et al (1998)	India	1/95 - 1/97	(7) 36mg pellets of quinacrine inserted between the 6th and 12th day of the patient's menstrual cycle repeated 4 weeks later	600	600	100%	7	1.2%	600
27	Kini et al (1998)	India	1997	(7) 36mg pellets of quinacrine inserted between the 6th and 14th day of the menstrual cycle repeated 4 weeks later	400	400	100%	3	0.8%	800
28	Sarin (1997)	India	1/95 - 9/96	(7) 36mg pellets of quinacrine and two diclofenac sodium pellets (50 mg) inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later. Depo-Provera shot after 1st insertion	98	98	100%	0	0.0%	147
29	Ghosh et al (1997)	India	1997	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle	251	251	100%	7	2.8%	251
30	Soroodi-Moghaddam (1996)	Iran	9/90 - 4/94	(7) 36mg pellets of quinacrine and (3) 18.5mg pellets of Ibuprofen inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	98	98	100%	1	1.0%	98
31	Bairagi et al (1995)	India	9/91 - 11/93	(6) 36mg pellets of quinacrine plus either three pellets of diclofenac (75 mg) or three pellets of ibuprofen (55.5 mg) inserted in the proliferative phase of the cycle repeated 4 weeks later	900	627	70%	35	3.9%	2720
32	El Kady et al (1995)	Egypt	1/88 - 4/89	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later, then if both tubes are not blocked confirmed by HSG then a 3rd insertion	159	148	93%	0	0.0%	148
33	Hieu et al (1995) Retrospective study#	Vietnam	4/89 - 12/93	24% had one insertion of (7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle, 74% had a 2nd insertion of quinacrine repeated 4 weeks later, and 2% had a 3rd insertion 4 weeks later	1679	1679	100%	222	13.2%	1679
34	Mullick et al (1995)	India	2/93 - 5/94	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle with diclofenac 75 mg (3 pellets). Depo-Provera shot after insertion	225	151	67%	1	0.4%	151
35	Hieu et al (1993)*	Vietnam	1/89 - 10/92	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	9461	9461	100%	249	2.6%	9461

Crude Pregnancy Rate

Case #	Investigator Publish (date)	Country	Study Dates	QS Insertion Method	# of Cases	Follow up Cases	Follow up (%)	# Pregnant	Fail Rate (%)	Women Years
36	Hieu et al (1993)*	Vietnam	1/89 - 10/92	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle	2225	2036	92%	105	4.7%	2036
37	Bashir (1993)	Pakistan	1/90 - 12/90	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle	2100	2100	100%	85	4.0%	2100
38	Nisa 1989	Pakistan	1/87 - 9/87	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later	105	105	100%	0	0.0%	158
39	Mullick et al (1987)*	India	8/79 - 6/84	200mg of pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	414	414	100%	29	7.0%	1242
40	Guzman - Serani et al (1985)*	Chile	3/79 - 12/79	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later, confirmed by HSG	151	123	81%	7	4.6%	369
41	Bhatt et al (1985)*	India	6/79 - 1/84	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	84	81	96%	4	4.8%	320
42	Kessel et al (1982)*	Chile	1/79 - 12/80	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	267	169	63%	4	1.5%	169
43	Zipper et al (1980)*	Chile	1/79 - 1/80	(7) 36mg pellets of quinacrine inserted during the proliferative phase of the menstrual cycle repeated 4 weeks later repeated 4 weeks later	139	139	100%	4.3	3.1%	139

Crude Pregnancy Rate (Summary)

Case #	Investigator Publish (date)	Country	Study Dates	QS Insertion Method	# of Cases	Follow up Cases	Follow up (%)	# Pregnant	Fail Rate (%)	Women Years
44	Total	3	1/77 - 7/10	1 insertion	2576	2502	97%	93	3.6%	2502
45	Total	1*	1/89 - 10/82	1 insertion	2225	2036	92%	105	4.7%	2036
46	Total	26	1/77 - 7/10	2 insertions	25742	24949	97%	529	2.1%	51464
47	Total	3*	1/77 - 7/11	2 insertions	13878	4372	32%	626	4.5%	38019
48	Total	3	6/79 - 8/06	3 insertions	501	490	98%	5	1.0%	2309
49	Total	6*	1/77 - 12/98	3 insertions	1939	1807	93%	94	4.9%	11049
50	Total	42	1/77 - 7/10	n insertions w/wo contraception	47000	36295	77%	1457	3.1%	107518

* Women not instructed to utilize contraception for 12 weeks after the 1st QS insertion

\# Not included in totals because it contains a variable # of insertions

Risk of Reproductive Cancer

Case #	Investigator Publish (date)	Country	Study Dates	QS Follow up Cases	Control Follow up Cases	Cancer Cases with QS	Cancer Cases with Control	Hazard Ratio QS vs Control	QS Women Years	QS Increases Cancer Risk
1	Jones et al (2017)	Vietnam	01/89 - 01/09	10503	9203	12	8	1.31	173,146	No
2	Sokal et al (2010)	Vietnam	1/01 - 12/06	1029	2999	12	33	1.06	32224*	No
3	Sokal et al (2010)	Chile	1/77 - 12/07	1492	1492	12	17	0.71	23,894	No
4	Sokal et al (2008)	Vietnam	1/01 - 12/06	2735	1623	23	13	1.05	28,697*	No
5	Zipper et al (2004)	Chile	3/77 - 10/90	3285	12355	8	22	1.37	42,705*	No
6	Sokal et al (2000)	Chile	1/77 - 12/96	1492	1492	25	22	1.14	13,444*	No
7	Tice et al (1999)	Chile	1/30 - 7/99	785	785	17	12	1.42	7,852*	No
8	Debancens et al (1995)	Chile	3/77 - 10/90	1000	1000	2.62	1.62	1.62	3,668*	No
9	Total	Vietnam and Chile	1/89 - 01/09	22321	30949	111.62	128.54	1.20	197,040	No

* Not used in total QS women years

Risk of Ectopic Pregnancy

Case #	Investigator Publish (date)	Country	Study Dates	QS Follow up Cases	Control Follow up Cases	Ectopic Pregnancy with QS	Ectopic Pregnancy with Control	Hazard Ratio QS vs Control	QS Women Years	QS Increases Risk
1	Jones et al (2018)	Vietnam	01/89 - 01/09	10503	10534	50	25	2.01	173,146	No
2	Sokal et al (2008)	Vietnam	1/95 - 12/02	2735	1623	27	12	1.34	28,697*	No
3	Zipper et al (2004)	Chile	1/89 - 12/95	2592	2592	9	22	0.41	49,248	No
4	Heiu et al (1997)	Vietnam	1/89 - 12/94	4511	18000	6	25	0.96	28,697*	No
5	Bashir (1993)	Pakistan	1/90 - 12/90	2100	2100	71	158	0.45	2,100	No
6	Kessel et al (1982)	Chile	1/79 - 12/80	1000	1000	0.34	2.15	0.16	2,000*	No
7	Total	Vietnam Chile and Pakistan	1/89 - 01/09	23441	35849	163.34	244.15	1.02	224494	No

* Not used in total QS women years

Risk of Ectopic Pregnancy or Hysterectomy

Case #	Investigator Publish (date)	Country	Study Dates	QS Follow up Cases	Control Follow up Cases	Hysterectomy with QS	Hysterectomy with Control	Hazard Ratio QS vs Control	QS Women Years	QS Increases Risk
1	Jones et al (2018)	Vietnam	01/89 - 01/09	10503	10534	168	146	1.15	173,146	No
2	Feldblum et al (2012)	Chile	3/77 - 10/89	1492	10534	143	1000	1.01	23,894	No
3	Sokal et al (2000)	Vietnam	1/89 - 10/96	2840	36	1658	9	2.34	51,120*	No
4	Total	Vietnam and Chile	1/89 - 01/09	14835	21104	1969	1155	2.43	197040	No

* Not used in total QS women years

in Vivo Mutagen or Cancer

Case #	Investigator Publish (date)	Country	Animal	Total Animal dosage mg/kg	Human dosage* multiple	# of doses	Applied	Pellet or Solution	Results
1	Haseman et al (2015)	United States	female Albino Rats	20	2.4	2	Transcervically to each uterine horn	Solution	Chronic inflammation Non-carcinogenic
2	McConnel et al (2010)	United States	female Albino Rats	20	2.4	2	Transcervically to each uterine horn	Solution	Chronic inflammation Non-carcinogenic
3a	Cancel et al (2010)	United States	female Albino Rats	20	2.4	2	Transcervically to each uterine horn	Solution	Non-carcinogenic
3b	Cancel et al (2010)	United States	female Albino Rats	140	16.7	2	Transcervically to each uterine horn	Solution	Non-carcinogenic
3c	Cancel et al (2010)	United States	female Albino Rats	320	38.1	2	Transcervically to each uterine horn	Solution	Non-carcinogenic
3d	Cancel et al (2010)	United States	female Albino Rats	420	50.0	2	Transcervically to each uterine horn	Solution	Non-carcinogenic
4a	Cancel et al (2006)	United States	male & female mice	20	2.4	2	Intraperitoneal injection	Solution	Non-carcinogenic
4b	Cancel et al (2006)	United States	male & female mice	100	12.0	2	Intraperitoneal injection	Solution	Non-carcinogenic
4c	Cancel et al (2006)	United States	male & female mice	250	30.0	2	Intraperitoneal injection	Solution	Non-carcinogenic
5	Clark et al (2001)	United States	male & female mice	110,000 ng/ml	550.0	3	Intraperitoneal injection	Solution	Non-carcinogenic
6	Fail et al (2000)	United States	Sprague-Dawley rats	350	42.0	1	Transcervically to each uterine horn	Solution	Non-carcinogenic
7a	Ray (1996)	United States	Sprague-Dawley rats	250	30.0	1	SCE Intraperitoneal	Solution	Non-carcinogenic
7b	Ray (1996)	United States	Sprague-Dawley rats	200	24.0	1	SCE Intraperitoneal	Solution	Non-carcinogenic
7c	Ray (1996)	United States	Sprague-Dawley rats	125	15.0	1	SCE Intraperitoneal	Solution	Non-carcinogenic
7d	Ray (1996)	United States	Sprague-Dawley rats	62	7.0	1	SCE Intraperitoneal	Solution	Non-carcinogenic
7e	Ray (1996)	United States	Sprague-Dawley rats	1.5	0.2	1	SCE Intraperitoneal	Solution	Non-carcinogenic
8	Dubin et al (1983)	United States	Cynomolgus monkeys	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
9a	Blake et al (1983)	United States	Cynomolgus monkeys	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
9b	Blake et al (1983)	United States	Sprague-Dawley rats	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
9c	Blake et al (1983)	United States	Sprague-Dawley rats	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
9d	Blake et al (1983)	United States	Sprague-Dawley rats	10	2.0	1	Intrauterine	Solution	Non-carcinogenic

in Vivo Mutagen or Cancer									
Case #	**Investigator Publish (date)**	**Country**	**Animal**	**Total Animal dosage mg/kg**	**Human dosage* multiple**	**# of doses**	**Applied**	**Pellet or Solution**	**Results**
10	Dubin et al (1982)	United States	Cynomolgus monkeys	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
11	Dubin et al (1982)	United States	Cynomolgus monkeys	10	2.0	1	Intrauterine	Solution	Non-carcinogenic
12a	Chandra et al (1981)	United States	Rhesus monkeys	65	15.0	1	Intrauterine	Solution	Non-carcinogenic
12b	Chandra et al (1981)	United States	Rhesus monkeys	65	15.0	1	Intrauterine	Solution	Non-carcinogenic
13	Bruce et al (1979)	United States	C57B1/6XC3 H/HEF1 male mice	500	119.0	1	Intraperitoneal injection	Solution	Non-carcinogenic
14	Epstein et al (1972)	United States	Swiss male mice	130	31.0	1	Intraperitoneal injection	Solution	Non-carcinogenic
15	Fitzhugh et al (1945)	United States	Albino Rats	4	1.0	1	Orally for 2 years	Powder	Non-carcinogenic

* 252mg dose in a 60kg woman is 4.2mg/kg

in Vitro / in Silico Mutagen or Cancer

Case #	Investigator Publish (date)	Country	Bacterial Tester Strain	Total dosage	Human dosage*	X Human dose	Methods	Results
1	Tice et al (2022)	United States	In Silico references	3000 ng/ml	200 ng/ml	19	Ames et al 1975, and Maron et al 1981	Non-carcinogenic
2	Chapman et al (2020)	United Kingdom	Human cell line TK6	2ng/ml	200 ng/ml	0.01	Wilde et al 2018	Non-carcinogenic
3a	Clark et al (2001)	United States	Bacterial TA98 with S9	333,333 ng/ml	200 ng/ml	1667	Ames et al 1975, and Maron et al 1983	Mutagenic and non-carcinogenic
3b	Clark et al (2001)	United States	Bacterial TA98 wo S9	400,000 ng/ml	200 ng/ml	2000	Ames et al 1975, and Maron et al 1983	Non-mutagenic
3c	Clark et al (2001)	United States	Bacterial TA100 w/wo S9	333,333 ng/ml	200 ng/ml	1667	Ames et al 1975, and Maron et al 1983	Non-mutagenic
3d	Clark et al (2001)	United States	Bacterial TA1535 w/wo S9	333,333 ng/ml	200 ng/ml	1667	Ames et al 1975, and Maron et al 1983	Non-mutagenic
3e	Clark et al (2001)	United States	Bacterial TA1537 w/wo S9	111,000 ng/ml	200 ng/ml	555	Ames et al 1975, and Maron et al 1983	Mutagenic and non-carcinogenic
3f	Clark et al (2001)	United States	Bacterial WP2 uvrA wo S9	333,333 ng/ml	200 ng/ml	1667	Ames et al 1975, and Maron et al 1983	Mutagenic and non-carcinogenic
3g	Clark et al (2001)	United States	Mouse lymphoma assay with S9	6667 ng/ml	200 ng/ml	33	Ames et al 1975, and Maron et al 1983	Non-mutagenic
3h	Clark et al (2001)	United States	Mouse lymphoma assay wo S9	3000 ng/ml	200 ng/ml	15	Ames et al 1975, and Maron et al 1983	Mutagenic and non-carcinogenic
3i	Clark et al (2001)	United States	Hamster ovary (CHO) cells w/wo S9	3850 ng/ml	200 ng/ml	19	Ames et al 1975, and Maron et al 1983	Clastegenic negative for polyploidy
4a	Tice et al (McCoy et al 1981) (1999)	United States	TA1537 and TA97 w/wo S9	3000 ng/ml	200 ng/ml	19	Ames et al 1975, and Maron et al 1984	Mutagenic and non-carcinogenic
4b	Tice et al (McCoy et al 1981) (1999)	United States	TA98, TA100, TA1535, TA1538, TA1977, TA1978 wo S9	3000 ng/ml	200 ng/ml	19	Ames et al 1975, and Maron et al 1984	Non-mutagenic

* highest quinacrine blood plasma level detected in women after QS insertion is < 200 ng/ml per Laufe et al Phase I study 1996

Section 1: Latest Research (2004 - 2023)

Regulatory Toxicology and Pharmacology 124 (2021) 104968

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

What happened to quinacrine non-surgical female sterilization?

Stephen D. Mumford

International Services Assistance Fund, P.O. Box 13067, Research Triangle Park, NC, 27709, USA

ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords
Quinacrine
Contraception
Non-surgical sterilization
Uterus
Tumorigenicity
Neoplasm
Carcinogenicity (CaBio)
Maximum tolerated dose (MTD)
Chronic inflammation
Biological relevance

ABSTRACT

Quinacrine sterilization (QS) is a nonsurgical female method used by more than 175,000 women in over 50 countries. With FDA approval, QS is expected to be used by hundreds of millions of women. The negative international health consequences of the results of a 2-year rat study in 2010 by Cancel et al. in Regulatory Toxicology and Pharmacology (RTP) (56:156–165) are incalculable. S1C(R2) was ignored in this study, including the fundamental concept of maximum tolerated dose (MTD), which resulted in the use of massive doses (up to 35 times the MTD) which killed many of the rats and destroyed the uterus of survivors. The design of this rat study was built on the false assertion that this study mimics what happens in women. Cancel et al. (2010), concludes it "seems most likely" that genotoxicity was a major factor in the carcinogenicity observed, prompting the FDA to halt further research of QS. In RTP, McConnell et al. (2010), and Haseman et al. (2015), using the authors' data, definitively determined the carcinogenicity to be secondary to necrosis and chronic inflammation. Decisions made in the design, conduct, analysis, interpretation and reporting in this study lack scientific foundation. This paper explores these decisions.

1. Introduction

Quinacrine sterilization (QS) is a nonsurgical female method used by more than 175,000 women in over 50 countries. QS is given in two doses of seven 36 mg pellets 28 days apart. In the United States, existing options of contraception are not meeting the needs of millions of women. According to the U.S. Department of Health and Human Services' Healthy People 2020 campaign, 51% of the 6.6 million pregnancies in the United States each year are unintended, (Guttmacher Institute Fact SheetJanuary, 2019). The U.S. Centers for Disease Control (CDC) reported 37.8% of the births from unintended pregnancies were in women who did not want that pregnancy or any more pregnancies in the future (unwanted as opposed to ill-timed) (Mosher et al., 2012).

According to a 2007 report for the United States Agency for International Development (USAID) (Duncan, 2006), if approved by the United States Food and Drug Administration (FDA): *"This [QS] method is a simple, inexpensive, easy-to-administer female non-surgical sterilization that requires minimal provider training and equipment; it could reach tens or even hundreds of millions of women wanting to limit births."*

On February 1, 1993, QS was "Accepted" as an approved use of quinacrine by the United States Pharmacopeial Convention (USP). It remained there until April 29, 1999.

2. Use of QS in humans

QS was developed in Chile in 1976 by Dr. Jamie Zipper. In 1977, the first clinical trial was conducted in Chile, India and Bangladesh by the International Fertility Research Program (IFRP) by Dr. Elton Kessel (Zipper and Kessel, 2003). This IFRP clinical trial was terminated by the funder, United States Agency International Development (USAID), before the end of 1977, with about half the 600 cases being completed (Bhatt et al. (1980), Zipper et al. (1980). IFRP prepared a project for the United States Food and Drug Administration (USFDA) that resulted in 5 pharmacologic and toxicologic studies: Dubin et al. (1982a), Dubin et al. (1982b), Blake et al. (1983), Dubin et al. (1983), Pharmley et al. (1983) and one pre-hysterectomy study (Laufe et al. (1996). In 1980, IFRP ended its work with USFDA. IFRP was renamed Family Health International (FHI). FHI never undertook another clinical trial.

Also in 1980, clinical trials were initiated by the International Federation for Family Health (IFFH) under the direction of Dr. Kessel (Zipper and Kessel, 2003). Following a report on 31,781 QS cases in Vietnam in *The Lancet* in 1993 (Hieu et al., 1993), the International Services Assistance Fund (ISAF) joined the QS effort in 1994. ISAF has raised and spent $8 million to attempt to gain FDA approval for QS.

In 1998, 18 years later, FHI approached the FDA. The FDA proposed that FHI undertake two animal studies, a one-year neonatal mouse carcinogenesis study and a 2-year rat CaBio. Cancel et al. (2006)

E-mail address: smumford@mindspring.com.

https://doi.org/10.1016/j.yrtph.2021.104968
Received 18 January 2021; Received in revised form 26 May 2021; Accepted 26 May 2021
Available online 29 May 2021

completed the mouse study that was negative for cancer. The CaBio was completed in 2006 but the study was not published until 2010 (Cancel et al., 2010).

Also in 1998, ISAF approached the FDA and proposed a Phase I Trial. In 2003, the International Journal of Gynecology and Obstetrics published a Supplement; Quinacrine Sterilization: Reports on 40,252 Cases (Lippes, 2003), which includes 25 articles. It documented nearly 100 clinical trials from the beginning of QS, including the Phase I trial, completed by Dr. Jack Lippes (Lippes et al., 2003).

ISAF then proposed a Phase III Trial of 500 American women at 18 Medical Schools and six Planned Parenthood clinics. The FDA approved this trial in 2006. In January 2007, the FDA placed a clinical hold on the trial that has never been lifted. The FDA used preliminary data from Cancel et al. (2010) to make its decision on the clinical hold.

3. How QS works

Growe et al. published a description of the mechanism of action of quinacrine to produce a permanent fibrotic occlusion in the human fallopian tube (Growe et al., 2013). The mechanism relies on a basic property of quinacrine that causes living epithelial cells to detach from one another and their basement membranes. In the human fallopian tube, this action triggers the innate immune system that induces a cascade of immune cell signaling, pro-inflammatory and pro-fibrotic proteins, and the deposit of dense collagen resulting in tubal closure. The effect of quinacrine with respect to fibrosis and occlusion is limited to the human fallopian tube and only in the intramural segment of the tube, 2–4 mm in length.

This natural immune response, specific to the human fallopian tube, has not been replicated in other animals or organ tissues. In studies conducted in species other than humans, including rats, pigs and monkeys (King et al., 1983; Dubin et al., 1982b; Zaneveld and Goldsmith, 1984; Fail et al., 2000; Jensen et al., 2004), the mechanism of action of quinacrine in the fallopian tube has never been replicated. From the considerable research that has been conducted on gonorrhea and chlamydia, diseases that elicit the same immune response, this mechanism is known to be unique to humans.

4. An appropriate FDA trial of QS

Quinacrine was developed in 1928 and was a widely known antimalarial used daily by more than 100 million people (dose 100 mg daily) including 4 million US military personnel. Quinacrine "is one of the best studied drugs ever introduced" (Ehsanian et al., 2011).

The Ames Salmonella test is positive for quinacrine, though the 'false positive' rate is approximately 20–30%. Despite its wide use and no obvious link to cancer in humans, the FDA could be justified in requiring a mouse study and a rat CaBio. The proposed use for quinacrine has the potential to be used in millions of women and scientifically rigorous studies should be used to ensure safety.

5. The Cancel et al. (2010) study: a lifetime cancer bioassay of quinacrine into the uterine horns of female rats

Both FHI and the FDA should have required the use of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Industry S1C(R2) (Revised March 11, 2008) for conducting rodent studies for regulatory use. These guidelines highlight the importance of ensuring that cancer bioassay studies are carefully designed and critically reviewed.

This study investigated if quinacrine can induce a tumorigenic response in rats when administered in a manner similar to the intended human use for female non-surgical sterilization. Young sexually mature female rats received two doses of quinacrine (or 1% methylcellulose control) into each uterine horn approximately 21 days apart, and were observed for 23 months after the second dose administration. Dose levels were 0/0, 0/0, 10/10, 70/70, and 70/250–350 mg/kg (first dose/second dose).

5.1. ICH S1C(R2) guidelines not followed

The FDA was a major contributor to the ICH Guidelines. The guidelines read: *"Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection (Note 1)." "Note 1. The US Interagency Staff Group on Carcinogens has defined the MTD as follows: The highest dose (*emphasis added*) currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity (*emphasis added*) without significantly altering the animal's normal lifespan due to the effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a subchronic study (usually 90 days duration) primarily on the basis of mortality, toxicity and pathology criteria. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. Such factors include … target organ toxicity …"*

This study was flawed from the outset. No valid subchronic study was performed to examine for evidence of mortality, toxicity and pathology in a 90-day or similar study. Range Finding Study #1's goal appeared to be to determine a dose of quinacrine that would cause fibrotic closure of the rat uterus on the second dose. Cancel et al. (2010) states, "These results suggested that the initial dose of quinacrine should be < 175 mg/kg, in order to allow a second dose to be administered consistently." In Range Finding Study #2 Cancel et al. state, "The main purpose of this range finding study was to identify a dose of quinacrine that allowed a second uterine dose." In "Range Finding Study #3," the authors chose a lower first dose (50 or 70 mg/kg) and higher second dose (250–350mg/kg), which differs from its use in women. These studies do not represent valid MTD studies.

5.2. A "dosing phase" and a "observation phase"

In an FDA Executive Cancer Assessment Committee (CAC) meeting on April 23, 2002 detailing the CaBio, there is no mention of a dosing and observation phase. Only a typical CaBio is discussed.

To dismiss the many early deaths in the high dose groups, Cancel et al. (2010) created an artificial construct and divided the study into two parts: a *"dosing phase"* (during which mortality is *"irrelevant")* and an *"observation phase"* (during which mortality is important).

The *"dosing phase"* was not a part of the original study design. It was defined *"after the fact"* and encompassed the many early deaths, during which time no histopathologic slides were done. Obviously, the high doses did not meet S1C(R2)'s criteria above, requiring that *"the exposure to the agent … is compatible with good survival ."*

5.3. Failure to produce the desired fibrosis and occlusion

In Cancel et al. (2010), erroneous understanding of the mechanism of action of quinacrine on the fallopian tube was the very basis for their high dose selection. The goal of their CaBio was to produce closure of the uterus. Did their high doses of 250 mg/kg and 350 mg/kg, 60 times and 83 times the human dose of 252 mg (4.2 mg/kg in a 60 kg woman) produce the desired fibrosis and occlusion?

In the woman, 2–4 mm of the intramural portion of the fallopian tube is completely filled with a dense white collagenous scar following QS. This 2-year rat study was designed to produce the same scar in the rat uterus—ignoring the MTD. It did not. The study's protocol stated that during the terminal necropsies, evidence of occlusive fibrosis would be evaluated as one of the noncancerous lesions. Occlusive fibrosis of the uterus or fallopian tube was not reported in the CaBio study (Cancel et al., 2010). Not only did they fail to produce the fibrosis of the fallopian tubes, as is the case in women, but they failed to produce the

occlusive fibrosis in the rat uterus, which was given as the justification for their dose selection. Remarkably, this observation was not reported.

5.4. Drug formulation used in rats differed from formulation used in women

The formulation used in the CaBio differed significantly from the human formulation. It consisted of a slurry of quinacrine mixed with saline and methylcellulose (MC), followed by a 3% methylcellulose cervical plug to prevent leakage of the slurry. Methylcellulose, like asbestos and talc, is an inert substance and the body has no mechanism for eliminating it. MC is a known tissue irritant (Haseman et al., 2015). The FDA guidelines state, *"The test substance used in toxicity studies should be the same substance that the petitioner/notifier intends to market"* (Redbook, 2002).

5.5. Rat study mimics what occurs in women?

Cancel et al. (2010) abstract reads: *"This study investigated if quinacrine can induce a tumorigenic response in rats when administered in a manner similar to the intended human use for female non-surgical sterilization."* Cancel et al. (2010) make no mention of the fact that none of their doses achieved FHI's goals. In a woman, only the fallopian tube, and not the uterus is permanently affected and, critically, the specialized cells affected by quinacrine in a woman's intermural portion of her fallopian tube are not present in her uterus. The endometrial lining of a woman's uterus is affected superficially by QS administration of quinacrine. The affected endometrium is shed during the normal menstrual cycle, usually within two to three weeks, and the endometrium returns to normal, usually within one month. (Merchant et al., 1995; Hieu et al., 1993, Lippes J., 2003). As predicted by previous researchers, it is not possible to mimic quinacrine's effects on the human fallopian tube in rats.

5.6. MTD never mentioned in the protocol, final report or in Cancel et al. (2010)

S1C(R2) prompts the reader to have MTD in a CaBio report: *"In all cases, appropriate dose ranging studies for MTD selection should be conducted."* Cancel et al. reported that these were feasibility studies to determine the maximum first dose that could be administered that would allow administration of the second dose, not studies to determine the MTD. Had the pre-chronic rats that died during dosing been histopathologically studied upon their deaths, rather than discarded, Cancel et al. (2010) would have recognized that these deaths were preceded by severe organ damage and leakage. Doses of 70, 250 and 350 mg/kg produced morphologic evidence of severe toxicity. Cancel et al.'s animal terminal necropsy data at mid and high doses proved beyond any doubt that there was severe and permanent damage to the target organ.

6. McConnell et al. (2010): An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats"

McConnell et al. made a good attempt at determining the MTD by focusing on Cancel et al. (2010) Range Finding Study #2. This study was not published. Dr. P.A. Fail was a Research Triangle Institute sub-contractor working with FHI. In 2008, Dr. Fail became a consultant to ISAF. This 30-day study offered McConnell et al. the opportunity to view the histopathology slides used for "Range Finding Study #2." In theory, uterine histopathology would have shown "*minimal toxicity without significantly altering the animal's normal lifespan due to the effects other than carcinogenicity … such factors include target organ toxicity*" (ICH S1C (R2) Guidelines). This 30-day study was adequate to show the high doses exceeded MTD because destruction to the uterus has already occurred by 30 days and ISAF's 4-day study allowed for the early sequential changes in the uterus. This 4-day study was done after the fact by ISAF at Dr. McConnell's supervision (Haseman et al., 2015). McConnell's histopathological assessment was that 10 mg/kg caused minimal toxicity to the rat uterus during the 30 day study. To comply with ICH guidelines, it should have been carried out to 90 days. However, it allowed McConnell to estimate the MTD at 10 mg/kg for quinacrine some 10 years after the fact.

Further evidence that the MTD was exceeded were the types of tumors reported by Cancel et al..

McConnell et al. note the reported tumors were unusual and rare, including primitive types of both epithelial and mesenchymal origin. These are unexpected and rare observations in a standard 2-year cancer CaBio assay. Another unusual feature is that only a single example of each of these rare tumors were found.

McConnell et al. concluded that the doses of 70, 250 and 350 mg/kg quinacrine causing uterine tumors in their study clearly exceeded the MTD, that the rat uterus was not a valid surrogate for the human fallopian tube, and that quinacrine was not genotoxic *in vivo,* as suggested by Cancel et al..

7. Haseman et al. (2015): A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat bioassay and its implications for human clinical use

Cancel et al. (2010) "summarized" their rat necropsy data, which documented extensive necrosis and chronic inflammation in the reproductive tract. Haseman et al. was given an opportunity to evaluate each individual rat by examining raw data collected by FHI. Rather than "summarize" the data, Haseman et al. looked at each outcome for each individual rat. *"The top 3 doses [70, 250 and* 350 mg/kg*] of quinacrine in the CaBio exceeded the MTD and produced chronic damage, including inflammation, resulting in reproductive tract tumors. Chronic inflammation was significantly correlated [$p = 0.002$] with the tumors; there was no evidence of treatment-related tumors in animals without chronic inflammation or other reproductive system toxicity."*

Haseman et al. note that the fact that quinacrine was negative in the mouse neonatal assay (Cancel et al., 2006) further supports the conclusion that it is not a genotoxic carcinogen, since validation studies of the neonatal mouse assay have shown that substances negative in this assay (like quinacrine) are not likely to be trans-species carcinogens or carcinogenic via a genotoxic mode of action (Flammang et al., 1997; McClain et al., 2001).

Haseman et al. concludes: *Because such permanent uterine damage and chronic toxicity have not been observed in humans under therapeutic conditions, we conclude that this mode of action for tumor production will not occur at clinically relevant doses in women who choose quinacrine for permanent contraception.* Haseman et al. (2015) documented that the tumors seen in the rat were due to necrosis and compensatory cell proliferation in the presence of chronic inflammation of the reproductive tract.

8. The FDA permanently ends QS

In November 2006, FHI announces its decision to terminate any further research of QS due to the outcome of its CaBio (Sokal et al., 2007). FHI notified the FDA. The FDA placed a Clinical Hold on ISAF's Phase III Clinical Trial. After years of discussion with the FDA, ISAF decided that it must undertake a Formal Dispute Appeal on December 21, 2012. Our Appeals process ended with the Commissioner of the FDA, Robert Califf on August 26, 2016. On December 9, 2016, ISAF received the final word that our appeal "*does not warrant further review*" by Luciana Borio, MD, Acting Chief Scientist of the FDA. This letter from Dr. Borio meant the end of QS at the FDA.

9. Conclusions

Cancel et al.'s study was flawed in the following ways:

1) Since no appropriate dosing studies were performed, the MTD was exceeded (up to 35x).
2) The CaBio study had a "dosing phase" and a "observational phase", which does not conform to the ICH standards.
3) The authors cite the intended outcome of the range finding studies was to "mimic" fibrotic closure of the uterine horn, but no uterine fibrotic closure were reported in any of the rats in the CaBio study.
4) The drug formulation used in the CaBio (slurry) differed from what is used in women (pellets), and contained a known tissue irritant.
5) Histopathologic examination found that the doses used in the CaBio study caused massive necrosis of the uterus and chronic inflammation.
6) The reported tumors originating from primitive cell types in the high dose groups likely indicated that other factors were influencing tumorigenesis, such as chronic inflammation.

The FHI 2-year rat study does not qualify as a study designed for Regulatory use. It does not conform to that described by the ICH in its S1C(R2) guidance. FHI's claim that quinacrine is a genotoxic carcinogen is unsubstantiated. FHI's flawed CaBio was sent to the FDA. It became the FDA's responsibility to ensure that the ICH guidance was followed. The FDA failed. The outcome is the termination of all clinical research of QS. QS should be an option for the hundreds of millions of women worldwide who want to avoid unwanted pregnancies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Stephen D. Mumford: Conceptualization, Investigation, Methodology, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The author is grateful to Dr. Ernest E. McConnell, DVM for serving as an unpaid science advisor from January 2007 to the present. Many thanks to Donald A. Collins, Jr., President of ISAF, for his comments and suggestions which were very useful and gratefully appreciated.

References

Bhatt, R., Jariwala, K.M., Bhiwandiwala, P., Laufe, L., 1980. Chemical female sterilization using quinacrine pellets. New Delhi. In: Hingorani, V., Pandit, R.D., Bhargava, V.L. (Eds.), Proceedings of the Third International Seminar on Maternal and Perinatal Mortality, Pregnancy Termination and Sterilization, pp. 370–377. October 3-5, 1980.

Blake, D.A., Dubin, M.C., Diblasi, M.C., Parmley, T.H., Stetten, G., King, T.M., 1983. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 71–88.

Cancel, A.M., Dillberger, J.E., Kelly, C.M., Bolte, H.F., Creasy, D.M., Sokal, D.C., 2010. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 156–165.

Cancel, A.M., Smith, T., Rehkemper, U., Dillberger, J.E., Sokal, D., McClain, R.M., 2006. A one-year neonatal mouse carcinogenesis study of quinacrine hydrochloride. Int. J. Toxicol. 25, 109–118.

Dubin, N.H., Blake, D.A., DiBlasi, M.C., Parmley, T.H., King, T.M., 1982a. Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. Fertil. Steril. 38, 735–740.

Dubin, N.H., Strandberg, J.D., Craft, C.F., Parmley, T.H., Blake, D.A., King, T.M., 1982b. Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry, and hematology in Cynomolgus monkeys. Fertil. Steril. 38, 741–747.

Dubin, N.H., Pharmley, T.H., Diblasi, M.C., Ghodgaonkar, R.B., Jiffry, M.T.M., Blake, D. A., King, T.M., 1983. Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 60–70.

Duncan, G.W., 2006. External Review of USAID's Current and Future Role in Contraceptive Research and Development. Links Media LLC, pp. 12–13.

Ehsanian, R., Van Waes, C., Feller, S.M., 2011. Beyond DNA binding – a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation and cancers. Cell Commun. Signal. 9, 13.

Fail, P.A., Martin, P., Sokal, D.C., 2000. Comparative effects of quinacrine and erythromycin in adult female rats: a non-surgical sterilization study. Fertil. Steril. 73, 387–394.

Flammang, T.J., von Tungeln, L.S., Kadlubar, F.F., Fu, P.P., 1997. Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Regul. Toxicol. Pharmacol. 26, 230–240.

Growe, G.G., Luster, M.I., Fail, P.A., Lippes, J., 2013. Quinacrine-induced occlusive fibrosis in the human fallopian tube is due to a unique inflammatory response and modification of repair mechanisms. J. Reprod. Immunol. 97, 159–166.

Guttmacher Institute Fact Sheet, January, 2019. Unintended Pregnancy in the United States, p. 1.

Haseman, J.K., Growe, R.G., Zeiger, E., McConnell, E.E., Luster, M.I., Lippes, J., 2015. A critical examination of the mode of action of quinacrine in the reproductive tract in a 2- year rat cancer bioassay and its implications for human clinical use. Regul. Toxicol. Pharmacol. 71, 371–378.

Hieu, D.T., Tan, T.T., Tan, D.N., Nguyet, P.T., Than, P., Vinh, D.Q., 1993. 31,781 cases of nonsurgical female sterilization with quinacrine pellets in Vietnam. Lancet 342, 213–217.

ICH Harmonized Tripartite Guideline. Guidance for Industry: S1C(R2) Dose Selection for Carcinogenicity Studies. Current Step 4 Version, Parent Guideline Dated 27 October 1994, (Addendum on a Limit Dose Dated 17 July 1997 and Incorporated in November 2005), Revised on 11 March 2008, This Guideline Has Been Developed by the Appropriate ICH Expert Working Group and Has Been Subject to Consultation by the Regulatory Parties, in Accordance with the ICH Process. At Step 4 of the Process, the Final Draft Is Recommended for Adoption to the Regulatory Bodies of the European Union, Japan, and USA.

Jensen, J.T., Rodriguez, M.J., Liechtenstein-Zabrak, J., Zalany, S., 2004. Transcervical polidocanol as a nonsurgical method of female sterilization: a pilot study. Contraception 70, 111–115.

King, T.M., Dubin, N.H., Blake, D.A., Parmley, T.H., 1983. Quinacrine Hydrochloride: future research. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 138–140.

Laufe, L.E., Sokal, D.C., Cole, L.P., Shoupe, D., Schenken, R.S., 1996. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception 54, 181–186.

Lippes, J., Brar, M., Gerbracht, K., Neff, P., Kokkinakis, S., 2003. An FDA Phase I clinical trial of quinacrine sterilization (QS). Int. J. Gynecol. Obstet. 83, S45–S49. Supp. 2.

Lippes, J., 2003. Guest editor, supplement: quinacrine sterilization: reports on 40,252 cases. Int. J. Gynecol. Obstet. 83, S3–S5. Supp. 2.

McClain, R.M., Keller, D., Casciano, D., Fu, P., MacDonald, J., Popp, J., Sagartz, J., 2001. Neonatal mouse model: review of methods and results. Toxicol. Pathol. 29 (Suppl. l), 128–137.

McConnell, E.E., Lippes, J., Growe, R.G., Fail, P., Luster, M.I., Zeiger, E., 2010. An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 166–173.

Merchant, R.N., Prabhu, S.R., Kessel, E., 1995. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. Int. J. Fertil. 40, 47–54.

Mosher, W.D., Jones, J., Abma, J.C., 2012. Intended and Unintended Births in the United States: 1982-2010. National Health Statistics Reports, 55.

Parmley, T.H., Dubin, N.H., Strandberg, J., Laufe, L.E., 1983. Histologic changes following intrauterine administration of quinacrine hydrochloride. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 89–93.

Redbook, 2002. Chapter IV. B. 1. General Guidelines for Designing and Conducting Toxicity Studies.

Sokal, D., Haneke, K., Robinson, E., Katz, K., Dorflinger, I., 2007. FHI's decision to halt development of quinacrine: why and how. Abstracts/Contraception P48 (76), 173–174.

Zaneveld, L.J., Goldsmith, A., 1984. Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception 30, 161–167.

Zipper, J., Kessel, E., 2003. Quinacrine sterilization: a retrospective. Int. J. Gynecol. Obstet. 83 (Suppl. 2), S7–S11.

Zipper, J., Cole, L.P., Goldsmith, R., Wheeler, R., 1980. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int. J. Gynecol. Obstet. 18, 275–279.

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE, 2018
https://doi.org/10.1080/13625187.2018.1449823

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH ARTICLE

Long-term risk of hysterectomy and ectopic pregnancy among Vietnamese women using the quinacrine hydrochloride pellet system vs. intrauterine devices or tubal ligation for contraception

Judith K. Jones[a], Arlene Tave[a], John C. Pezzullo[b]†, Sharon Kardia[c] and Jack Lippes[d]

[a]The Degge Group Ltd., Fairfax, VA, USA; [b]Department of Biomathematics and Biostatistics, Georgetown University, Washington, DC, USA; [c]School of Public Health, University of Michigan, Ann Arbor, MI, USA; [d]School of Medicine, State University of New York at Buffalo, Buffalo, NY, USA

ABSTRACT

Objectives: Determine the long-term risk of hysterectomy and ectopic pregnancy in women using the quinacrine hydrochloride pellet system of permanent contraception (QS) relative to the comparable risk in women using Copper T intrauterine device (IUD) or tubal ligation surgery (TL) for long-term or permanent contraception.

Methods: This was a retrospective cohort study, conducted in the Northern Vietnamese provinces of Ha Nam, Nam Dinh, Ninh Binh and Thai Binh. Women who had their first QS procedure, last IUD insertion or TL between 1989 and 1996 were interviewed regarding post-procedure health outcomes approximately 16 years post exposure.

Results: A 95% response rate resulted in 21,040 completed interviews. Overall incidence rates were low for both outcomes (91/100,000 women years of follow-up and 22/100,000 women years of follow-up for hysterectomy and ectopic pregnancy, respectively). After accounting for variations in baseline characteristics between women choosing QS vs. the other two contraceptive methods, no significant excess hazard of either hysterectomy or ectopic pregnancy was associated with QS.

Conclusions: No significant excess long-term risk of hysterectomy or ectopic pregnancy was found among a large group of women using QS vs. IUD or TL for contraception after an average 16 years of follow-up.

ARTICLE HISTORY
Received 17 September 2017
Revised 25 February 2018
Accepted 3 March 2018
Published online 20 April 2018

KEYWORDS
Quinacrine; retrospective cohort study; survival analysis; non-surgical permanent contraception; female; hysterectomy; ectopic pregnancy

Introduction

The quinacrine hydrochloride pellet system of permanent contraception (QS) is a non-surgical procedure that can be performed outside of a hospital setting. The procedure follows a standardised protocol: transcervical application of seven 36 mg quinacrine pellets, administered in the proliferative phase of the menstrual cycle, using a device similar to a Copper T intrauterine device (IUD) inserter. The currently recommended dosage regimen is two insertions applied one month apart. The quinacrine pellets dissolve and lead to sclerosis and subsequent occlusion of the fallopian tubes [1]. A plausible mechanism for the cellular and molecular events involved in occlusion of the fallopian tubes by this contraceptive method was reported by Growe et al. in 2013. That work found the occlusion occurs as a pro-inflammatory response to the drug in the uterus and fallopian tubes. While the uterus returns to normal, mature collagen forms in the lumen of the fallopian tube, resulting in its permanent occlusion [2].

Between 1989 and 1993 an estimated 50,000 Vietnamese women participated in a governmental clinical trial of QS. All procedures for the clinical trial were conducted at commune level clinics, which are the most local layer in Vietnam's four-level public health service delivery hierarchy. The four levels of health care correspond to the four administrative levels of the government (i.e., national, provincial, district and commune levels). Residents are expected to seek primary healthcare from commune level health centres, which are their main contact with the public health system. Commune health centres also supervise village health workers who make house calls in local communal areas [3].

Despite early indications of QS being an easy and safe method for long-term contraception, concerns arose regarding potential reproductive health risks. Those concerns were particularly focused on reproductive tract cancers, hysterectomy, ectopic pregnancy and death. A laboratory study suggesting the possibility of QS being carcinogenic [4] was later shown to have a design inappropriate for testing the stated hypothesis and/or extrapolating its findings to humans [5]. Previous analysis of data from the large, long-term follow-up study discussed in this manuscript found no significant excess risk of reproductive tract cancer among women treated with QS vs. comparators using IUD or tubal ligation surgery (TL) for contraception [6]. Previous studies among various subsets of the Vietnam clinical trial participants compared risk of hysterectomy and ectopic pregnancy between women using QS vs. other contraceptive methods. No excess hysterectomy risks were identified and observed differences in ectopic pregnancies were generally accounted for by factors other than contraceptive method (e.g., small sample sizes, small numbers of events or high failure rates prior to refinement of the QS procedure) [7–11].

In order to address the reproductive health concerns in a more definitive manner than previous attempts, a

CONTACT Arlene Tave atave@deggegroup.com The Degge Group Ltd., 9302 Lee Highway, Suite 700, Fairfax 22031, VA, USA
†Deceased 2 June 2016.

Supplemental data for this article can be accessed here.

carefully controlled retrospective cohort study was conducted between 2007 and 2008 among a large group of the clinical trial participants to determine long-term health status following the QS procedures. Women in four provinces, along with age-clinic-date-matched controls who used IUDs or TL for contraception, were interviewed an average 16 years following their contraceptive procedures. Low migration rates among rural Vietnamese [12] combined with the country's health care system centred around local area clinics, facilitated identification of women for interview in this long-term follow up study.

Results from that study regarding comparative long-term incidence and risk between the QS and control cohorts of hysterectomy and ectopic pregnancy are reported herein.

Methods

Cohort identification

The maximum number of interviews, within the constraints of available funding, was conducted with women in the northern Vietnamese provinces of Ha Nam, Nam Dinh, Ninh Binh and Thai Binh. All participants had their first QS procedure, last IUD insertion or TL between 1989 and 1996.[1] QS-exposed subjects were identified from procedure logbooks at commune level health clinics in each province. The study's sponsoring organization (ISAF[2]) identified clinics known to have regularly provided permanent contraception services as potential study sites. All 784 health communes in the four provinces were included in the survey, although some had few women treated with QS. Dr. Do Trong Hieu served as the Vietnam in-country study coordinator, and worked with The Institute for Development and Community Health (LIGHT) to conduct the study. Lists of comparator subjects who had IUD insertions or TL were compiled from clinic logbooks and district health centre records in three provinces. In the fourth province (Nam Dinh), IUD and TL patient records had been destroyed in a flood. TL comparators in that province were identified from district health centre records, and IUD comparators were located via community survey. From women identified by community survey in Nam Dinh as having used IUDs for contraception, two potential comparators per QS subject were randomly selected from all potential matches. The assigned interviewer chose which of the two women to contact for the study. In all provinces, the goal was to match comparators to QS women by the clinic at which the procedure was done, quarter of the calendar year in which their procedure was completed, and age at the time of their qualifying contraceptive procedure (±2 years). Matching by age at procedure took precedence over matching by quarter year of the procedure. As the primary impetus for the study was an examination of long-term risk of reproductive tract cancers, women with cancers prior to their procedure were excluded from the study. At least one comparator match was identified for each QS woman. In cases where multiple matching comparators were found, one comparator was randomly selected from the group.

Data collection

English language case report forms (CRFs) were developed by The Degge Group (see Supplemental Information A). Questions were modelled on questionnaires from previously published studies collecting similar types of data, with redundant questions included for verification purposes [13–27]. The CRFs were independently reviewed by a panel of three cancer epidemiologists. CRFs were translated into Vietnamese by an employee of the Vietnam Ministry of Health, and the LIGHT staff revised the documents as needed to accommodate practical aspects of the data collection process. Data collection procedures were approved by a Vietnamese institutional review board prior to implementation.

Local clinic staff first abstracted demographic data and information about each subject's first QS procedure, last IUD insertion or TL from health centre records for most women. For IUD comparators in Nam Dinh, the data were collected as part of the community survey. Each woman's qualifying procedure was identified as her Index Procedure (IP).

Interviews were then attempted for all women identified as having undergone the QS procedure, for all matched comparators in the provinces of Ha Nam, Ninh Binh and Thai Binh, and for the selected comparators in Nam Dinh. All interviews were conducted by physicians[3] who were carefully trained by LIGHT in proper administration of the health status questionnaires.

After obtaining informed consent survey participants (or proxies) were asked about their post-IP history of obstetric and gynaecologic events (including IP/post-IP details), histories of chronic diseases, hospitalisations and surgeries, family history of cancer and environmental exposures. The majority of interviews (98%) were held in person, although in a few cases (e.g., when a woman had moved away from the clinic area) contact was via telephone. Interviewers probed for details about reported outcomes, in particular any surgeries or hospitalisations.

Staff familiarity with women seen at area clinics facilitated review and correction of responses at the local level, as needed. Completed CRFs were reviewed by LIGHT staff including four physicians, one from each of the four provinces involved in the survey, and doubts about any responses were discussed by that team. Reviewers' questions were returned to the local clinics for verification.

Data entry

Degge developed an MS-Access database for computerised entry and storage of the study data. Laptop computers on which the database programme was installed were provided to the Vietnam research staff at LIGHT. Information collected on the CRFs was translated from Vietnamese to English as it was transcribed by the project officers into the computerised database. Translation of unfamiliar terms was verbally provided to the project officers by Dr. Nguyen Bich Ngoc in consultation with Dr. Do Trong Hieu. Data files were transferred to ISAF and then to the Degge investigators for cleaning and analysis.

Steps were implemented to maximise the accuracy and completeness of the data entry. While the interviews were underway, a 5% random sample of questionnaires and their corresponding MS-Access records were provided to the Degge staff for review. The small number of data entry errors and translation issues identified in the sample were corrected and feedback provided to interviewers and data entry operators through LIGHT.

Data verification

Upon receipt of digitised survey data, Degge Group staff compiled lists of all outcomes identified from the interview database, and returned those lists to LIGHT for review, confirmation and/or correction by the local health clinics. Three Vietnamese cancer pathologists independently adjudicated reported outcomes through examination of hospital records, although missing records allowed only a small number of events to be verified in this way.

Following completion of all data collection and verification, a separate academic epidemiologist conducted a detailed examination of the data to identify any patterns of missing and/or biased data[4]. The data were examined according to various patient demographic and health characteristics, and also by procedure cohorts, provinces and interviewers. Equitable completeness of survey responses across the examined groupings confirmed the quality of interviewer training and data entry.

Table 1. Baseline characteristics included in logistic regression model for calculation of propensity score.

	Included in:	
Variable	Preliminary model	Reduced model
Procedure date	✓	✓
Date of birth	✓	✓
Height	✓	✓
Weight	✓	✓
Occupation	✓	✓
Age at first period	✓	✓
Age at first pregnancy	✓	✓
Age at first live birth	✓	✓
Total pregnancies	✓	✓
Total live births	✓	✓
Breast fed	✓	✓
Years of breast feeding	✓	✓
Exposure to pesticides	✓	✓
Exposure to asbestos	✓	✓
Exposure to silica	✓	✓
Exposure to exhaust	✓	✓
Years of education	✓	–
Age at first intercourse	✓	–
Exposure to X-rays	✓	–
Exposure to minerals	✓	–

Statistical Analysis

Separate analyses were conducted for hysterectomy and ectopic pregnancy outcomes. Follow-up time was measured from the IP date to the earliest of the outcome of interest (i.e., hysterectomy or ectopic pregnancy), death or interview date.

Hysterectomy and ectopic pregnancy incidence rates for the contraceptive cohorts were calculated as:

$$[\text{number of outcomes in cohort}/\text{total women years of follow-up time in the cohort}] * 100{,}000.$$

Cox proportional hazards regression (CPH) analyses were conducted to compare risks of hysterectomy and ectopic pregnancy over time between the QS and IUD/TL cohorts. A propensity score (PS) [28,29], designed to account for differences in potentially confounding baseline characteristics of women enrolled in the QS vs. IUD/TL cohorts, was included as a covariate in adjusted versions of the CPH models. (See Table 1 for the list of variables included in the preliminary and reduced PS models).

Results

Respondents

A total of 11,107 women who had undergone the QS procedure, and 16,268 women who had IUD insertions or TL were identified. Between December 2007 and January 2009, a total of 21,040 interviews were completed, for an overall response rate of 95%. Interviews were conducted for 10,503 QS subjects (94.6% response rate) and a combined 10,537 IUD/TL subjects (95.3% response rate) (Figure 1). Most of the identified women were available for in-person interviews ($N = 20{,}588$; 93% of all women with whom interviews were attempted). A small proportion of interviews (2% overall) were conducted with family or well acquainted clinic staff members. Those surrogate interviewees were typically enlisted when a subject was unavailable due to death or relocation.

Data from 21,037 of the 21,040 interviews conducted were analysed. One IUD case was omitted from the analysis because the respondent reported a cancer event that occurred earlier than their IUD insertion. Two TL cases reported hysterectomy dates that preceded their TL surgeries. Those interviews were also dropped, as the date ambiguity could not be clarified.

Similarities between women in the QS vs. comparator cohorts with regard to age and follow-up time reflect the efficiency of the system used to match subjects (Table 2).

While QS subjects were slightly older than IUD comparators at the time of their procedure, the average difference was less than two months. QS women were younger than the TL comparators by less than four months, on average ($p < .01$). At the time of the survey, the QS group was slightly older (by less than three months, on average) than both comparator groups ($p < .01$ and $p < .05$ for comparisons to the IUD and TL cohorts, respectively). The average length of total follow-up ranged from 16.04 years in the TL cohort (median 16.08 years), to 16.33 years in the QS cohort (median 16.38 years) and 16.62 years in the IUD cohort (median 16.42 years). Roughly half the subjects in the QS and IUD groups lived in Nam Dinh, while a similar proportion of the TL women were in Ha Nam. At least 95% of women in each procedure group were married. The QS and TL groups had similar levels of completed education (6.7 and 6.6 years on average, respectively), while IUD cohort members' education slightly exceeded that of the QS cohort with an average of 6.8 years ($p < .01$).

Women in the QS cohort reported more lifetime pregnancies, on average, than women in the IUD and TL cohorts (4.5 vs. 3.8 and 4.0, respectively, $p < .01$ for each comparison). The proportions of the QS cohort reporting ectopic pregnancies (0.5%), abortions (36.7%), and stillbirths (1%) in their lifetimes (i.e., either before or after the procedure that qualified them for their study cohort membership) exceeded the corresponding proportions in the IUD cohort (0.2, 25.6 and 0.6%, respectively, $p < .01$ for each comparison). The proportion of QS women reporting at least one miscarriage in their lifetime was significantly higher than in the IUD or TL cohorts (12.1% vs. 10% and 9.6%, respectively, $p < .01$ for both comparisons).

Two-thirds of women in the QS cohort (66%) reported use of other contraceptive methods in their lifetime, compared to 58% of the TL cohort ($p < .01$) and 20% of the IUD

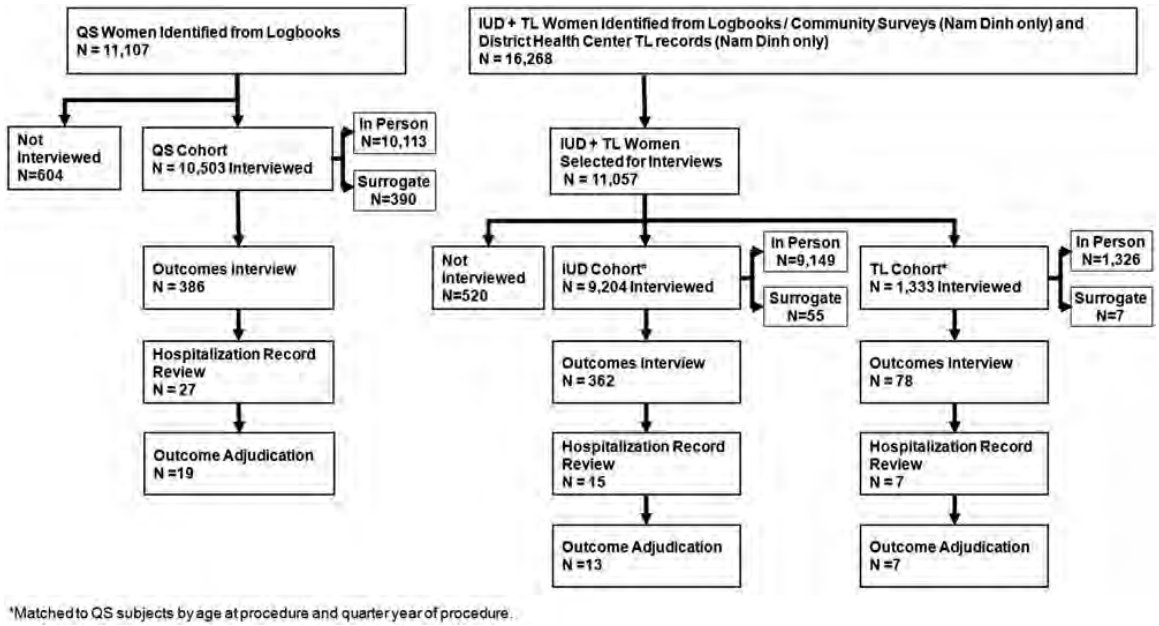


Figure 1. Subject selection and interviews.

Table 2. Subject characteristics.

Characteristics	Cohort					
	QS		IUD		TL	
	N	%	N	%	N	%
Total women	10,503	100.00	9203	100.00	1331	100.00
Age at procedure						
Mean ± SD	34.71 ± 4.25		34.61 ± 4.32		35.03 ± 3.95	
(range)	(14–50)		(19–51)		(17–47)**	
Age at interview						
Mean ± SD	51.08 ± 4.32		50.89 ± 4.38**		50.84 ± 3.97*	
(range)	(30–66)		(35–68)		(33–64)	
Follow-up time						
Mean ± SD	16.33 ± 1.27		16.62 ± 1.02		16.04 ± 1.20	
Median	16.38		16.42		16.08	
(range)	(0–19.5)		(0.8–19.6)		(2.8–19.3)	
Marriage status						
Single	12	0.11	9	0.10	2	0.15
Married	9976	94.98	8967	97.44	1267	95.19
Divorced	16	0.15	10	0.11	2	0.15
Separated	12	0.11	1	0.01	0	0.00
Widowed	381	3.63	173	1.88	55	4.13
Missing	106	1.01	43	0.46	5	0.38
Years of education						
Mean ± SD	6.66 ± 1.78		6.84 ± 1.88**		6.63 ± 1.61	
<6 years	2329	22.17	1877	20.4	253	19.01
≥6 years	7996	76.13	7248	78.75	1064	79.94
Missing	178	1.69	79	0.86	14	1.05
Province of residence***						
Ha Nam	2017	19.20	1309	14.22	733	55.07
Nam Dinh	4979	47.41	4926	53.53	48	3.61
Ninh Binh	1586	15.10	1447	15.72	126	9.47
Thai Binh	1921	18.29	1521	16.53	424	31.86

*Significantly different from QS cohort for $p < .05$.
**Significantly different from QS cohort for $p < .01$.
***Distributions of IUD and TL cohorts are significantly different from QS cohort for $p < .01$.

cohort ($p < .01$) (Table 3). In the specific context of contraceptive use, 499 (2.4%) of all women reported ever using birth control pills. Those 499 women reported an average of 2.4 years' total use. Combined with additional information from a general health question asking whether women had ever used any hormones in their lifetime, birth control pills or other reproductive hormones that might have been prescribed to treat gynaecological maladies were mentioned by 554 women (2.6%). While still quite low in absolute terms, proportionally fewer women in the QS group reported the use of these hormones compared to the IUD cohort (1.3% vs. 4.4%, $p < .01$). A similarly low proportion of the TL cohort reported use of birth control pills or other reproductive hormones (1.4%).

Hysterectomy results

Hysterectomy incidence

A total of 314 hysterectomies were reported during the post-IP time period, representing 1.5% of all study participants. Table 4 shows the distribution of the 314 hysterectomies among women in the QS, IUD and TL cohorts. For the entire study group, hysterectomies occurred at a rate of 91 per 100,000 women years of follow-up time. The rate in the QS group was higher than that of the IUD comparator group and lower than the TL rate (97.6 vs. 75.2 and 151.3, respectively, per 100,000 women years of follow-up time; $p < .05$ for both comparisons). The median interval between IP and hysterectomy was 12 years overall, and was not markedly different between cohorts.

Retrospective calculations indicate that the reported number of hysterectomies provide 80% power to detect a hazard ratio of 1.4 in this study population.

Hysterectomy survival analysis

The unadjusted CPH analyses found a significant excess risk of hysterectomy associated with QS, compared to IUD users, during the follow-up period (HR = 1.4; 95% CI = 1.1–1.7, $p = .01$) although there was no significant difference in risk after adjusting for baseline differences by inclusion of the PS (Table 4). Compared to the TL group, on the other hand, the QS cohort had a significantly lower risk of hysterectomy through the follow-up period for both the unadjusted (HR = 0.6; 95% CI = 0.4–0.9, $p = .02$) and PS adjusted models (HR = 0.6; 95% CI = 0.4–0.8, $p < .01$).

Table 3. Reproductive history.

Characteristics	Cohort					
	QS		IUD		TL	
	N	%	*N*	%	*N*	%
Total women	10,503	100.00	9203	100.00	1331	100.00
Lifetime pregnancies						
Mean ± SD	4.50 ± 1.55		3.77 ± 1.31***		4.04 ± 1.54***	
Number of pregnancies						
1	13	0.12	57	0.62***	12	0.90***
2	398	3.79	1234	13.41	135	10.14
3	2465	23.47	2995	32.54	387	29.08
4 or more	7561	72.18	4899	53.23	795	59.73
Missing	46	0.44	18	0.20	2	0.15
Parity						
Mean ± SD	3.71 ± 1.12		3.30 ± 1.10***		3.32 ± 1.01***	
Number of live births						
1	16	0.15	83	0.90***	16	1.20***
2	933	8.88	2066	22.45	236	17.73
3	4177	39.77	3694	40.14	581	43.65
4 or more	5371	51.14	3359	36.50	498	37.42
Missing	6	0.06	1	0.01	0	0.00
Women reporting at least one instance of each event in their lifetime						
Ectopic pregnancy	50	0.48	21	0.23***	6	0.30
Abortion	3849	36.65	2351	25.55***	452	33.96
Stillbirth	107	1.02	57	0.62***	11	0.83
Miscarriage	1270	12.09	919	9.99***	128	9.62***
Used contraceptives other than their index procedure in their lifetime						
Number of women	6845	65.5	1848	20.2***	764	57.5***
Used birth control pills in their lifetime*						
Number of women	106	1.01	377	4.10***	16	1.20
Number of years used (Mean ± SD)	2.43 ± 2.90		2.41 ± 2.12		2.44 ± 2.16	
Used birth control pills or other reproductive hormones in their lifetime**						
Number of women	134	1.28	402	4.37***	18	1.35
Menopausal status at time of interview						
Pre- and peri-menopausal	4387	41.77	4149	45.08***	577	43.29
Post-menopausal	5978	56.92	5004	54.37	746	56.05
Missing	138	1.31	50	0.54	8	0.60

*Based on specific question regarding number of years woman used birth control pills in her lifetime, in the context of ob/gyn history.
**Based on responses to specific question regarding number of years woman used birth control pills in her lifetime in the context of ob/gyn history, and question regarding whether woman ever used hormones in her lifetime in the context of general medical history.
***Mean or distribution is significantly different from QS cohort for $p < .01$.

Table 4. Hysterectomies reported, incidence rates and hazard ratios.

Characteristics	Cohort									
	All women		QS		IUD		TL		IUD + TL	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
All women	21,037	100.00	10,503	100.00	9203	100.00	1331	100.00	10,534	100.00
Women years of follow-up	344,870		172,214		151,501		21,155		172,656	
Hysterectomies	314	1.5	168	1.6	114	1.2*	32	2.4*	146	1.4
Rate/100,000 women years of follow-up (95% CI)	91.05 (81.52–101.70)		97.55 (83.86–113.48)		75.25* (62.63–90.41)		151.26* (106.97–213.90)		84.56 (71.90–99.45)	
Median years to diagnosis	12.0		11.5		13.0		10.2		12.0	
HR QS vs. comparator cohorts (95% CI, *p* value)										
Unadjusted					1.4 (1.1–1.7, 0.01)		0.6 (0.4–0.9, 0.02)		1.2 (1.0–1.5, 0.12)	
PS adjusted					1.0 (0.8–1.4, 0.9)		0.6 (0.4–0.8, <0.01)		0.9 (0.7–1.2, 0.36)	

*Significantly different from QS for $p < .05$.

Reasons for hysterectomy

Interviewers probed to determine the underlying reasons for hysterectomies among women reporting this outcome. Uterine fibroids were cited as the reason for their hysterectomy by the vast majority of the 314 women who had this surgery (90%) (Table 5). Ovarian cysts were reported by a total of 13 women (4%) and several other reasons were each reported by no more than four women.

Characteristics of women with and without hysterectomies

Table 6 compares gynaecologic histories of women in this study who did/did not report hysterectomies during the post-procedure time period. Women in the two groups were similar with regard to age at procedure, age at birth of first child and numbers of live births. However, the distribution of lifetime pregnancies varied between the two groups ($p < .01$). Among women with hysterectomies the proportion reporting five or more pregnancies was 12 percentage points higher than those who did not have the surgery (45.6% vs. 33.1%). Women reporting hysterectomies were also more likely to have had at least one abortion in their lifetime (46.2% vs. 31.4%, $p < .01$), and more likely to have used a contraceptive other than the one qualifying them for inclusion in the study (57.3% vs. 44.8%, $p < .01$).

Ectopic pregnancy results

Ectopic pregnancy incidence

A total of 75 ectopic pregnancies (22/100,000 women years of follow-up) after their IP were reported by women surveyed in this study (Table 7). The QS cohort accounted for two-thirds (66.7%) of the reported ectopic pregnancies, with an incidence rate of 29/100,000 women years of follow-up. That rate was significantly higher than the corresponding rate in the IUD comparator group (13.8/100,000 women years of follow-up; $p < .05$). The median time between procedure and ectopic pregnancy, among women who experienced these events, was 4 years overall (4.5, 4.0 and 1.4 years for the QS, IUD and TL cohorts, respectively).

Retrospective calculations indicate that the reported number of ectopic pregnancies provide 80% power to detect a hazard ratio of 1.9.

Ectopic pregnancy survival analysis

Unadjusted CPH analysis found the risk of an ectopic pregnancy over the follow-up period among women treated with QS to be roughly double that of the women choosing IUDs for long-term contraception (HR = 2.1, 95% CI = 1.3–3.5, $p < .01$). However, introduction of the PS as a covariate in the CPH model to control for differences in women's baseline characteristics yielded an adjusted HR of 1.4 (95% CI = 0.7–2.4, $p = .3$). No significant excess risk of ectopic pregnancy was associated with QS when compared to women who had undergone TL.

Characteristics of women with and without ectopic pregnancies

Average numbers of pregnancies were similar between women with and without ectopic pregnancies (4.9 in each group), although the distribution of number of pregnancies varied between the groups ($p < .01$). Particularly notable is the higher proportion of those experiencing ectopic pregnancies who reported five or more pregnancies (54.0% vs. 33.3% of women with no ectopic pregnancy) (Table 8).

In contrast to its higher proportion of women with five or more pregnancies, average parity in the ectopic pregnancy group was slightly lower than that of women without ectopic pregnancies (3.2 vs. 3.5, $p < .01$). The distribution of live births also differed between the two groups ($p < .01$). While barely one fourth (24.4%) of women experiencing ectopic pregnancies had four or more live births, the corresponding proportion among women with no ectopic pregnancies was 43.9%.

The proportion of women reporting ectopic pregnancies who used contraceptives other than their qualifying procedure was one third higher than in the group with no reported ectopic pregnancy (60.0% vs. 44.9%, $p < .01$). Lifetime use of birth control pills was reported by four (5.3%) of the 75 women reporting ectopic pregnancies and 550 (2.6%) of all others.

More than three-fourths (77.2%) of all QS recipients in this study had two or more insertions. While the distribution of QS users with no ectopic pregnancy who received one vs. two or more insertions mirrored the distribution in the overall QS cohort, the sub-group of QS users reporting ectopic pregnancies were more likely to have received only one insertion (36% vs. 22.8%, $p < .05$) (Table 9).

Table 5. Reasons reported for hysterectomy by procedure.

	Procedure name							
	All women		QS		IUD		TL	
	N	%*	*N*	%*	*N*	%*	*N*	%*
Reason for hysterectomy								
All hysterectomies	314		168		114		32	
Uterine fibroid	282	89.8	150	89.3	103	90.4	29	90.6
Ovarian cyst	13	4.1	7	4.2	5	4.4	1	3.1
Uterine polyp	4	1.3	2	1.2	1	0.9	1	3.1
Cervical polyp	3	1.0	3	1.8	0	0.0	0	0.0
Endometrial inflammation	3	1.0	3	1.8	0	0.0	0	0.0
Menorrhagia	3	1.0	1	0.6	2	1.8	0	0.0
Uterine cancer	3	1.0	2	1.2	1	0.9	0	0.0
Hydatidiform mole	1	0.3	0	0.0	1	0.9	0	0.0
Ovarian cancer	1	0.3	1	0.6	0	0.0	0	0.0
Polio	1	0.3	0	0.0	1	0.9	0	0.0
Stillbirth	1	0.3	1	0.6	0	0.0	0	0.0
Vaginal bleeding	1	0.3	1	0.6	0	0.0	0	0.0
Missing	1	0.3	1	0.6	0	0.0	0	0.0

*Column adds to more than 100% because some women reported more than one reason for hysterectomy.

Discussion

Findings and interpretations

Controlling for differences in baseline characteristics of women choosing to use QS vs. IUD or TL for long-term contraception, analysis of an average 16 years of follow-up data from this large population of rural Vietnamese women found no excess risk of hysterectomy among the QS cohort compared to the IUD or TL users. Neither was there any significant difference between cohorts with regard to risk of ectopic pregnancy throughout the average 16 years of follow-up, after controlling for variations in personal baseline characteristics.

Elevated likelihood of hysterectomy has been previously linked to intense bleeding, uterine fibroids, high parity, and history of TL, among other factors [30,31].

Higher rates of ectopic pregnancy have been associated with low socioeconomic status, older age, prior spontaneous or medically induced abortion, previous ectopic pregnancy, history of long-term contraceptive use (including IUD use prior to or at the time of conception), and TL. Despite the number of factors found to be associated with ectopic pregnancy, an estimated 50% of these rare events occur in women with none of the established risk factors [32–35].

Roughly 1.5% of the women interviewed in this study reported hysterectomies during the average 16 years following their qualifying contraceptive procedure (314 hysterectomies among 21,037 women). Proportions reported in the QS and IUD cohorts (1.6 and 1.2%, respectively) are similar to those reported by Sokal et al., in their 10-year follow-up with a smaller subset of women who participated in the Vietnamese clinical trial (weighted proportions of 1.2 and 0.8%, respectively) [8]. Consistent with other research, the hysterectomy incidence rate was highest among women who had undergone TL (151/100,000 women years of follow-up) [36,37]. Women in this study reported typical reasons for their hysterectomies (e.g., uterine fibroids, uterine/cervical polyps and menorrhagia),

Table 6. Characteristics of women according to hysterectomy status.

	Women reporting hysterectomy		Women not reporting hysterectomy	
Characteristics	*N*	%	*N*	%
All women	314	100%	20,723	100%
Age at procedure*	34.8	4.0	34.7	4.3
<20	0	0.0	4	0.0
20–24	2	0.6	170	0.8
25–29	38	12.1	2963	14.3
30–35	118	37.6	7551	36.4
35–40	127	40.4	7613	36.7
40+	29	9.2	2422	11.7
Age at first birth*	22.8	2.8	23.0	24.6
<15	0	0.0	1	0.0
15–19	26	8.3	2273	11.0
20–24	209	66.6	14488	70.1
25–29	72	22.9	3506	17.0
30+	7	2.2	394	1.9
Total pregnancies*	4.6	1.7	4.9	27.7
Number of pregnancies**				
1	1	0.3	81	0.4
2	21	6.7	1746	8.5
3	71	22.6	5776	28.0
4	78	24.8	6212	30.1
5	69	22.0	3685	17.8
6+	74	23.6	3157	15.3
Total live births*	3.5	1.1	3.5	1.1
Number of live births				
1	1	0.3	114	0.6
2	49	15.6	3186	15.4
3	133	42.4	8319	40.2
4	88	28.0	5798	28.0
5	29	9.2	2236	10.8
6+	14	4.5	1063	5.1
Abortion in lifetime	145	46.2	6507	31.4***
Menorrhagia after index procedure	56	17.8	1774	8.6
Used other contraceptives in lifetime	180	57.3	9277	44.8***
Used birth control pills in lifetime	14	4.5	540	2.6
Mean years birth control pills*	1.7	0.8	2.4	2.3

*For this row the value in *N* columns represents mean value, and value in % column represents standard deviation. Only cases with non-missing values for the variable are included in calculation of means.
**Distributions differ significantly between women reporting hysterectomy and not reporting hysterectomy ($p < .01$).
***Significantly different from group reporting hysterectomy for $p < .01$.

Table 7. Ectopic pregnancies reported, incidence rates and hazard ratios.

	Cohort									
Characteristics	All women		QS		IUD		TL		IUD + TL	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
All women	21,037	100.00	10 503	100.00	9203	100.00	1331	100.00	10,534	100.00
Women years of follow-up	345,785		172,593		151,885		21,307		173,192	
Ectopic pregnancies	75	0.4	50	0.5	21	0.2**	4	0.3	25	0.2
Rate/100,000 women years of follow-up (95% CI)	21.7 (17.3–27.2)		29.0 (22.0–38.2)		13.8* (9.0– 21.2)		18.8 (7.0–50.0)		14.4 (9.8–21.4)	
Median years to diagnosis	4.0		4.5		5.0		1.4		4.0	
HR QS vs. comparator cohorts (95% CI, *p* value)										
Unadjusted					2.1 (1.3–3.5, <0.01)		1.6 (0.6–4.4, 0.4)		2.0 (1.2–3.2, <0.01)	
PS adjusted					1.4 (0.7–2.4, 0.3)		1.4 (0.5–3.9, 0.5)		1.4 (0.8–2.4, 0.2)	

*Significantly different from QS for $p < .05$.
**Significantly different from QS for $p < .01$.

and also exhibited personal/health characteristics known to be associated with hysterectomies (e.g., high parity and history of TL) [30,31]. While uterine fibroids were identified as the reason for hysterectomy in the vast majority (roughly 90%) of responses to the specific question on this topic, it is also noted that roughly 18% of women who had hysterectomies reported experiencing menorrhagia after their IP. Although menorrhagia is also a common reason for hysterectomy, it might have been considered a symptom of one or more of the conditions more frequently cited in response to the question, and therefore less frequently reported as the specific reason for hysterectomy.

Ectopic pregnancies were reported by 0.4% of all women surveyed, and the incidence rate was 21.7/100,000 women years of follow-up. While slightly lower in absolute terms, the relative proportions in the QS and IUD cohorts (0.5 and 0.2%) are similar to those reported in Sokal et al.'s 10-year follow-up of QS in Vietnam [10]. The ectopic pregnancy rate among QS users (29/100,000 women years of follow-up) was similar to the finding in Hieu and Luong's report on ectopic pregnancies among Vietnamese QS users, although the rates in the IUD and TL cohorts were lower than in that earlier study [9].

The more balanced risk of ectopic pregnancy between QS and IUD users in this study, after controlling for

Table 8. Characteristics of women according to ectopic pregnancy status.

	Women reporting ectopic pregnancy		Women not reporting ectopic pregnancy	
Characteristics	*N*	%	*N*	%
All women	75	100%	20,962	100%
Age at procedure*	32.9	3.5	34.7	4.3***
<20	0	0	4	0.0
20–24	0	0	172	0.8
25–29	15	20.0	2986	14.2
30–35	40	53.3	7629	36.4
35–40	19	25.3	7721	36.8
40+	1	1.3	2450	11.7
Age at first birth*	22.1	2.1	23.0	24.5
<15	0	0.0	1	0.0
15–19	9	12.2	2290	11.0
20–24	53	71.6	14644	70.1
25–29	12	16.2	3566	17.1
30+	0	0.0	401	1.9
Total pregnancies*	4.9	1.3	4.9	27.5
Number of pregnancies**				
1	1	0.0	82	0.4
2	0	0.0	1767	8.5
3	6	8.1	5841	28.0
4	28	37.8	6262	30.0
5	18	24.3	3736	17.9
6+	22	29.7	3209	15.4
Total live births*	3.2	0.8	3.5	1.1***
Number of live births**				
1	0	0.0	115	0.5
2	12	16.2	3223	15.4
3	44	59.5	8408	40.1
4	12	16.2	5874	28.0
5	5	6.8	2260	10.8
6+	1	1.4	1076	5.1
Abortion in lifetime	25	33.3	6627	31.6
Menorrhagia in lifetime	10	13.3	1820	8.7
Used other contraceptives in lifetime	45	60.0	9412	44.9***
Used birth control pills in lifetime	4	5.3	550	2.6
Mean years birth control pills*	2.0	–	2.4	2.3

*For this row the value in *N* columns represents mean value, and value in % column represents standard deviation. Only cases with non-missing values for the variable are included in calculation of means.
**Distributions differ significantly between women reporting hysterectomy and not reporting hysterectomy ($p < .01$).
***Significantly different from group reporting ectopic pregnancy for $p < .01$.

Table 9. Ectopic pregnancy status according to number of QS insertions.

	All women in QS cohort		Women reporting ectopic pregnancy		Women not reporting ectopic pregnancy*	
Number of insertions	*N*	%	*N*	%	*N*	%
Total	10,503	100.0	50	100.0	10,453	100.0
1	2397	22.8	18	36.0	2379	22.8
2+	8106	77.2	31	62.0	7909	75.7

*Distribution differs significantly from group reporting ectopic pregnancies ($p < .05$).

differences in women's baseline characteristics in the CPH model, suggests that QS users' higher risk of ectopic pregnancy identified in the unadjusted model was likely due to factors other than the selected contraceptive method. Some previously identified risk factors for ectopic pregnancy are also seen among women in this study. As previously described, a significantly higher proportion of the QS cohort had used other contraceptive methods in their lifetimes, compared to the IUD or TL cohorts. They also had more pregnancies, births and abortions than women in the comparator cohorts. The collected data do not identify whether previous contraceptive methods included IUD use, although given their high prevalence in Vietnam during the time of the study cohorts' IPs [38] it is likely that some portion of women in the QS group had attempted to use an IUD at some point prior to their QS procedure. These findings suggest that other available contraceptive methods had failed those women. Those circumstances might have contributed to their higher reported lifetime ectopic pregnancy rates, while also motivating them to choose QS. Further, it has been suggested that while successful use of contraceptives is effective for prevention of intrauterine as well as ectopic pregnancies, pregnancies resulting from contraceptive failure could be more likely to be ectopic [33]. Relatedly, Hieu et al. reported a substantially increased probability of contraceptive failure with only one QS insertion, which suggests that strict adherence to the protocol of two QS insertions would be expected to reduce the incidence of ectopic pregnancies among QS users [7]. Consistent with Hieu et al.'s reporting, the disproportionately high number of QS users with ectopic pregnancies who reported only one QS insertion could provide another likely reason for the excess risk of ectopic pregnancy in the group.

Strengths and weaknesses of the study

Study strengths

Data for this study are from the largest interview-based epidemiological study of QS-treated women in the world, to

date. All women exposed to QS in four northern Vietnamese provinces ($N = 11,107$) were identified from health clinic records. Women from the same clinic areas who received IUD insertions or TL, during the same time periods and at similar ages, were comparators. A total of 21,037 completed interviews eligible for analysis, with a mean respondent follow-up in excess of 16 years, provided adequate data from which to observe the outcomes of interest. The 10,503 interviews of women (or, in a few cases, their surrogates) treated with QS represented roughly one-fifth of all those who participated in Vietnam's clinical trial of QS.

Interviewers drawn from local health clinic staffs were valuable assets of the study. Initially, their familiarity with the community health system was instrumental in achieving the survey's 95% response rate. Subsequently, although only a small number of events could be verified via hospital records, the Vietnam staff's ability to verify potential outcomes of interest and clarify anomalies identified in the digitised interview data instilled a high level of confidence in the study findings.

Exhaustive sensitivity analyses detected no biases resulting from disparate locations and interviewers nor from an unexpected deviation from the prescribed matching procedure in one province.

Study weaknesses

Identification of potential IUD subjects in Nam Dinh via community survey, rather than from logbooks as was done in the other provinces, may have resulted in omission of some women from that comparator pool who were ill or dead at the time of the study. Because roughly half the interviewed women came from Nam Dinh, and the alternate identification method occurred only in the IUD group, this sampling bias may have underestimated the number of hysterectomies and ectopic pregnancies in the IUD cohort. A bias towards comparators who were alive, healthy, and/or otherwise readily available for interview was also introduced by allowing interviewers to select which subject to interview, from each pair of potential IUD comparators in Nam Dinh. Lacking data about women not interviewed from the IUD pool precluded analysing the exact consequences of this selection system, although the expectation would be an interviewed group of IUD women who were healthier than the QS group. While acknowledged as a limitation, this bias would only tend to overestimate the relative long-term risks of hysterectomy and ectopic pregnancy in the QS cohort. Since adjusted results found no significant excess risk in the QS group, for either outcome, it can be concluded that any bias introduced by the subject selection method in Nam Dinh is not relevant to the conclusions of this analysis.

Another study limitation was a lack of hospital records for outcomes adjudication. While the study protocol called for hospital verification of all outcomes, shortage of space in Vietnamese hospitals translated into missing records for most events. Nonetheless, 49 outcomes were adjudicated from hospital records, including 27 of the reported hysterectomies and one ectopic pregnancy. Among outcomes that could be checked in this way, discrepant event dates were the most common inconsistencies identified between interview and hospital data. While suggestive of potential recall bias, sensitivity analysis indicated that the distribution of mismatched dates did not favour one cohort or the other. Furthermore, notwithstanding some incorrectly recalled dates, the reported events were confirmed to have occurred at some point during the follow-up period. In addition, findings were further substantiated by review of all interview outcomes and verification by local clinics.

With regard to the IUD cohort, and consistent with the cohort's average age of 51 years at the time of their interviews, more than half the group reported being post-menopausal and therefore unlikely to be still using any method of birth control.

Differences in results and conclusions

This study's findings are fairly consistent with previous reports of hysterectomies and ectopic pregnancies among women choosing QS, IUD or TL for long-term contraception. The large number of women surveyed allows for assignment of statistical significance to the results.

Relevance of the findings: implications for clinicians and policymakers

Controlling for baseline differences in characteristics of women choosing the three different forms of long-term contraception, no excess risk of hysterectomy or ectopic pregnancy was found in women selecting QS vs. IUD or TL in a large cohort of rural Vietnamese women during an average 16-year follow-up period. These findings complement previous findings of no excess risk of reproductive cancer associated with QS in this study population [6] and further assuage speculation regarding health risks associated with the use of QS for permanent contraception.

Unanswered questions and future research

Clinical trials of QS, with carefully designed patient follow-up, will provide more specific details regarding the relationship between QS and women's reproductive health. Optimally, further understanding of the risks and benefit of these contraceptive procedures would be enhanced by a detailed longitudinal history and analysis of events preceding and following the particular contraceptive's use in individual women. It is possible that more detailed information on the sequence of different types of events and/or contraceptive use could provide more insight regarding the findings in this very large cohort study.

Conclusions

After accounting for differences in personal baseline characteristics, this large retrospective cohort study found no significant excess long-term risk of either hysterectomy or ectopic pregnancy among women exposed to QS, when compared to matched cohorts of IUD and TL users. Identification and interview of more than 21,000 QS, IUD and TL users with an average follow-up exceeding 16 years, coupled with local clinic staffs' personal knowledge of survey participants, allowed adequate time for development of procedure-related outcomes and the ability to verify survey responses. The findings reported herein provide further support for use of QS as a safe method of non-surgical permanent contraception.

Notes

1. Women surveyed for this study were part of a large field trial that included more than 1300 clinicians in 24 provinces and resulted in approximately 55,000 QS cases. Most of the 11,105 QS procedures (97.5%) performed in the four provinces included in this study had been completed by the end of 1992, and another 4% (449 cases) in 1993. Although the Vietnamese government halted the trial at the end of 1993 and recalled the small quantities of quinacrine pellets that had not been administered to women, clinic records identified 33 additional procedures performed in these provinces between 1994 and 1996. Based on discussions with the study sponsors, who have extensive history with the reproductive health community in Vietnam, it appears that some physicians in the rural areas kept their remaining small supplies of QS pellets and used them to perform the additional procedures in 1994–1996.
2. International Services Assistance Fund (ISAF), 104 T.W. Alexander Drive, Bldg. 1, Research Triangle Park, NC 27709.
3. Physicians working at the provincial/district levels of Vietnam's reproductive health system were trained to conduct all interviews for the survey. Use of physicians as interviewers was intended to enhance women's comfort levels when discussing their health, and also to make certain that appropriate follow-up questions would be used to ensure that the women surveyed were properly citing cancer diagnoses. In addition, employing physicians trained consistently in interview procedures was also intended to minimise any possible effect on survey results from use of multiple interviewers.
4. This review entailed modelling multiple scenarios that would reveal different biases in all stages of data collection.

Disclosure statement

ISAF had sponsored previous reproductive research in Vietnam and other countries and had an impact on the selection of sites for this study. Originally ISAF hired a Contract Research Organization (CRO) to operationalise the study, and the authors were requested to design the study, design and carry out the analysis, and publish the report. Subsequent to the start of the study, ISAF took over the CRO functions. They also reviewed and provided comments on the study report and draft manuscript.

Funding

This work was supported by the non-profit International Services Assistance Fund (ISAF).

References

[1] Institute for Development Training. Female voluntary non-surgical sterilization: the quinacrine method. Module 12 of Training Course in Women's Health. Chapel Hill (NC): IDT; 1996.
[2] Growe RG, Luster MI, Fall PA, et al. Quinacrine-induced occlusive fibrosis in the human fallopian tube is due to a unique inflammatory response and modification of repair mechanisms. J Reprod Immunol. 2013;97:159–166.
[3] Oanh TTM, Tien TV, Luong DH, et al. Assessing provincial health systems in Vietnam: lessons from two provinces. Bethesda (MD): Abt Associates Inc.; 2009.
[4] Cancel AM, Dillberger JE, Kelly CM, et al. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol. 2010;56:156–165.
[5] Haseman JK, Growe RG, Zeiger E, et al. A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat cancer bioassay and its implications for human clinical use. Regul Toxicol Pharmacol. 2015;71:371–378.
[6] Jones JK, Tave A, Pezzullo JC, et al. Long-term risk of reproductive cancer among Vietnamese women using the quinacrine hydrochloride pellet system vs. intrauterine devices or tubal ligation for contraception. Eur J Contracept Reprod Health Care. 2017;22:123–130.
[7] Hieu DT, Tan TT, Tan DN, et al. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. Lancet. 1993;342:213–217.
[8] Sokal DC, Hieu DT, Weiner DH, et al. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. Fertil Steril. 2000;74:1092–1101.
[9] Hieu DT, Luong TT. The rate of ectopic pregnancy for 24,589 quinacrine sterilization (QS) users compared to users of other methods and no method in 4 provinces in Vietnam, 1994–1996. Int J Gynaecol Obstet. 2003;83(2):S35–S43.
[10] Sokal DC, Hieu DT, Loan ND, et al. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. Contraception. 2008;78:66–72.
[11] Feldblum PJ, Wheeless A, Trujillo V, et al. Pelvic surgery and hospitalization among Chilean women after nonsurgical sterilization with quinacrine pellets between 1977 and 1989. Contraception. 2012; 86:106–109.
[12] Anh DN, Tacoli C, Thanh HX, Migration in Vietnam, A review of information on current trends and patterns, and their policy implications. Paper presented at: Regional Conference on Migration, Development and Pro-Poor Policy Choices in Asia. 2003 June 22–24; Dhaka, Bangladesh. [cited 2017 July 26]; Available from: http://www.eldis.org/vfile/upload/1/document/0903/Dhaka_CP_7.pdf
[13] Westman J, Hampel H, Bradley T. Efficacy of a touchscreen computer based family cancer history questionnaire and subsequent cancer risk assessment. J Med Genet. 2000;37:354–360.
[14] Peipert JF, Gutmann J. Oral contraceptive risk assessment: a survey of 247 educated women. Obstet Gynecol. 1993; 82:112–117.
[15] Michels KB, Willett WC, Rosner BA, Manson JE, et al. Prospective assessment of breastfeeding and breast cancer incidence among 89,887 women. Obstet Gynecol Surv. 1996;51:468–469.
[16] Shlay JC, Dunn T, Byers T, et al. Prediction of cervical intraepithelial neoplasia grade 2–3 using risk assessment and human papillomavirus testing in women with atypia on papanicolaou smears. Obstet Gynecol Surv. 2001;56:87–88.
[17] Kindermann G, Maassen V, Kuhn W. Laparoscopic management of ovarian tumors subsequently diagnosed as malignant: a survey from 127 German departments of obstetrics and gynecology. Obstet Gynecol Surv. 1998;53:212–213.
[18] Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. Am J Prev Med. 2004; 27:239–245.
[19] Hughes KS, Roche C, Campbell CT, et al. Prevalence of family history of breast and ovarian cancer in a single primary care practice using a self-administered questionnaire. Breast J. 2003; 9:19–25.
[20] McWilliams RR, Rabe KG, Olswold C, et al. Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. Cancer. 2005;104:388–394.
[21] Hall IJ, Burke W, Coughlin S, et al. Population-based estimates of the prevalence of family history of cancer among women. Community Genet. 2001;4:134–142.
[22] Euhus DM, Leitch AM, Huth JF, et al. Limitations of the Gail model in the specialized breast cancer risk assessment clinic. Breast J. 2002;8:23–27.
[23] Lee JS, John EM, McGuire V, et al. Breast and ovarian cancer in relatives of cancer patients, with and without BRCA mutations. Cancer Epidemiol Biomarkers Prev. 2006;15:359–363.
[24] Rauscher GH, Sandler DP, Poole C, et al. Family history of cancer and incidence of acute leukemia in adults. Am J Epidemiol. 2002;156:517–526.
[25] Walter FM, Emery J. 'Coming down the line' – patients' understanding of their family history of common chronic disease. Ann Fam Med. 2005;3:405–414.
[26] Lamon JM. Cancer surveillance. Who stands to benefit? Postgrad Med. 1985;78:55–8, 63–70.
[27] Spangler E, Zeigler-Johnson CM, Malkowicz SB, et al. Association of prostate cancer family history with histopathological and clinical characteristics of prostate tumors. Int J Cancer. 2005;113:471–474.
[28] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.

[29] D'Agostino RB. Propensity score methods for bias reduction in the comparison of treatment to a non-randomized control group. Stat Med. 1998;17:2265–2281.
[30] Aziz S. Indication of emergency hysterectomy in Pakistani patients. J Soc Obstet Gynaecol Pakistan. 2017;7:45–49.
[31] Heinonen PK, Helin R, Nieminen K. Long-term impact and risk factors for hysterectomy after hysteroscopic surgery for menorrhagia. Gynecol Surg. 2006;3:265–269.
[32] Barnhart KT, Sammel MD, Gracia CR, et al. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril. 2006; 86:36–43.
[33] Li C, Zhao WH, Meng CX, et al. Contraceptive use and the risk of ectopic pregnancy: a multi-center case-control study. PLoS One. 2014;9:e115031.
[34] Tahmina S, Daniel M, Solomon P. Clinical analysis of ectopic pregnancies in a tertiary care centre in southern India: a six-year retrospective study. J Clin Diagn Res. 2016;10:QC13–QC16.
[35] Karaer A, Avsar FA, Batioglu S. Risk factors for ectopic pregnancy: a case-control study. Aust N Z J Obstet Gynaecol. 2006; 46:521–527.
[36] Templeton AA, Cole S. Hysterectomy following sterilization. Br J Obstet Gynaecol. 1982;89:845–848.
[37] Hillis SD, Marchbanks PA, Tylor LR, et al. Higher hysterectomy risk for sterilized than nonsterilized women: findings from the U.S. collaborative review of sterilization. The U.S. collaborative review of sterilization working group. Obstet Gynecol. 1998;91:241–246.
[38] Hieu DT, Van HT, Donaldson PJ, et al. The pattern of IUD use in Vietnam. Int Fam Plan Perspect. 1995;21:6–10.

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE, 2017
VOL. 22, NO. 2, 123–130
http://dx.doi.org/10.1080/13625187.2017.1285880

Taylor & Francis
Taylor & Francis Group

EPIDEMIOLOGICAL STUDY

OPEN ACCESS

Long-term risk of reproductive cancer among Vietnamese women using the quinacrine hydrochloride pellet system vs. intrauterine devices or tubal ligation for contraception

Judith K. Jones[a], Arlene Tave[a], John C. Pezzullo[b]†, Sharon Kardia[c] and Jack Lippes[d]

[a]The Degge Group, Ltd, Fairfax, VA, USA; [b]Department of Biomathematics and Biostatistics, Georgetown University, Washington, DC, USA; [c]Department of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, MI, USA; [d]Department of Obstetrics and Gynecology, State University of New York at Buffalo, Buffalo, NY, USA

ABSTRACT

Objectives: To determine the long-term risk of reproductive tract cancer in women using the quinacrine hydrochloride pellet system of permanent contraception (QS) relative to the comparable risk in women using Copper T intrauterine device (IUD) or tubal ligation surgery (TL) for long-term or permanent contraception.

Methods: This was a retrospective cohort study, conducted in the Northern Vietnamese provinces of Ha Nam, Nam Dinh, Ninh Binh and Thai Binh. Women who had their first QS procedure, last IUD insertion or TL between 1989 and 1996 were interviewed regarding post-procedure health outcomes, particularly reproductive tract cancers.

Results: A 95% response rate resulted in 21,040 completed interviews. Reproductive cancer incidence rates were very low (5.77/100,000 women years of follow-up time; 95%CI = 3.72–8.94). No significant excess hazard of reproductive tract cancer was associated with QS.

Conclusions: No significant excess long-term risk of reproductive tract cancer was found after an average 16 years of follow-up among a large group of women using QS vs. IUD/TL for contraception.

ARTICLE HISTORY
Received 26 September 2016
Revised 15 January 2017
Accepted 18 January 2017
Published online 8 February 2017

KEYWORDS
Quinacrine; retrospective cohort study; survival analysis; non-surgical permanent contraception; female

Introduction

The quinacrine hydrochloride pellet system of permanent contraception (QS) is a non-surgical procedure that can be performed outside of a hospital setting. The procedure follows a standardised protocol: transcervical application of seven 36 mg quinacrine pellets, administered in the proliferative phase of the menstrual cycle, using a device similar to a Copper-T intrauterine device (IUD) inserter. The currently recommended dosage regimen is two insertions applied one month apart. The quinacrine pellets dissolve and lead to sclerosis and subsequent occlusion of the fallopian tubes [1].

QS was first used among women in Chile in 1977 [2], and was introduced to Vietnam in 1989 via a governmental clinical trial involving an estimated 50,000 total participants [3]. Responding to a World Health Organization (WHO) expression of concern about potential human carcinogenicity associated with QS, the Vietnam trial was halted in 1993. Additional concerns were raised by a rat study [4] that was ultimately found to be flawed [5].

Previous studies found no increased risk of reproductive tract cancers among QS users, although none had sufficient statistical power to confirm their conclusions [6–10]. This manuscript reports on a retrospective cohort study of women in Vietnam who had undergone the QS procedure, and age-clinic-date-matched controls, undertaken to include enough subjects to measure any differences between groups in the long-term risk of reported reproductive cancer diagnoses.

Methods

Cohort identification

The maximum number of interviews, within the constraints of available funding, was conducted. Women were interviewed in the northern Vietnamese provinces of Ha Nam, Nam Dinh, Ninh Binh and Thai Binh who had their first QS procedure, last IUD insertion or tubal ligation surgery (TL) between 1989 and 1996[1]. QS subjects in each province were identified from procedure logbooks at commune level health clinics. All 784 health communes in the four provinces were included in the survey, although some had few women treated with QS. Dr Do Trong Hieu, former Director of Family Planning and Maternal and Child Health of the Ministry of Health of Vietnam, served as the Vietnam in-country study coordinator, and worked with The Institute for Development and Community Health (LIGHT) to conduct the study. Lists of comparators who had IUD insertions or TL were compiled from clinic logbooks and district health centre records in three provinces. In the fourth province (Nam Dinh), IUD and TL patient records had been destroyed in a flood. TL comparators in that province were identified from district health centre records, and IUD comparators were located via community survey. In Nam Dinh, two potential comparators were randomly selected from all potential matches for a given QS subject, and the assigned interviewer chose which one to contact. In all provinces, the goal was to match comparators to QS women by the clinic at which the procedure was done, quarter of the

CONTACT Arlene Tave atave@deggegroup.com The Degge Group, Ltd., 9302 Lee Highway, Suite 700, Fairfax, VA 22031, USA
†Deceased 2 June 2016.

calendar year in which their procedure was completed, and age at the time of their qualifying contraceptive procedure (±2 years). Matching by age at procedure took precedence over matching by the quarter of the year of the procedure. Women with cancer prior to their procedure were excluded from the study. At least one comparator match was identified for each QS woman. In cases where multiple matching comparators were found, one comparator was randomly selected from the group.

Data collection and verification

Data collection procedures were approved by a Vietnamese institutional review board prior to implementation. Each subject's first QS procedure, last IUD insertion or TL was identified as her index procedure (IP).

Demographic data and information about the IP were abstracted from health centre records for most women. For IUD comparators in Nam Dinh those data were collected as part of the community survey.

Health status interviews were conducted with survey participants (or proxies) by specially trained physicians[2] after obtaining informed consent. Women were asked about current and historical medical conditions, obstetric/gynaecologic history (including IP/post-IP details) and history of cancer in both the woman and her family. Interviewers probed for details about reported cancers. Interviews were attempted for all women identified as having undergone the QS procedure, for all matched comparators in the provinces of Ha Nam, Ninh Binh and Thai Binh, and for the selected comparators in Nam Dinh.

Degge Group staff compiled lists of all outcomes identified from the digitised interview database, and returned those lists to the local health clinics for review, confirmation and/or correction. Adjudication of reported outcomes through hospital records review was also attempted, but patient records were available for only a small proportion of events.

To ensure that data collection was equitable across subgroups of respondents, Degge contracted with Dr Sharon Kardia, Professor and Chair of the Department of Epidemiology at the University of Michigan, to conduct a sensitivity analysis of the data. Dr Kardia methodically examined the data from all four provinces for patterns of missing data by interview status, cancer diagnosis, age at procedure, years of follow-up time, interviewer and procedure. Findings of Dr Kardia's investigations indicated that completeness of survey responses was similar across the categories examined.

Statistical analysis

Due to very small numbers reported for individual reproductive tract cancers, uterus, cervix and ovarian cancers were combined for this analysis. Follow-up time was measured from the IP date to the earliest of reproductive cancer diagnosis, death or interview date.

Reproductive cancer incidence rates for the contraceptive cohorts were calculated as: [number of reproductive cancers in cohort/total women years of follow-up time in the cohort] × 100,000.

Cox proportional hazards regression (CPH) analyses were conducted to compare the risk of reproductive tract cancer over time between the QS and IUD/TL cohorts, and separately for QS vs. IUD only, in the years following the IP. A propensity score (PS) [11,12], designed to account for differences in potentially confounding baseline characteristics of women enrolled in the QS vs. IUD/TL cohorts, was included as a covariate in separate versions of the CPH models. (See Table 1 for the list of variables included in the preliminary and reduced propensity score models).

The relatively small number of TL cases (1331) precluded statistical analysis of those women as a separate group. Thus, we conducted two separate analyses. One compared QS vs. the combination of the IUD and TL groups, and the other compared QS vs. only the IUD group.

Kaplan–Meier curves were used to graphically depict survival time without a reproductive tract cancer diagnosis for women in each cohort.

Results

Respondents

A total of 11,107 women who had undergone the QS procedure, and 16,268 women who had IUD insertions or TL were identified. Between December 2007 and January 2009, a total of 21,040 women (or their surrogates) were interviewed, for an overall response rate of 95%. Interviews were conducted for 10,503 QS subjects (94.6% response rate) and a combined 10,537 IUD/TL subjects (95.3% response rate) (Figure 1). Most of the identified women were available for in-person interviews ($N = 20,588$; 93% of all women with whom interviews were attempted). Surrogate interviews (with family or well acquainted clinic staff members) were conducted for an additional 452 women (2% of all women with whom interviews were attempted).

Initial power calculations for the study, based on interviews with an anticipated 12,000–15,000 women, assigned power of roughly 95% to detect a twofold increase in risk for breast cancer among these Vietnamese women. Budgetary constraints limited the survey to women in only four provinces, resulting in fewer interviews than originally planned. *Post hoc* calculations, based on the number of

Table 1. Baseline characteristics included in logistic regression model for calculation of propensity score.

	Included in	
Variable	Preliminary model	Reduced model
Procedure date	✓	✓
Date of birth	✓	✓
Height	✓	✓
Weight	✓	✓
Occupation	✓	✓
Age at first period	✓	✓
Age at first pregnancy	✓	✓
Age at first live birth	✓	✓
Total pregnancies	✓	✓
Total live births	✓	✓
Breast fed	✓	✓
Years of breast feeding	✓	✓
Exposure to pesticides	✓	✓
Exposure to asbestos	✓	✓
Exposure to silica	✓	✓
Exposure to exhaust	✓	✓
Years of education	✓	
Age at first intercourse	✓	
Exposure to X-rays	✓	
Exposure to minerals	✓	

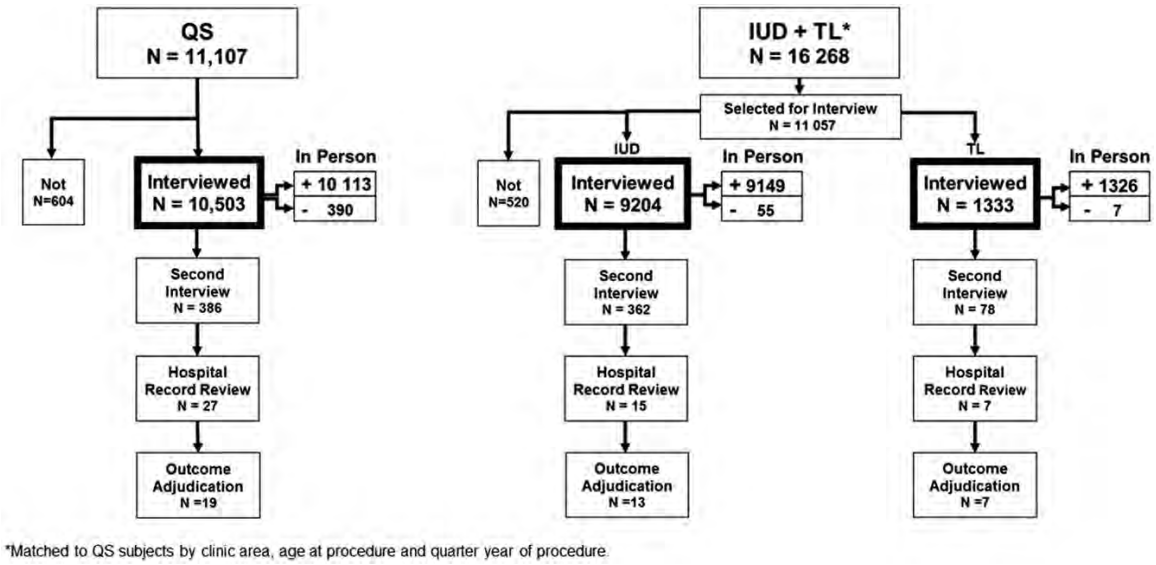


Figure 1. Subject selection and interviews.

interviews used in the analyses (10,503 QS exposed and 10,534 controls), determined a power of 76% to obtain $p < .05$ in a one-sided test if the true breast cancer HR is 2.0. This was considered to be a reasonable level of power for a study of this type.

Similarities of women in the QS cohort vs. the comparator groups with regard to age and follow-up time reflect the accuracy of the system used to match subjects (Table 2). QS subjects were slightly older than IUD comparators at the time of their procedure (by less than two months, on average), and slightly younger than TL comparators (by less than four months, on average). At the time of the survey, the QS group was slightly older (by less than three months, on average) than both comparator groups. The average length of follow-up ranged from 16.04 years in the TL cohort (median 16.08 years) to 16.62 years in the IUD cohort (median 16.42 years). Roughly half the subjects in the QS and IUD groups lived in Nam Dinh, while a similar proportion of the TL women were in Ha Nam. At least 95% of women in each procedure group were married.

QS women reported more lifetime pregnancies and births, on average, than the comparators. The QS group also had the highest proportions reporting at least one abortion, stillbirth or miscarriage in their lifetimes. While numbers were small in all cohorts, more than double the proportion of QS women and nearly three times the proportion of TL women reported an ectopic pregnancy, as compared to the IUD group.

Overall survival analysis

A total of 20 reproductive tract cancers were reported in the interviews. Four of the 20 reproductive tract cancer reports were confirmed by hospital records, and the remainder were double-checked and confirmed by physicians in the communal health clinics. Six of the reproductive tract cancers were reported in interviews directly with the study subject. The other 14 were reported in interviews with surrogates (nine health centre personnel and five family members) because the subjects were reported to have died. It should be noted that because of the complexity of the outcome of mortality, it was specifically not a focus of the study. Therefore, no effort was made to validate the reported deaths.

Table 3 shows the distribution, by cohort and region, of the 20 reproductive tract cancers (0.10% of all women; incidence rate = 5.77/100,000 women years of follow-up; 95%CI = 3.72–8.94). Overall, 12 reproductive tract cancers were reported in the QS cohort (0.11% of QS respondents; incidence rate 6.93/100,000 women years of follow-up; 95%CI = 3.94–12.20), eight in the IUD group (0.09% of IUD respondents; incidence rate 5.26/100,000 women years of follow-up; 95%CI = 2.63–10.52), and none in the TL cohort. Among all study participants reporting reproductive tract cancers, median time from IP to diagnosis was 12 years.

Uterine cancers accounted for 14 of the 20 total reproductive tract cancers (70%), and represented similar proportions within both the QS and IUD cohorts. There were three cervical cancers reported (one in the QS cohort; two in the IUD cohort). The remaining three cancers were ovarian, all of which were in the QS cohort.

Cox proportional hazards (CPH) analyses for all women surveyed show no significant association of QS with time to reproductive tract cancer in either the unadjusted (HR = 1.6; 95%CI = 0.6–3.8) or PS-adjusted model (HR = 2.0; 95%CI = 0.73–5.5) comparing QS to the combination of IUD and TL (Table 3). Nor was a significant association found for either unadjusted or PS-adjusted models comparing QS to only IUD respondents (unadjusted HR = 1.4; 95%CI = 0.6–3.4; PS-adjusted model (HR = 1.7; 95%CI = 0.6–4.9).

The Kaplan–Meier graph in Figure 2 charts survival time, from patients' index date to end of follow-up time, without a reproductive tract cancer diagnosis. As the total number of reproductive tract cancers in the QS and IUD groups is very small, the scale of the *Y* axis on the graph runs only between 99.86% and 100%. The graph shows the first losses to reproductive tract cancer post-IP period at years 5 and 7 for the QS and IUD cohorts, respectively, with gradual loss of members to reproductive cancers through year 15 and 17. In the TL group, no reproductive cancers were

Table 2. Subject characteristics.

	Cohort					
	QS		IUD		TL	
Characteristics	*N*	%	*N*	%	*N*	%
Total women	10,503	100.00	9203	100.00	1331	100.00
Age at procedure						
Mean ± SD (range)	34.71 ± 4.25 (14–50)		34.61 ± 4.32 (19–51)		35.03 ± 3.95 (17–47)	
Age at Interview						
Mean ± SD (Range)	51.08 ± 4.32 (30–66)		50.89 ± 4.38 (35–68)		50.84 ± 3.97 (33–64)	
Follow-up time						
Mean ± SD	16.33 ± 1.27		16.62 ± 1.02		16.04 ± 1.20	
Median (Range)	16.38 (0–19.5)		16.42 (0.8–19.6)		16.08 (2.8–19.3)	
Marriage status						
Single	12	0.11	9	0.10	2	0.15
Married	9976	94.98	8967	97.44	1267	95.19
Divorced	16	0.15	10	0.11	2	0.15
Separated	12	0.11	1	0.01	0	0.00
Widowed	381	3.63	173	1.88	55	4.13
Missing	106	1.01	43	0.46	5	0.38
Lifetime pregnancies						
Mean ± SD	4.50 ± 1.55		3.77 ± 1.31		4.04 ± 1.54	
1	13	0.12	57	0.62	12	0.90
2	398	3.79	1234	13.41	135	10.14
3	2465	23.47	2995	32.54	387	29.08
4 or more	7561	72.18	4899	53.23	795	59.73
Missing	46	0.44	18	0.20	2	0.15
Parity						
Mean ± SD	3.71 ± 1.12		3.30 ± 1.10		3.32 ± 1.01	
1	16	0.15	83	0.90	16	1.20
2	933	8.88	2066	22.45	236	17.73
3	4177	39.77	3694	40.14	581	43.65
4 or more	5371	51.14	3359	36.50	498	37.42
Missing	6	0.06	1	0.01	0	0.00
Women reporting at least one instance of each event in their lifetime						
Ectopic pregnancy	61	0.58	26	0.28	10	0.75
Abortion	3849	36.65	2351	25.55	452	33.96
Stillbirth	107	1.02	57	0.62	11	0.83
Miscarriage	1270	12.09	919	9.99	128	9.62

Table 3. Reproductive tract cancer diagnoses, incidence rates and hazard ratios.

	Cohort							
	All Women		QS		IUD		TL	
Characteristics	*N*	%	*N*	%	*N*	%	*N*	%
All women	21,037	100.00	10,503	100.00	9203	100.00	1331	100.00
Women years of follow-up	346,599		173,146		152,087		21,366	
All reproductive cancers	20	0.10	12	0.11	8	0.09	0	0.00
Uterine	14	0.07	8	0.08	6	0.07	0	0.00
Cervix	3	0.01	1	0.01	2	0.02	0	0.00
Ovarian	3	0.01	3	0.03	0	0.00	0	0.00
Rate of all reproductive cancers/100,000 women years of follow-up (95% CI)	5.77 (3.72–8.94)		6.93 (3.94–12.20)		5.26 (2.63–10.52)		–	
Median years to diagnosis	12.0		12.0		14.0		–	
HR QS vs. IUD/TL (95%CI, *p* value)								
Unadjusted	1.55 (0.64–3.80, 0.33)							
PS adjusted	2.00 (0.73–5.47, 0.18)							
HR QS vs. IUD (95%CI, *p* value)								
Unadjusted	1.37 (0.56–3.35, 0.49)							
PS adjusted	1.74 (0.62–4.86, 0.29)							

reported. Their survival was therefore constant across the roughly 20 years of maximum follow-up time.

Sensitivity analysis by province

Loss of IUD and TL patient records to flooding in the province of Nam Dinh dictated that IUD comparators in that province were located by surveying community members. This method may have led to a healthier group of IUD comparators from Nam Dinh, which could distort the study results. In order to examine the potential impact on study findings of any possible difference in health status of women in the IUD cohort from Nam Dinh vs. those from the other provinces, analyses were conducted separately for only the women from Nam Dinh and only the women from the other three provinces.

As seen in Table 4, reproductive cancers in the QS group were split proportionally between Nam Dinh and the other half of the cohort in the remaining three provinces (six from Nam Dinh and a total of six from the other three provinces). This is expected, given the roughly equal distribution of the overall QS population between Nam Dinh and the other provinces (47.4% vs. 52.6%). In contrast, only

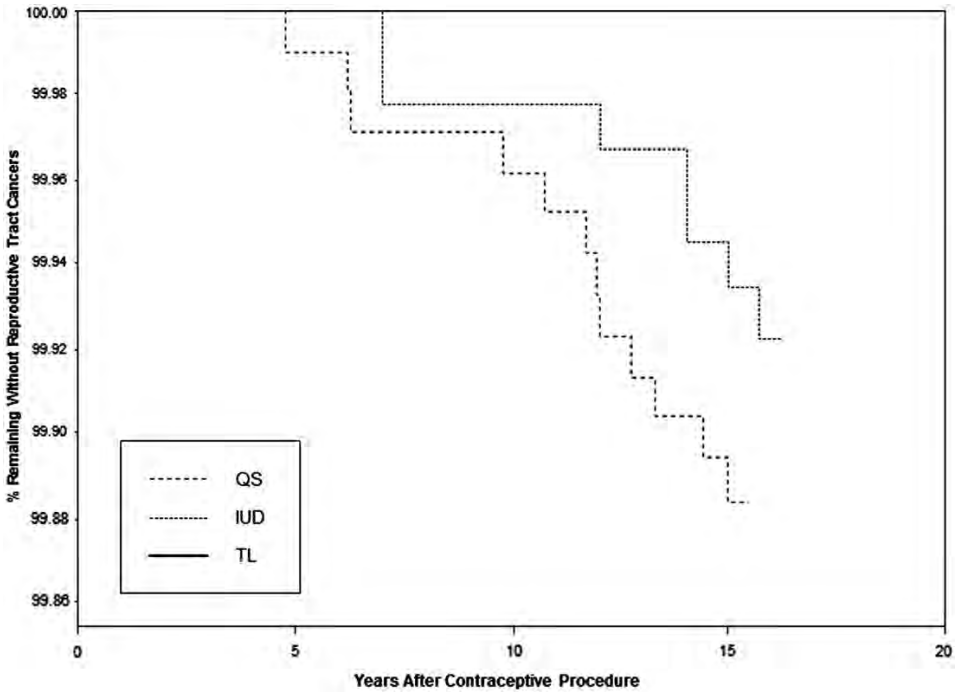


Figure 2. Kaplan–Meier analysis of reproductive tract cancers (Uterine-Ovarian-Cervical) by contraceptive procedure cohort.

one-fourth of the IUD cohort's reproductive tract cancers were from Nam Dinh (2/8 total reproductive tract cancers) despite over half of all IUD respondents (53.5%) living in Nam Dinh.

Also seen in Table 4, the reproductive tract cancer incidence rate per 100,000 women years of follow-up was higher among QS women from Nam Dinh than among the IUD comparators in that province (7.32/100,000 women years of follow-up; 95%CI = 3.29–16.29 vs. 2.44/100,000 women years of follow-up; 95%CI = 0.61–9.77, respectively). In contrast, the corresponding rate for QS women was below that of the IUD group among women surveyed in the other three provinces (6.58/100,000 women years of follow-up; 95%CI = 2.96–14.65 vs. 8.55/100,000 women years of follow-up; 95%CI = 3.84–19.02, respectively).

The disproportionately low number of reproductive cancers among the IUD cohort from Nam Dinh also influenced the hazard ratio comparing these cancers over time for the QS vs. IUD cohorts. As seen in the table, the unadjusted hazard ratio for only the Nam Dinh women was 3.01 (95%CI = 0.61–14.91), and the PS adjusted hazard ratio was 5.21 (95%CI = 0.95–28.68). Despite their magnitude, neither hazard ratio was significant. Comparing QS vs. IUD survey participants from the combination of Ha Nam, Ninh Binh and Thai Binh cohorts only, the unadjusted hazard ratio for QS vs. IUD was 0.77 (95%CI = 0.25–2.40) and the corresponding PS adjusted hazard ratio was 0.66 (95%CI = 0.16–2.70).

Discussion

Findings and interpretations

Post-IP reproductive tract cancer diagnoses were reported by 0.10% of all women in this study. The corresponding incidence rate was 5.77 reproductive tract cancer diagnoses per 100,000 women years of follow-up. Survival analysis found no significant difference in risk of reproductive tract cancer diagnosis in the average 16 years following the contraceptive procedure among women exposed to QS vs. comparators who used IUD/TL for contraception.

To assess the impact of an unexpected deviation in data collection methodology for IUD comparators in one province (Nam Dinh), data were analysed separately for that province and for the group of three other study provinces. Partitioning the analyses in this way reinforces the overall findings of no significant difference in the long-term hazard of reproductive tract cancers between women treated with QS vs IUD/TL. Despite the fact that reproductive tract cancers appear to be underreported among the large group of IUD users from Nam Dinh, there is no significant difference in the hazard of reproductive tract cancer over time among the QS women in that province. If the reported reproductive tract cancers were proportional to the percentage of the IUD cohort surveyed in Nam Dinh, the overall hazard ratio would be even closer to unity.

Strengths and weaknesses of the study

Study strengths

The findings reported herein are from the largest interview-based epidemiological study of QS-treated women in the world, to date. All women exposed to QS in four northern Vietnamese provinces ($N = 11,107$) were identified from health clinic records. Women from the same clinic areas who received IUD insertions or TL, during the same time periods and at similar ages, were comparators. Interviews completed for a total 21,040 women, with a mean follow-up in excess of 16 years, provided adequate data from which to observe the outcomes of interest. The 10,503

Table 4. Reproductive tract cancer diagnoses, incidence rates and hazard ratios: Nam Dinh alone vs. all other provinces.

	Cohort							
	All women		QS		IUD		TL	
Characteristics	*N*	%	*N*	%	*N*	%	*N*	%
All women	21,037	100.00	10,503	100.00	9203	100.00	1331	100.00
Nam Dinh women only	9953	100.00	4979	100.00	4926	100.00	48	100.00
% of all women from Nam Dinh		47.31		47.41		53.53		3.61
Women years of follow-up	164,621		81,964		81,883		774	
Reproductive cancers	8	0.08	6	0.12	2	0.04	0	0.00
Rate/100,000 women years of follow-up (95%CI)	4.86 (2.43–9.72)		7.32 (3.29–16.29)		2.44 (0.61–9.77)		–	
Median years to diagnosis	13.5		13.0		14.5		–	
HR QS vs. IUD/TL (95%CI, *p* value)								
Unadjusted	3.03 (0.61–15.05, 0.17)							
PS adjusted	5.25 (0.96–28.84, 0.06)							
HR QS vs. IUD (95%CI, *p* value)								
Unadjusted	3.01 (0.61–14.91, 0.18)							
PS adjusted	5.21 (0.95–28.68, 0.06)							
Nam Dinh women excluded	11,084	100.00	5524	100.00	4277	100.00	1283	100.00
% of all women not from Nam Dinh		52.69		52.59		46.47		96.39
Women years of follow-up	181,978		91,182		70,204		20,592	
Reproductive cancers	12	0.11	6	0.11	6	0.14	0	0.00
Rate/100,000 women years of follow-up (95%CI)	6.59 (3.74–11.61)		6.58 (2.96–14.65)		8.55 (3.84–19.02)		–	
Median years to diagnosis	12.0		11.5		13.0		–	
HR QS vs. IUD/TL (95%CI, *p* value)								
Unadjusted	0.997 (0.32–3.09, 1.00)							
PS adjusted	1.00 (0.28–3.66, 0.99)							
HR QS vs. IUD (95%CI, *p* value)								
Unadjusted	0.77 (0.25–2.40, 0.65)							
PS adjusted	0.66 (0.16–2.70, 0.57)							

interviews of women (or, in a few cases, their surrogates) treated with QS represented roughly one-fifth of all those who participated in Vietnam's clinical trial of QS.

Interviewers drawn from local health clinic staffs were valuable assets of the study. Initially, their familiarity with the community health system was instrumental in achieving the survey's 95% response rate. Subsequently, although only a small number of events could be verified via hospital records, the Vietnam staff's ability to verify potential outcomes of interest and clarify anomalies identified in the digitised interview data assigned a high level of confidence to the study findings.

Exhaustive sensitivity analyses detected neither biases resulting from disparate locations and interviewers nor biases from an unexpected deviation from the prescribed matching procedure in one province.

Study weaknesses

Identification of potential IUD subjects in Nam Dinh via community survey, rather than from logbooks as was done in the other provinces, may have resulted in omission of some women from that comparator pool who were ill or dead at the time of the study. Because roughly half the interviewed women came from Nam Dinh, and the alternate identification method occurred only in the IUD group, this sampling bias appears to have contributed to an overall underestimate of reproductive cancers in the IUD cohort. Table 5 shows that a disproportionately low percentage of the reproductive tract cancers reported for the IUD cohort were from Nam Dinh, compared to the proportion of all IUD interviews conducted in the province (25% of reported cancers vs. 54% of all interviews). The proportion of the Nam Dinh IUD cohort reporting reproductive tract cancers is also much lower than corresponding proportions in the other three provinces (0.04% vs. 0.13%–0.15%). As it is reasonable to assume that the true proportion of the Nam Dinh IUD cohort with reproductive tract cancers is more like the proportions observed in the other three provinces, it is likely that the true risks of post-procedure reproductive tract cancer in the QS and IUD cohorts are probably even more similar than these data indicate. Furthermore, no excess risk of reproductive cancer diagnosis for QS vs. comparators was identified in either a separate analysis excluding Nam Dinh or in an analysis of only the Nam Dinh data.

A bias toward comparators who were alive, healthy, and/or otherwise readily available for interview was also introduced by allowing interviewers to select which subject to interview, from each pair of potential IUD comparators in Nam Dinh. Lacking data about women not interviewed from the IUD pool precluded analysing the exact consequences of this selection system, although the expectation would be an interviewed group of IUD women who were healthier than the QS group. While acknowledged as a limitation, this bias would only further increase overestimation of the relative risk of post-procedure reproductive cancers in the QS cohort. Despite the possible under-ascertainment of outcomes among the IUD comparator group from Nam Dinh, the hazard ratios for the long-term risk of reproductive cancer in QS vs. IUD/TL or QS vs. IUD only users were not significant. Indeed, the difference in incidence rates between the QS and IUD cohorts in this very large group of women (6.93/100,000 women years of follow-up vs. 5.26/100,000 women years of follow-up, respectively) is so small that it would be insignificant from an epidemiological perspective [13]. Even at the hazard ratio's upper confidence limit (3.35 unadjusted; 4.86 PS adjusted) the actual number of expected reproductive tract cancer outcomes would still be extremely small.

Another limitation involved a lack of hospital records. While the study protocol called for hospital verification of all outcomes, shortage of space in Vietnamese hospitals translated into missing records for most events. However, 49 outcomes were able to be adjudicated from hospital

Table 5. Number and proportion of women reporting reproductive tract cancers by cohort and province for QS and IUD cohorts.

	Total interviews				Reproductive tract cancers reported				% Reporting reproductive cancer	
	QS		IUD		QS		IUD			
	N	%	*N*	%	*N*	%	*N*	%	QS	IUD
Total	10,503	100.0	9203	100.0	12	100.0	8	100.0		
Nam Dinh	4979	47.4	4926	53.5	6	50.0	2	25.0	0.12	0.04
Ha Nam	2017	19.2	1309	14.2	0	0.0	2	25.0	0.00	0.15
Thai Binh	1921	18.3	1521	16.5	3	25.0	2	25.0	0.16	0.13
Ninh Binh	1586	15.1	1447	15.7	3	25.0	2	25.0	0.19	0.14

records, including four of the reported reproductive tract cancers. Among outcomes that could be checked in this way, discrepant event dates were the most common inconsistencies identified between interview and hospital data. While suggestive of potential recall bias, sensitivity analysis indicated that the distribution of mismatched dates did not favour one cohort or the other. Furthermore, notwithstanding some incorrectly recalled dates, the reported events were confirmed to have occurred at some point during the follow-up period. In addition, findings were further substantiated by review of all interview outcomes and verification by local clinics.

Finally, numbers of reported reproductive tract cancers were very small in all cohorts. Whether the low numbers accurately reflect the incidence of reproductive cancers in this rural population cannot be readily determined. With an average interview conducted ~16 years after QS exposure in women aged ~51 years, it is possible that at least some of these women had not reached the age at which reproductive cancers typically appear [14,15]. Further, Vietnam has shared the problem of insufficient facilities for diagnosis and treatment of cancer faced by many developing countries [16]. Yet similar rates of uterine and ovarian cancers reported for the nearby country of Thailand suggest that the rates found in this study population accurately reflect the numbers of cancer diagnoses among these Vietnamese women [17]. In addition, whether underreported or not, comparable proportions of outcomes in the QS and IUD groups (with the exception of the IUD cohort in Nam Dinh) indicate that data were collected in a consistent fashion across cohorts and provinces. In the event that a reporting bias exists, it is consistent across groups and therefore has no effect on the risk estimates.

Differences in results and conclusions

This study's findings are consistent with previous reports of no apparent increased risk of reproductive tract cancer among women using QS [6–10]. Earlier studies, however, might not have had sufficient statistical power or length of follow-up to reach a definitive conclusion on this issue. The findings reported here, combined with previous research, provide convincing evidence that there is no increased risk of reproductive tract cancer among women using QS.

Relevance of the findings: implications for clinicians and policymakers

Previous concerns about an association between use of QS for permanent contraception and development of reproductive tract cancer led to discontinuation of clinical trials in Vietnam and other countries [4,18]. Results reported herein serve as a robust basis for mitigating those concerns in the consideration of QS as an option for women seeking permanent contraception.

Unanswered questions and future research

Clinical trials of QS, with carefully designed patient follow-up, will provide more specific details regarding the relationship between QS and women's reproductive health.

Conclusions

This large retrospective cohort study found no significant excess long-term risk of reproductive tract cancer among women exposed to QS, when compared to a matched cohort of IUD/TL users. Identification and interview of more than 21,000 QS, IUD and TL users with an average follow-up exceeding 16 years, coupled with local clinic staffs' personal knowledge of survey participants, allowed adequate time for development of procedure-related outcomes and the ability to verify survey responses.

The study's many strengths make it a valuable addition to the body of research pertaining to the topic of non-surgical permanent sterilisation, and to QS in particular [19].

Disclosure statement

This work was supported by the non-profit International Services Assistance Fund (ISAF), P.O. Box 13067, Research Triangle Park, NC 27709. ISAF had sponsored previous reproductive research in Vietnam and other countries and had impact on the selection of sites for this study. Originally ISAF hired a Contract Research Organization (CRO) to operationalise the study, and the authors were requested to design the study, design and carry out the analysis, and publish the report. Subsequent to the start of the study, ISAF took over the CRO functions. They also reviewed and provided comments on the study report and draft manuscript.

Notes

1. Women surveyed for this study were part of a large field trial that included more than 1300 clinicians in 24 provinces and resulted in approximately 55,000 QS cases. Most of the 11,105 QS procedures (97.5%) performed in the four provinces included in this study had been completed by the end of 1992, and another 4% (449 cases) in 1993. Although the Vietnamese government halted the trial at the end of 1993 and recalled the small quantities of quinacrine pellets that had not been administered to women, clinic records identified 33 additional procedures performed in these provinces between 1994 and 1996. Based on discussions with the study sponsors, who have extensive history with the reproductive health community in Vietnam, it appears that some physicians in the rural areas kept their remaining small supplies of QS pellets and used them to perform the additional procedures in 1994–1996.
2. Physicians working at the provincial/district levels of Vietnam's reproductive health system were trained to conduct all interviews for the survey. Use of physicians as interviewers was intended to enhance women's comfort levels when discussing their health, and also to make certain that appropriate follow-up questions would be used to ensure that the women surveyed were properly citing cancer diagnoses. In addition, employing physicians trained consistently in interview procedures was also intended to minimise any possible effect on survey results from use of multiple interviewers.

References

[1] Institute for Development Training. Female voluntary non-surgical sterilization: The quinacrine method. Module 12 of Training Course in Women's Health. Chapel Hill, (NC): IDT; 1996.

[2] Zipper J, Kessel E. Quinacrine sterilization: a retrospective. Int J Gynaecol Obstet. 2003;83(Suppl 2):S7–S11.

[3] Sokal D, Hieu DT, Weiner DH, et al. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. Fertil Steril. 2000;74:1084–1091.

[4] Cancel AM, Dillberger JE, Kelly CM, et al. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol. 2010; 56:156–165.

[5] Haseman JK, Growe RG, Zeiger E, et al. A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat cancer bioassay and its implications for human clinical use. Regul Toxicol Pharmacol. 2015; 71:371–378.

[6] Sokal DC, Zipper J, Guzman-Serani R, et al. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril. 1995;64:325–334.

[7] Sokal DC, Dabancens A, Guzman-Serani R, et al. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril. 2000; 74:169–171.

[8] Sokal DC, Trujillo V, Guzman SC, et al. Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort. Contraception. 2010;81:75–78.

[9] Sokal D, Hieu DT, Weiner DH, et al. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. Fertil Steril. 2000;74:1092–1101.

[10] Sokal DC, Vach TH, Nanda K, et al. Quinacrine sterilization and gynecologic cancers: a case-control study in northern Vietnam. Epidemiology. 2010;21:164–171.

[11] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.

[12] D'Agostino RB. Propensity score methods for bias reduction in the comparison of treatment to a non-randomized control group. Stat Med. 1998;17:2265–2281.

[13] Kirk RE. Practical significance: a concept whose time has come. Educ Psychol Meas. 1996;56:746–759.

[14] American Cancer Society [Internet]. Key statistics for endometrial cancer. 2016 [cited 2016 Sep 17]. Available from: http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-key-statistics

[15] American Cancer Society [Internet]. What are the risk factors for ovarian cancer. 2016 [cited 2016 Sep 17]. Available from: http://www.cancer.org/cancer/ovariancancer/detailedguide/ovarian-cancer-risk-factors

[16] Anh PTH, Duc NB. The situation with cancer control in Vietnam. Jpn J Clin Oncol. 2002;32(Suppl 1):S92–S97.

[17] Wilailak S. Epidemiologic report of gynecologic cancer in Thailand. J Gynecol Oncol. 2009;20:81–83.

[18] Editorial: Death of a Study: WHO, what and why. Lancet 1994;343:987–988.

[19] Lippes J. Quinacrine sterilization (QS): time for reconsideration. Contraception. 2015;92:91–95.

Regulatory Toxicology and Pharmacology 71 (2015) 371–378

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat cancer bioassay and its implications for human clinical use

Joseph K. Haseman [a], Roger G. Growe [b,*], Errol Zeiger [c], Ernest E. McConnell [d], Michael I. Luster [e], Jack Lippes [f]

[a] J.K. Haseman Consulting, 1054 Tacketts Pond Drive, Raleigh, NC 27614-7886, United States
[b] International Federation for Family Health, 1127 River Forest Road, Pittsboro, NC 27312, United States
[c] Errol Zeiger Consulting, 800 Indian Springs Road, Chapel Hill, NC 27514, United States
[d] Toxpath, Inc., 3028 Ethan Lane, Raleigh, NC 27613, United States
[e] M.I. Luster Associates, 39 Quail Road, Morgantown, WV 26508, United States
[f] State University of New York at Buffalo, School of Medicine, 31 Hampton Hill Drive, Buffalo, NY 14221, USA

ARTICLE INFO

Article history:
Received 17 September 2014
Available online 10 February 2015

Keywords:
Quinacrine
Contraception
Carcinogenicity bioassay (CaBio)
Maximum tolerated dose (MTD)
Chronic inflammation
Mode of action
Biological relevance

ABSTRACT

A rat carcinogenicity bioassay (CaBio) of quinacrine was reanalyzed to investigate its mode of tumor induction. Quinacrine's effects in the rat uterus when administered as a slurry in methylcellulose were contrasted with the human clinical experience which uses a solid form of the drug, to determine the relevance of the tumors produced in the rat to safe clinical use of quinacrine for permanent contraception (QS). A review was performed of the study report, dose feasibility studies, and clinical evaluations of women who had undergone the QS procedure. The top three doses of quinacrine in the CaBio exceeded the maximum tolerated dose, and produced chronic damage, including inflammation, resulting in reproductive tract tumors. Chronic inflammation was significantly correlated with the tumors; there was no evidence of treatment-related tumors in animals without chronic inflammation or other reproductive system toxicity. Because such permanent uterine damage and chronic toxicity have not been observed in humans under therapeutic conditions, we conclude that this mode of action for tumor production will not occur at clinically relevant doses in women who choose quinacrine for permanent contraception.

1. Introduction

Since its development in the 1920s, quinacrine has been successfully used for a wide variety of indications (Ehsanian et al., 2011; Wallace, 1989), including as an oral treatment and prophylactic for malaria in millions of American soldiers in the South Pacific during World War II. These soldiers were administered quinacrine on a daily basis, sometimes for years. Quinacrine has also been used to treat parasitic infections such as amoeba, giardia and tapeworm. The discovery of the anti-inflammatory properties of quinacrine led to its use in the treatment of refractory lupus erythematosus, rheumatoid arthritis, bronchial asthma, and other inflammatory and autoimmune disorders. Quinacrine is commonly administered to patients for months at a time to control symptoms of these diseases. Although other drugs have been developed that have superseded quinacrine for some indications, it has remained USFDA-approved for malaria, giardia and tapeworm, and has never been removed from use for safety concerns (Ehsanian et al., 2011).

Quinacrine's potential use as a nonsurgical method of permanent contraception for women has been investigated for more than 35 years. Briefly, seven pellets containing a total of 252 mg quinacrine are placed transcervically into a woman's uterus in two administrations, one month apart, during the proliferative phase of her menstrual cycle. The quinacrine interacts with fallopian tube tissue to produce a 2–3 mm occlusive scar in the intramural portion of the tube that permanently closes the tubal lumen, thereby preventing the passage of sperm or egg. The quinacrine is either expelled through the vagina (~30%) or is absorbed by the vascular system (Laufe et al., 1996). Since 1977, over 150,000 women have used the quinacrine system of permanent contraception (QS), with no deaths or adverse events requiring hospitalization reported (Lippes et al., 2003).

* Corresponding author.
E-mail addresses: hasemanjk@aol.com (J.K. Haseman), growe.roger@gmail.com (R.G. Growe), zeiger@nc.rr.com (E. Zeiger), toxpathmcc@bellsouth.net (E.E. McConnell), miklus22@comcast.net (M.I. Luster), jlip@buffalo.edu (J. Lippes).

http://dx.doi.org/10.1016/j.yrtph.2015.02.006
0273-2300/

Quinacrine is mutagenic in the presence and absence of rat liver S9 in the Salmonella mutagenicity (Ames) assay (Clarke et al., 2001; Zeiger et al., 1988) and in the mouse lymphoma (L1578Y) assay only without S9 (Clarke et al., 2001), and produces chromosome damage in mammalian cells *in vitro* (Clarke et al., 2001; Krishnaja and Chauhan, 2000; Schuler et al., 2010). In contrast, quinacrine is not clastogenic in the *in vivo* mouse bone marrow micronucleus assay (Clarke et al., 2001) or in peripheral blood lymphocytes of female cynomolgus monkeys administered quinacrine via intrauterine or i.v. routes (Blake et al., 1983).

Because of its *in vitro* mutagenicity, quinacrine was tested for carcinogenicity in the mouse and rat. It was not carcinogenic in the neonatal mouse assay when administered intraperitoneal (i.p.) to male and female mice (Cancel et al., 2006), but did induce tumors in the female rat when administered directly into the rat uterus at doses exceeding the maximum tolerated dose (MTD), i.e., doses that produced high mortality and/or irreparable (chronic) target organ damage including ulceration, abdominal adhesions, reproductive tract chronic inflammation, necrosis, atrophy, and cystic degeneration (Cancel et al., 2010).

Although epidemiological studies of women receiving QS have reported no increased risk of reproductive tract cancer, because of quinacrine's mutagenicity, the FDA and WHO recommended that the molecular mechanisms of tumor induction in the rat cancer bioassay (CaBio) study be investigated. They also recommended that an additional epidemiology study be performed among women who had received QS contraception.

This article presents an extended reanalysis of the original data from the rat CaBio laboratory report in the context of the acute and chronic toxicity of quinacrine to test the potential mode of action of tumor development suggested by McConnell et al. (2010). The goal of this reanalysis was: (a) to determine the probable underlying cause for the tumors in the rat CaBio; (b) to propose a likely mode of action for the tumor induction; and (c) to assess the relevance of the rat study with respect to the human clinical experience with QS, and its potential risk to humans under conditions of use.

The findings from short-term rat studies and the prechronic studies (McConnell et al., 2010) are also included in the total weight of evidence evaluation of the induction and significance of the reproductive tract tumors seen in the rat CaBio, in addition to the human clinical experience and cancer epidemiology studies of women receiving QS.

1.1. Cancer studies of quinacrine

1.1.1. Neonatal mouse studies

Quinacrine 2HCl dihydrate was not carcinogenic in male or female Crl:CD-1 mice using two i.p. doses of 10, 50, and 150 mg/kg, suspended in 1% (w/v) carboxymethylcellulose in saline, on postpartum days 8 and 15, and examined for tumors 52 weeks following dosing (Cancel et al., 2006). The 150 mg dose was lethal to 9/28 males (32%) and 5/28 (18%) females following the second (day 15) administration – the deaths occurring either during, or shortly after, dosing. Because of the anticipated toxicity, additional animals were added after the initial dosing. As a consequence, the second dose was lowered to 100 mg/kg. Of the additional eight males added and dosed with 100 mg/kg on day 15, three died during dosing. The animals were necropsied 52 weeks following quinacrine administration; no increases in tumors over control group levels were seen in either sex (Cancel et al., 2006).

1.1.2. Rat 2-year CaBio

A 2-year cancer bioassay of quinacrine 2HCl dihydrate using the route of exposure (transcervical instillation) intended for women undergoing QS was conducted in rats. This CaBio reported high, treatment-related mortality at the top doses, and an increased incidence of unusual and rare types of neoplasms in the uterus, vagina and/or cervix at the top three doses (Cancel et al., 2010). A preliminary assessment of the neoplasms reported in this study was presented in a companion paper by McConnell et al. (2010).

The design of this 2-year rat study is addressed in detail here because a description of the protocol design, and its consequences, is critical to an understanding of the mechanisms and relevance of tumor induction.

Young, sexually mature (approximately 57–68 days old), albino female Crl:CD(SD)IGS BR rats received two doses of quinacrine 2HCl as slurry in 1% methylcellulose (MC) into each uterine horn via the vagina and cervix using a 22 gauge spinal needle with a blunted end fitted on a syringe approximately 21 days apart during diestrus (because the day of administration depended on the animal being in diestrus, animals could not be dosed on the same day). The uteri were 'sealed' after each dosing with a plug of 3% MC to prevent leakage of the slurry. Despite information from prior range-finding studies that the higher doses would be toxic to the animals and would produce inflammation among the survivors (Cancel et al., 2010), the high doses were used in an attempt to mimic, in the rat uterus, the fibrosis of the fallopian tube that is found in humans.

The rats were observed for 23 months after administration of the second dose. The study design included two identical MC control groups, but there was no untreated, or sham-treated, control group (Table 1). The original study design called for three quinacrine treatment groups, with Day 0/Day 21 doses of 10/10, 70/70, and 70/350 mg/kg, respectively, with half of each dose delivered to each of the rats' two uterine horns.

The CaBio was divided into two "phases": (1) a "dosing phase," extending one month after the administration of the second dose, and, (2) an "observation phase," where the surviving animals were observed for the remainder of the experiment. Since high mortality

Table 1
Experimental design of rat the 2-year quinacrine cancer bioassay.

Group no.	Test material	Dose (mg/kg)[a]		Number of animals		
				Dosed	Entering "observation phase"	Survived to terminal sacrifice
		Day 0	Day 21			
1	1% MC[b]	0	0	60	50	13
2	1% MC[b]	0	0	60	50	14
3	Quinacrine 2HCl[c]	10	10	60	50	13
4	Quinacrine 2HCl[c]	70	70	60	50	17
6	Quinacrine 2HCl[c]	70	250	35	24	5
5	Quinacrine 2HCl[c]	70	350	33	21	10

[a] Doses represent active ingredient (quinacrine dihydrochloride dihydrate). Each animal was dosed with ½ dose per uterine horn. A plug of 3 μl of 3% methylcellulose was injected into the end of each uterine horn in an attempt to minimize leakage of the quinacrine.
[b] 1% (w/v) methylcellulose in 0.9% saline.
[c] Slurry in 1% (w/v) methylcellulose in 0.9% saline.

Table 2
Incidence of reproductive system neoplasms in the quinacrine rat CaBio.[a]

Quinacrine (mg/kg)[b]	0/0	0/0	10/10	70/70	70/250	70/350
Group number	1	2	3	4	6	5
Total number of rats	50	50	50	50	24	21
Cervix: number examined	49	49	50	49	23	21
Benign squamous cell papilloma	0	0	0	1 (2)	1 (4)	0
Benign fibroma	0	1 (2)	1 (2)	0	0	0
Malignant squamous cell carcinoma	0	0	0	0	1 (4)	2 (10)
Malignant basal-squamous cell carcinoma	0	0	0	0	1 (4)	0
Malignant schwannoma	0	0	1 (2)	1 (2)	0	0
Uterus: number examined	50	50	50	50	24	21
Benign endometrial stromal polyp	5 (10)	9 (18)	4 (8)	1 (2)	2 (8)	1 (5)
Benign hemangioma	0	0	0	1 (2)	0	1 (5)
Benign granular cell tumor	0	0	0	1 (2)	0	0
Benign mixed mullerian tumor	0	0	0	1 (2)	0	0
Malignant endometrial carcinoma	0	0	0	1 (2)	0	2 (10)
Malignant carcino-sarcoma	0	0	0	0	1 (4)	0
Malignant stromal sarcoma	0	0	0	1 (2)	1 (4)	0
Malignant squamous cell carcinoma	0	0	0	1 (2)	0	0
Malignant yolk sac carcinoma	0	0	0	1 (2)	0	0
Malignant leiomyosarcoma	0	0	1 (2)	0	0	1 (5)
Malignant schwannoma	1 (2)	0	0	0	0	2 (10)
Malignant hemangiosarcoma	0	0	0	0	0	1 (5)
Vagina: number examined	50	49	48	49	24	18
Malignant squamous cell carcinoma	0	0	0	1 (2)	4 (17)*	0
Reproductive tract: number of uncommon neoplasms[c]	1	1	3	10	9	9
Reproductive tract: number of animals with uncommon neoplasms	1 (2)	1 (2)	3 (6)	9 (18)*	7 (29)*	6 (29)*

[a] Values in the table represent incidence of the finding and % incidence (in parentheses).
[b] Split doses administered on Days 0 and 21 of study.
[c] Excludes endometrial stromal polyps, which are common tumors in rats.
* $p < 0.01$ versus pooled controls by Fisher's exact test.

(up to 20%) was planned for and expected in the high dose group, ten extra animals were added to each group, with the plan of culling the groups to 50 animals each at the beginning of the "observation phase."

During the "dosing phase," 12 of the 33 rats (36%) in the high-dose group (Group 5) died or were euthanized in a moribund condition shortly after administration of the second 350 mg dose. Due to this higher than anticipated mortality, the remaining 27 rats in Group 5 that had received the first dose of 70 mg/kg but had not received the second dose were combined with eight reserve rats that had also been given a first dose of 70 mg/kg, to form a new group (Group 6; see Table 1) that received a second quinacrine dose of 250 mg/kg. Of the 35 rats in this new group, 11 (31%) died during the dosing phase.

This mortality in Groups 5 and 6 was associated with ulceration through the uterine wall that resulted in quinacrine entering the abdominal cavity. Death soon followed after administration or within 30 days, following the development of quinacrine-induced enteromegaly of the intestinal tract. During the "observation phase" there were no significant differences in mortality among groups. Microscopic pathology was performed only on those animals entering the "observation phase."

2. Statistical approach

For this re-assessment of the rat CaBio data, Groups 1 and 2 (-control animals) were pooled, since there were no significant differences between the groups in any of the parameters analyzed (see e.g., Tables 3–5 from Cancel et al., 2010). For this analysis, Groups 5 and 6 were also pooled for the following reasons:

(1) Both dose groups produced the same percentage of animals with uncommon reproductive system neoplasms: Group 6 – 7/24 (29%); Group 5 – 6/21 (29%)).
(2) Mortality of animals immediately following Day 21 dosing was similar in both groups: Group 5 – 12/33 (36%); Group 6 – 11/35 (31%).
(3) Low initial animal numbers due to toxicity: Group 6 – 35, Group 5 – 33; and low subsequent 2-year survival numbers in both groups (Group 6 – 5/24, Group 5 – 10/21), both of which decrease the statistical power for detecting adverse effects if the two groups are evaluated separately.

There were no statistically significant differences in the incidences of reproductive system tumors or in the incidence of any of the reproductive tract non-neoplastic lesions among Groups 4, 5 and 6. Hence, these three groups were combined for the purpose of assessing the possible association between these tumors and reproductive system non-neoplastic lesions. In addition to the individual organs, statistical analyses were conducted on all reproductive tract (i.e., uterus, cervix, and vagina) neoplastic and non-neoplastic lesions (Rhomberg et al., 2007).

Pairwise comparisons of the incidences of neoplastic and non-neoplastic lesions between groups were made by Fisher's exact tests (Fisher, 1954) and also by the G-test (Sokal and Rohlf, 1981). These tests were also used to assess the correlation between neoplastic and non-neoplastic lesions, and produced virtually identical results. The results given in the text are from Fisher's exact test, which was carried out using http://www.langsrud.com/fisher.htm.

3. Results

3.1. Findings of the extended analysis of the rat CaBio

3.1.1. Gross necropsy results

At gross necropsy, there was clear evidence of damage to the uterus, as reflected by significantly increased incidences of large

Table 3
Summary of non-neoplastic reproductive tract lesion incidence in the quinacrine CaBio.

Quinacrine (mg/kg) Group number	0/0 1 and 2 I/N (%)[a]	10/10 3 I/N (%)	70/70 4 I/N (%)	70/250 and 70/350 5 and 6 I/N (%)
Vagina				
Subacute (chronic active)/chronic inflammation	2/99 (2)	3/48 (6)	7/49 (14)**	8/42 (19)**
Erosion(s)/ulcer(s)	0/99 (0)	0/48 (0)	0/49 (0)	3/42 (7)*
Fibrosis	0/99 (0)	0/48 (0)	1/49 (2)	0/42 (0)
Cervix				
Subacute (chronic active)/chronic inflammation	7/98 (7)	2/50 (4)	9/49 (18)*	14/44 (32)**
Fibrosis	0/98 (0)	1/50 (2)	1/49 (2)	0/44 (0)
Uterus (uterine horns)				
Necrosis (with/without dystrophic mineral deposits)	0/100 (0)	2/50 (4)	6/50 (12)**	5/45 (11)**
Acute/subacute inflammation	2/100 (2)	1/50 (2)	5/50 (10)*	5/45 (11)*
Atrophy	12/100 (12)	13/50 (26)*	30/50 (60)**	34/45 (76)**
Erosion(s)/ulcer(s)	2/100 (2)	1/50 (2)	4/50 (8)	4/45 (9)
Cystic degeneration	0/100 (0)	0/50 (0)	18/50 (36)**	16/45 (36)**
Subacute (chronic active)/chronic inflammation	14/100 (14)	5/50 (10)	21/50 (42)**	20/45 (44)**
Endometrium – stromal fibrosis	31/100 (31)	18/50 (36)	14/50 (28)	6/45 (13)
Serosa – fibrosis	1/100 (1)	0/50 (0)	2/50 (4)	0/45 (0)
Other				
Adhesions (abdominal cavity)	0/100 (0)	2/50 (4)	5/50 (10)**	11/45 (24)**
Hypercellular marrow any bone	32/100 (32)	16/50 (32)	24/50 (48)*	26/45 (58)**
Subacute (chronic active)/chronic inflammation of the reproductive tract	20/100 (20)	9/50 (18)	31/50 (62)**	25/45 (56)**
Inflammatory/mixed inflammatory cells of the reproductive tract	100/100 (100)	50/50 (100)	50/50 (100)	44/45 (98)

[a] I/N, incidence/number of animals examined.
* $p < 0.05$ by Fisher's exact test (comparison to controls).
** $p < 0.01$ by Fisher's exact test (comparison to controls).

Table 4
Correlation between reproductive tract chronic inflammation and uncommon reproductive system tumors in Groups 4–6.

	Tumor incidence
Animals with no chronic inflammation	8% (3/39)
Animals with chronic inflammation	34% (19/56)*
Animals with chronic inflammation at >1 site (vagina, cervix and uterus)	67% (12/18)**

* $p = 0.002$ (compared to animals with no chronic inflammation); Fisher's exact test.
** $p < 0.001$ (compared to animals with no chronic inflammation); Fisher's exact test.

Table 5
Incidence of reproductive tract chronic inflammation in the quinacrine study.

Group number (dose)	1 and 2 (control)	3 (10/10 mg/kg)	4–6 (70/70; 70/350; 70/250 mg/kg)	
			No tumor	Tumor
Chronic inflammation	20% (20/100)	18% (9/50)	51% (37/73)	86% (19/22)

or distended horns, abnormal uterine contents, and/or abscesses in Groups 4–6 relative to controls (data not shown).

3.1.2. Reproductive tract neoplasms

The only neoplasms that showed a relationship to quinacrine administration were in the reproductive tract. The overall incidence of uncommon (those not normally found in the rat reproductive tract) neoplasms was significantly increased ($p < 0.01$) in Groups 4–6 relative to controls (Table 2).

3.1.3. Non-neoplastic lesions of the reproductive tract

The incidences of selected non-neoplastic lesions are shown in Table 3. Many lesions in the rats dosed with 70/70 mg/kg and higher were clearly associated with exposure to quinacrine and MC. These included subacute (chronic active)/chronic inflammation, necrosis, atrophy, and cystic degeneration.

The results presented in this table clearly show that chronic inflammatory lesions of the reproductive tract were induced in Groups 4–6, and that Group 3 did not show any increase in inflammatory lesions when compared to the MC control Groups 1 and 2.

Relevant to the rationale for selection of the doses, i.e., production of fibrosis in the rat uterus to mimic the fallopian tube fibrosis produced clinically in women, there was no increase in such fibrosis in the treated animals. The incidence of fibrosis in the reproductive tract either decreased with respect to dose or remained statistically equivalent to controls (see Table 3). No lumen closure or uterine occlusions were noted in the individual animal data.

3.1.4. Lesions in other tissues related to quinacrine exposure

Adhesions between organs in the abdominal cavity were increased in incidence relative to controls ($p < 0.01$) in Groups 4–6 (Table 3). Based on the acute study performed following completion of the CaBio (McConnell et al., 2010; unpublished results), these adhesions appeared to be the result of perforations of the uterine horn and leakage of quinacrine and MC into the abdominal cavity due to the ulcerative effects of the chemical at the high dose levels administered. Hypercellular bone marrow (sternal, femoral and tibial combined) also showed a significantly increased incidence relative to controls in Groups 4 ($p < 0.05$), 5 and 6 ($p < 0.01$), and was attributed to the secondary effects of the chronic inflammation in the reproductive tract.

3.1.5. Correlation of non-neoplastic lesions and tumor development

One lesion showing a highly significant ($p = 0.002$) correlation with the reproductive system tumors in Groups 4–6 was chronic inflammation (Table 4). The correlation was even stronger ($p < 0.001$) for those animals having chronic inflammation at more than one reproductive tract site (vagina, cervix, and uterus; Table 4).

Only three animals in Groups 4–6 had reproductive system tumors in the absence of chronic inflammation. One of these animals had necrosis, another toxic lesion that showed a highly

significant ($p < 0.001$) association with tumor development, i.e., 73% (8/11) of the animals in Groups 4–6 with necrosis had reproductive system tumors compared with 17% (14/84) tumor incidence for animals in those groups without necrosis. It is likely that the two remaining animals with reproductive system tumors in Groups 4–6 reflect the background incidence, since two animals with reproductive system tumors were also seen in the controls (see Table 2).

Alternatively, one animal had a malignant schwannoma. Since a malignant schwannoma was seen in the control group this could be considered a background tumor. The second animal had necrosis, uterine tumors metastasized to several organs and a 7.9 cm mass that could have obscured the chronic inflammation present. The presence of chronic inflammation in the third animal could have been overlooked since it is the only animal in the study (1/245) where the presence of inflammatory cells is not recorded. Regardless, the evidence is very strong that the induction of chronic inflammation and other chronic toxicities in the reproductive tract is responsible for the formation of the reproductive tract tumors.

Another way to demonstrate the association between chronic inflammation and reproductive system tumors is given in Table 5. Chronic inflammation was not increased in Group 3 relative to controls, but was increased in the Groups 4–6 tumor-free animals, and further increased in the tumor-bearing animals. This supports the conclusion that the chronic inflammation preceded tumor development, created a uterine environment that fostered tumor development, and was clearly not due to tumor formation. Chronic inflammation was also reported in a short-term (42 day duration) feasibility study described by Cancel et al. (2010).

3.2. Cancer studies of QS in humans

Studies of relatively small cohorts of women in Vietnam ($N > 2,800$) and Chile ($N = 1,492$) treated with QS in clinical trials showed no increased risk of reproductive tract cancer or other serious adverse events compared to IUD controls (Feldblum et al., 2012; Sokal et al., 2000, 2008, 2010). Those findings were replicated in a large retrospective cohort study in Vietnam. Interviews were conducted with 10,503 women who received QS between 1989 and 1996, and a similar number of controls who had IUD insertions. With an average 16 years of post-treatment follow-up time, survival analysis found no significant excess of reproductive tract cancer risk in the QS group compared to the IUD recipients (Tave et al., 2012).

4. Discussion

4.1. Flaws in the design of the rat CaBio

There are a number of aspects of the rat carcinogenicity study which led to the formation of reproductive tract tumors that negate its relevance for the clinical use of quinacrine intrauterine administration. These include:

- the administration of quinacrine at doses that exceeded the MTD and produced chronic toxicity and permanent damage to the uterus;
- the use of a methylcellulose slurry rather than the clinically designed pellets, and the methylcellulose cervical ‘plug’ to retain the slurry; and
- the inability to produce the sought-after fibrosis in the rat uterus.

4.1.1. Administration of quinacrine at doses that exceeded the MTD and produced chronic toxicity and permanent damage to the uterus

Dose setting for rodent carcinogenicity studies designed for regulatory use is based on the concept of the MTD (Maximum Tolerated Dose; sometimes called Minimally Toxic Dose) (ICH, 2008; OECD, 2009, 2010). This is a dose “which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study,” or “is just high enough to elicit signs of minimal toxicity without significantly altering the animal’s normal lifespan due to effects other than carcinogenicity. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study” (ICH, 2008). The MTD is chosen as the high dose to avoid carcinogenic and other effects secondarily associated with toxicity (Rhomberg et al., 2007).

Doses in this study were selected based on the goal of producing a fibrotic occlusion (lumen closure) of the rat uterus at the high dose. High mortality was expected and considered justified by the need to duplicate the effect of quinacrine in the human fallopian tube. Additional animals were therefore included in the protocol as potential replacements for those that died shortly after dosing (Cancel et al., 2010).

As anticipated, in many animals quinacrine administration produced immediate lethality, and chronic toxicity in the surviving animals, which was manifested by chronic inflammation, necrosis, and compensatory cell proliferation, any of which, alone, can be considered a mode of action for tumor induction. Such chronic uterine destruction is far more than “minimal toxicity.” A significant increase in reproductive tract tumors was seen only in animals displaying this toxicity (Tables 4 and 5), and can be considered an artifact secondarily associated with toxicity. Moreover, on an individual animal basis, this toxicity was demonstrated to be correlated with tumor development. Importantly, no significant increase in reproductive tract tumors was observed in rats receiving the 10/10 mg/kg dose which, based on the results of the prechronic study, would qualify as the appropriate MTD. It was the only dose that did not produce chronic damage to the reproductive tract.

4.1.2. Use of a methylcellulose slurry rather than the clinically designed pellets, and the methylcellulose cervical ‘plug’ to retain the slurry

The quinacrine was delivered as a slurry in 1% methylcellulose/saline followed by insertion of 3% methylcellulose plugs at the ends of each uterine horn after each administration (Cancel et al., 2010). This is an administration route and technique with no prior history or supporting data. Methylcellulose is a biodurable, biologically active substance when injected intraperitoneally (Glomski et al., 1982; Hall and Hall, 1962; Machado et al., 1966; Pfrimmer et al., 1978; Teoh, 1961), and is not included in the formulation for humans. Methylcellulose has also been shown to be mildly irritating to the eye and skin of rabbits (Obara et al., 1992).

However, because no untreated, or sham-treated, control groups were included in the design, there is no way to determine the extent to which the tumors seen at the high doses were related to the use of methylcellulose, the use of quinacrine, and/or the possible interaction of methylcellulose with quinacrine to produce effects (i.e., chronic inflammation and tumors) that would not be induced by either substance alone.

One consequence of these design parameters (i.e., instillation techniques and/or methylcellulose) was a 20% chronic inflammation rate and a 100% incidence of mixed inflammatory cells in the control animals (see Table 3). Inflammation of any type is rarely observed in control rat uteri in 2-year carcinogenicity studies (http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/index.html).

Another concern is that there is no indication in the published study protocol (Cancel et al., 2010) whether the instillation techniques were conducted in a sterile manner. The instillation needle passing through the non-sterile environment of the vagina has the potential to introduce potential pathogens into the uterus. A resulting infection, and the inability to clear the uterine contents

because of the methylcellulose plug, could lead to chronic inflammation and possibly account for the extraordinarily high incidence of this inflammation in methylcellulose control animals as well as in the quinacrine-dosed groups.

4.1.3. Inability to produce the sought-after fibrosis in the rat uterus

The high dose was selected based on the anticipation that sufficient concentrations of quinacrine would cause fibrosis and occlusion in the rat uterus, similar to the fibrotic occlusion seen in the fallopian tubes of women at the therapeutic dose (Cancel et al., 2010). However, the structures of the uterus of the rat and the fallopian tube in women differ in important ways. The fallopian tube is a relatively simple structure, i.e., the lumen is lined with a mucosa comprised of a single layer of a mix of ciliated and non-ciliated cells, with a thin lamina propria covered by a myometrium of three layers of muscle tissue. In contrast, the rat uterus is highly complex, consisting of an epithelial surface, a complex stromal and glandular structure, and a thick wall of smooth muscle.

The experimental design of the CaBio did not address these differences in the anatomy of the rat uterus and the human fallopian tube (or between the rat and human uterus), nor the evidence from earlier studies showing that the mechanism of action of quinacrine in the human fallopian tube cannot be replicated in the rat or other animal models, including pigs and monkeys (Dubin et al., 1984; Fail et al., 2000; King et al., 1983; Zaneveld and Goldsmith, 1984). This was confirmed in the rat CaBio. Contrary to what was expected based on the fibrotic response in women, the incidence of fibrosis in the rat reproductive tract either decreased with respect to dose or remained equivalent to controls in quinacrine-treated groups, even at the doses that produced chronic inflammation and necrosis (see Table 3). No lumen closures or occlusions of the uterus were noted in the treated rats.

Although the rat uterus is not an appropriate surrogate for the human fallopian tube, it is a valid organ in which to study the potential carcinogenic activity of quinacrine, because that is the organ that receives the majority of the exposure to quinacrine for permanent contraception in women.

4.2. The proposed mode of action of quinacrine's carcinogenicity in the rat CaBio

All the evidence leads to the conclusion that chronic inflammation caused by high-dose quinacrine-plus-methylcellulose administration is likely responsible for the reproductive tract cancers. While acute inflammation is required for recovery from injury or infection, chronic inflammation often leads to disease, including cancer. In this respect, the association between inflammation and cancer is estimated to be responsible for approximately 25% of all cancers in humans (Balkwill et al., 2005; Kundu and Surh, 2005). Animal and human studies have revealed that a number of agents that produce chronic inflammation lead to tumor formation, including particulates such as asbestos and silica, and infectious agents such as hepatitis B and C, *Helicobacter pylori* and Schistosoma (Aggarwal et al., 2006). Medical conditions associated with chronic inflammation and cellular changes, such as inflammatory bowel disease, pancreatitis, hepatitis and prostatitis, are also associated with an increased cancer risk (Arnott et al., 2002; Houghton et al., 2007). Chronic inflammatory products can be involved in multiple stages of tumorigenesis, including DNA damage, angiogenesis and cell transformation, proliferation and invasion (Mantovani, 2005).

Several byproducts of chronic inflammation, including reactive oxygen (ROS) and reactive nitrogen (RNS) species, produce oxidative stress that cause DNA strand breaks, cross-linking and genomic instability (Matés et al., 2008). Proinflammatory products, including cytokines, chemokines, cyclooxygenase-2, and prostaglandins, facilitate proliferation of initiated cells, suppression of apoptosis, tumor neovascularization, histone modification, and DNA methylation. For a detailed analysis of the relationship between chronic inflammation and cancer the reader is referred to several excellent reviews (Aggarwal et al., 2006; Balkwill et al., 2005; Coussens and Werb, 2002; O'Byrne and Dalgleish, 2001).

4.3. The mutagenicity of quinacrine and its relevance as a possible mode of action for tumor induction in the rat CaBio

In vitro, quinacrine is mutagenic in Salmonella with and without S9, producing frameshift mutations with and without S9 (Clarke et al., 2001; Zeiger et al., 1988); mutagenic in cultured mammalian (L5178Y) cells without S9 and negative with S9 (Clarke et al., 2001); and clastogenic in cultured mammalian and human cells with and without S9 (Clarke et al., 2001; Krishnaja and Chauhan, 2000; Schuler et al., 2010). It did not induce micronuclei (MN) in rodent bone marrow (Clarke et al., 2001) or chromosome aberrations in cynomolgus monkey lymphocytes (Blake et al., 1983). Although there had been earlier reports of MN induced in rodent bone marrow cells (Hart and Hartley-Asp, 1983; Jenssen et al., 1974), these effects were contradicted by subsequent studies that demonstrated that the cellular inclusions scored as MN in those studies were actually quinacrine, or other, inclusions, and not MN (Ashby et al., 1990; Hitotsumachi et al., 1990; Maier and Schmid, 1975). Quinacrine's genetic activity *in vitro* has been attributed to its ability to intercalate into the DNA helix without forming an adduct (Ferguson and Denny, 2007). This weak mutagenicity was the basis for its subsequent testing for carcinogenicity in mice and rats.

It is well established that the mutagenicity or clastogenicity of a substance *in vitro* is not equivalent to its being a carcinogen, and a number of studies have shown that the 'false positive' rate for the Ames Salmonella test is approximately 20–30% (Kirkland et al., 2005; Zeiger, 1998) depending on the study and the mix of chemicals evaluated. The (false positive) predictivity of positive responses in the *in vitro* mammalian cell chromosome aberration test and gene mutation tests can be higher, from 20% to 52%, depending on the test and endpoint (Kirkland et al., 2005; Zeiger, 1998).

Because cancer can be caused through a number of mechanisms, the induction of cancer by a mutagenic chemical is not sufficient to ascribe that induction to mutagenicity. The weight of evidence for quinacrine strongly suggests that the tumors induced in the rat uterus at the high doses were not via a mutagenic mode of action. This evidence includes the negative findings in the mouse bone marrow micronucleus assay at i.p. doses up to 110 mg/kg/d (80% of the LD_{50}) for 3 days, negative chromosome aberration findings in lymphocytes of female monkeys dosed with quinacrine either intra-uterine or i.v., and the fact that tumor occurrence in the rat CaBio was strongly correlated with chronic inflammation and tissue necrosis, lesions which were, in part, attributable to the use of methylcellulose. In addition, the lack of tumorigenicity in the mouse neonatal study when quinacrine was administered in doses sufficient to cause 20% mortality at the high dose, provides additional support to the conclusion that the tumors seen in the rat were not induced via a mutagenic mechanism. Validation studies of the neonatal mouse assay have shown that substances negative in this assay are not likely to be trans-species carcinogens or carcinogenic via a genotoxic mode of action (Flammang et al., 1997; McClain et al., 2001).

4.4. The human clinical experience following quinacrine administration (QS procedure)

The response to quinacrine in humans following intrauterine administration has many similarities to non-malignant pleural fibrosis, which is characterized by complex interactions between

resident and inflammatory cells that result in profibrotic mediators and activation of fibrinolytic pathways (Growe et al., 2013). Specifically, quinacrine is thought to disrupt cell adhesion in the cells of the uterotubal junction and transmural segment of the fallopian tube, initiating a pro-fibrotic cytokine cascade and resulting in formation of mature collagen in the lumen of the fallopian tube and permanent occlusion. The inflammation that occurs in a woman's uterus is transient and the uterus rapidly returns to normal.

The lesions reported in the CaBio rats two years after treatment at doses $\geqslant$70/70 mg/kg included abdominal cavity adhesions, atrophy, cystic degeneration, chronic inflammation, necrosis, and toxicity-induced uterine perforations (Cancel et al., 2010; McConnell et al., 2010; Fail et al., 2000; this study). The cellular destruction and subsequent chronic inflammation in the rat uterine endometrium were likely the result of the inability of the uterus to undergo normal repair processes as a result of the initial excessive tissue damage, and are the probable cause of the tumors reported by Cancel et al. (2010).

No evidence of unresolved wounding in the human uterus similar to that produced in the rat has been reported in the more than 35 years of follow-up of women who have received one, two, or three administrations of QS. Histopathological examinations of uteri following QS administration in study volunteers undergoing hysterectomies (Bhatt et al., 1980; el-Kady et al., 1991; Laufe et al., 1996; Merchant et al., 1995; Zipper et al., 1970) showed that the endometrium rapidly returned to normal after instillation of quinacrine. This was further confirmed with post-QS sonographic studies (Ferreira et al., 2003), post-administration biopsies (Lu et al., 2003), and also by uterine hysteroscopy following QS (El Sahwi et al., 1992, 2003).

These studies showed that tissue damage to the human endometrium occurs immediately after quinacrine administration, but that the effect is transient and the uterus rapidly returns to normal, usually within two menstrual cycles, with no chronic inflammation or persistent necrosis being seen in the fallopian tubes or uterus. Permanent changes were limited to specialized cells of the fallopian tube, and lumen closure resulting from the development of collagenous scar tissue was limited to approximately 2–3 mm of the intramural portion of the tube (Ferreira et al., 2003; Zipper et al., 1970). None of the lesions seen in the rat CaBio were observed in any of these studies, and none of the collagenous scar tissue seen in women was seen in the treated rats.

5. Conclusion

The weight of evidence from rodent studies, mechanistic investigations, human clinical observations, and epidemiology studies supports the conclusion that the mode of action leading to the tumors seen in the rat CaBio was necrosis and compensatory cell proliferation in the presence of chronic inflammation of the reproductive tract, brought about by the high, toxic doses of quinacrine-plus-methylcellulose. Tumors were not produced in the absence of these chronic toxicities. Based on the different mode of quinacrine administration (pellets instead of methylcellulose slurry) and the absence of chronic toxicity and tumors in women receiving QS, it can be concluded that the mode of action of tumor induction in the rat is not relevant to its use in women undergoing permanent contraception with quinacrine. This conclusion is supported by the human epidemiology studies that have demonstrated no increase in reproductive tract tumors in women who have received QS treatment compared to women using other forms of contraception.

Funding source

International Services Assistance Fund (ISAF) sponsored this research. ISAF provided editorial and technical support during the article's preparation, and suggested the journal for potential publication.

Conflict of interest

The authors declare that this work has not been published previously, nor is it under consideration for publication elsewhere. All authors contributed to writing and/or editing sections of this article and approve its submission for publication. Dr. McConnell is an unpaid science advisor to ISAF and therefore has no conflict of interest. Dr. Lippes has been the principal investigator on the Phase I and Phase III studies. Roger Growe, and Drs. Haseman, Luster and Zeiger are paid consultants to ISAF.

Acknowledgments

The authors are grateful to Family Health International, the sponsor of the rodent carcinogenesis studies, for providing the original laboratory reports and other information related to the conduct of the studies. Drs. Patricia Fail and Carol Danielson's comments and suggestions were very useful and are greatly appreciated. The authors also want to acknowledge the untiring support of Margaret Miller Growe, Vice President, ISAF, for her encouragement and behind-the-scenes help in assembling the material for this manuscript, and skillful and constructive comments.

References

Aggarwal, B.B., Shishodia, S., Sandur, S.K., Pandey, M.K., Sethi, G., 2006. Inflammation and cancer: how hot is the link? Biochem. Pharmacol. 72, 1605–1621. http://dx.doi.org/10.1016/j.bcp.2006.06.029.

Arnott, C.H., Scott, K.A., Moore, R.J., Hewer, A., Phillips, D.H., Parker, P., Balkwill, F.R., Owens, D.M., 2002. Tumour necrosis factor-alpha mediates tumour promotion via a PKC alpha- and AP-1-dependent pathway. Oncogene 21, 4728–4738. http://dx.doi.org/10.1038/sj.onc.1205588.

Ashby, J., Tinwell, H., Gulati, D., Heddle, J.A., 1990. Overview of the study in relation to protocol design for the rodent bone-marrow micronucleus assay. Mutat. Res. 234, 223–248.

Balkwill, F., Charles, K.A., Mantovani, A., 2005. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 7, 211–217. http://dx.doi.org/10.1016/j.ccr.2005.02.013.

Bhatt, R.V., Aparicio, A., Laufe, L.E., Parmley, T., King, T.M., 1980. Quinacrine-induced pathologic changes in the fallopian tube. Fertil. Steril. 33, 666–667.

Blake, D.A., Dubin, N.H., Diblasi, M.C., Parmley, T.H., King, T.M., 1983. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 71–88.

Cancel, A.M., Dillberger, J.E., Kelly, C.M., Bolte, H.F., Creasy, D.M., Sokal, D.C., 2010. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 156–165.

Cancel, A.M., Smith, T., Rehkemper, U., Dillberger, J.E., Sokal, D., McClain, R.M., 2006. A one-year neonatal mouse carcinogenesis study of quinacrine dihydrochloride. Int. J. Toxicol. 25, 109–118. http://dx.doi.org/10.1080/10915810600605773.

Clarke, J.J., Sokal, D.C., Cancel, A.M., Campen, D.B., Gudi, R., Wagner, V.O., San, R.H., Jacobson-Kram, D., 2001. Re-evaluation of the mutagenic potential of quinacrine dihydrochloride dihydrate. Mutat. Res. 494, 41–53.

Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860–867. http://dx.doi.org/10.1038/nature01322.

Dubin, N.H., Parmley, T.H., Ghodgaonkar, R.B., Strandberg, J.D., Rosenshein, N.B., King, T.M., 1984. Effect of intrauterine administration of tetracyclines on cynomolgus monkeys. Contraception 29, 561–571.

Ehsanian, R., Van Waes, C., Feller, S.M., 2011. Beyond DNA binding – a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. Cell Commun. Signal. 9, 13. http://dx.doi.org/10.1186/1478-811X-9-13.

el-Kady, A.A., Mansy, M.M., Nagib, H.S., Kessel, E., 1991. Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. Adv. Contracept. 7, 1–9.

El Sahwi, S., Kamel, M., el Faham, M., el Makhzangy, I., 2003. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization: results in 180 women. Int. J. Gynaecol. Obstet. 83 (Suppl. 2), S101–S106.

El Sahwi, S., Kamel, M., Haiba, N., Osman, M., 1992. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization. Adv. Contracept. Deliv. Syst. 8, 151–159.

Fail, P.A., Martin, P., Sokal, D., 2000. Comparative effects of quinacrine and erythromycin in adult female rats: a nonsurgical sterilization study. Fertil. Steril. 73, 387–394.

Feldblum, P.J., Wheeless, A., Trujillo, V., Guzman, S., Halpern, V., Sokal, D.C., 2012. Pelvic surgery and hospitalization among Chilean women after nonsurgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 86, 106–109. http://dx.doi.org/10.1016/j.contraception.2011.11.072.

Ferguson, L.R., Denny, W.A., 2007. Genotoxicity of non-covalent interactions: DNA intercalators. Mutat. Res. 623, 14–23.

Ferreira, C.R., Magalhães, D.R., Ferreira, D.C., Hanan, M.Z., Camargos, A.F., 2003. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women. Int. J. Gynaecol. Obstet. 83 (Suppl. 2), S59–S66.

Fisher, R.A., 1954. Statistical Methods for Research Workers, 12th ed. Oliver and Boyd Ltd, Edinburgh and London.

Flammang, T.J., von Tungeln, L.S., Kadlubar, F.F., Fu, P.P., 1997. Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Regul. Toxicol. Pharmacol. 26, 230–240. http://dx.doi.org/10.1006/rtph.1997.1125.

Glomski, C.A., Chao, C.F., Zuckerman, G.B., 1982. Haemolytic anaemia in rhesus monkeys induced by methylcellulose. Lab. Anim. 16, 310–313.

Growe, R.G., Luster, M.I., Fail, P.A., Lippes, J., 2013. Quinacrine-induced occlusive fibrosis in the human fallopian tube is due to a unique inflammatory response and modification of repair mechanisms. J. Reprod. Immunol. 97, 159–166. http://dx.doi.org/10.1016/j.jri.2012.12.003.

Hall, C.E., Hall, O., 1962. Glomerulonephritis and hypertension produced by parenteral administration of methylcellulose. Am. J. Pathol. 40, 167–183.

Hart, J.W., Hartley-Asp, B., 1983. Induction of micronuclei in the mouse. Revised timing of the final stage of erythropoiesis. Mutat. Res. 120, 127–132.

Hitotsumachi, S., Kimura, Y., Nakajima, Y., Hayashi, M., Ishidate Jr., M., 1990. Micronucleus test on quinacrine dihydrochloride in mice: a comparison of dosage regimens. Mutat. Res. 234, 141–145.

Houghton, J., Morozov, A., Smirnova, I., Wang, T.C., 2007. Stem cells and cancer. Semin. Cancer Biol. 17, 191–203. http://dx.doi.org/10.1016/j.semcancer.2006.04.003.

ICH. Guidance for Industry: S1C(R2) Dose Selection for Carcinogenicity Studies, 2008. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1C_R2/Step4/S1C_R2__Guideline.pdf>.

Jenssen, D., Ramel, C., Göthe, R., 1974. The induction of micronuclei by frameshift mutagens at the time of nucleus expulsion in mouse erythroblasts. Mutat. Res. 26, 553–555.

King, T.M., Dubin, N.H., Blake, D.A., Parmley, T.M., 1983. Quinacrine hydrochloride: future research. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 138–140.

Kirkland, D., Aardema, M., Henderson, L., Müller, L., 2005. Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens I. Sensitivity, specificity and relative predictivity. Mutat. Res. 584, 1–256. http://dx.doi.org/10.1016/j.mrgentox.2005.02.004.

Krishnaja, A.P., Chauhan, P.S., 2000. Quinacrine dihydrochloride, the non-surgical female sterilant induces dicentrics, rings, and marker chromosomes in human peripheral blood lymphocytes treated in vitro: a preliminary report. Mutat. Res. 466, 43–50.

Kundu, J.K., Surh, Y.-J., 2005. Breaking the relay in deregulated cellular signal transduction as a rationale for chemoprevention with anti-inflammatory phytochemicals. Mutat. Res. 591, 123–146. http://dx.doi.org/10.1016/j.mrfmmm.2005.04.019.

Laufe, L.E., Sokal, D.C., Cole, L.P., Shoupe, D., Schenken, R.S., 1996. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception 54, 181–186.

Lippes, J., Brar, M., Gerbracht, K., Neff, P., Kokkinakis, S., 2003. An FDA phase I clinical trial of quinacrine sterilization (QS). Int. J. Gynaecol. Obstet. 83 (Suppl. 2), S45–S49.

Lu, W., Zhu, J., Zhong, C., Zhao, Y., 2003. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province. China. Int. J. Gynaecol. Obstet. 83 (Suppl. 2), S51–S58.

Machado, E., Lozzio, B.B., Lew, V., 1966. Erythrocyte destruction induced by methylcellulose. Arch. Pathol. 82, 590–595.

Maier, P., Schmid, W., 1975. The non-induction of micronuclei by quinacrine. Mutat. Res. 30, 299–301.

Mantovani, A., 2005. Cancer: inflammation by remote control. Nature 435, 752–753. http://dx.doi.org/10.1038/435752a.

Matés, J.M., Segura, J.A., Alonso, F.J., Márquez, J., 2008. Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. Arch. Toxicol. 82, 273–299. http://dx.doi.org/10.1007/s00204-008-0304-z.

McClain, R.M., Keller, D., Casciano, D., Fu, P., MacDonald, J., Popp, J., Sagartz, J., 2001. Neonatal mouse model: review of methods and results. Toxicol. Pathol. 29 (Suppl.), 128–137.

McConnell, E.E., Lippes, J., Growe, R.G., Fail, P., Luster, M.I., Zeiger, E., 2010. An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats". Regul. Toxicol. Pharmacol. 56, 166–173. http://dx.doi.org/10.1016/j.yrtph.2009.12.007.

Merchant, R.N., Prabhu, S.R., Kessel, E., 1995. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. Int. J. Fertil. Menopausal Stud. 40, 47–54.

O'Byrne, K.J., Dalgleish, A.G., 2001. Chronic immune activation and inflammation as the cause of malignancy. Br. J. Cancer 85, 473–483. http://dx.doi.org/10.1054/bjoc.2001.1943.

Obara, S., Muto, H., Kokubo, H., Ichikawa, N., Kawanabe, M., Tanaka, O., 1992. Primary dermal and eye irritability tests of hydrophobically modified hydroxypropyl methylcellulose in rabbits. J. Toxicol. Sci. 17, 21–29.

OECD, Test No. 451: Carcinogenicity Studies. Paris, France: Organisation for Economic Co-operation and Development, 2009. <http://www.oecd-ilibrary.org/docserver/download/9745101e.pdf?expires=1407257937&id=id&accname=guest&checksum=F46C0858CDBAD29F2046E8AC4FE8DD18>.

OECD, Series on Testing and Assessment No. 116. Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453. First Edition Including the General Introduction and the Section on Dose Selection. Paris, France: Organisation for Economic Co-operation and Development, 2010. <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)47&doclanguage=en>.

Pfrimmer, W., Joyce, R.A., Turner, A.R., Boggs, D.R., 1978. Kinetics of the development of methylcellulose-induced hepatic hematopoiesis in adult mice. Blood 51, 611–622.

Rhomberg, L.R., Baetcke, K., Blancato, J., Bus, J., Cohen, S., Conolly, R., Dixit, R., Doe, J., Ekelman, K., Fenner-Crisp, P., Harvey, P., Hattis, D., Jacobs, A., Jacobson-Kram, D., Lewandowski, T., Liteplo, R., Pelkonen, O., Rice, J., Somers, D., Turturro, A., West, W., Olin, S., 2007. Issues in the design and interpretation of chronic toxicity and carcinogenicity studies in rodents: approaches to dose selection. Crit. Rev. Toxicol. 37, 729–837. http://dx.doi.org/10.1080/10408440701524949.

Schuler, M., Gudi, R., Cheung, J., Kumar, S., Dickinson, D., Engel, M., Szkudlinska, A., Colman, M., Maduka, N., Sherman, J., Thiffeault, C., 2010. Evaluation of phenolphthalein, diazepam and quinacrine dihydrochloride in the in vitro mammalian cell micronucleus test in Chinese hamster ovary (CHO) and TK6 cells. Mutat. Res. 702, 219–229. http://dx.doi.org/10.1016/j.mrgentox.2010.04.004.

Sokal, D.C., Dabancens, A., Guzman-Serani, R., Zipper, J., 2000. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil. Steril. 74, 169–171.

Sokal, D.C., Hieu, D.T., Loan, N.D., Hubacher, D., Nanda, K., Weiner, D.H., Vach, T.H., 2008. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. Contraception 78, 66–72. http://dx.doi.org/10.1016/j.contraception.2008.02.011.

Sokal, D.C., Vach, T.H., Nanda, K., McCann, M.F., Weiner, D.H., Drobnes, C., Rochanawutanon, M., Duc, N.B., Loan, N.D., 2010. Quinacrine sterilization and gynecologic cancers: a case–control study in northern Vietnam. Epidemiology 21, 164–171. http://dx.doi.org/10.1097/EDE.0b013e3181cb41c8.

Sokal, R.R., Rohlf, F.J., 1981. Biometry: the Principles and Practice of Statistics in Biological Research. Freeman, New York.

Tave, A.K., Pezzullo, J.C., Li, J., Kardia, S., Jones, J.K., Kamani, S., 2012. Comparison of long term cancer risk between Vietnamese women undergoing QS vs. IUD contraceptive procedures. Poster, presented at the 7th Asian Conference on Pharmacoepidemiology, Bengaluru, India.

Teoh, T.B., 1961. The effects of methyl cellulose in rats with special reference to splenomegaly, anaemia and the problem of hypersplenism. J. Pathol. Bacteriol. 81, 33–44.

Wallace, D.J., 1989. The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. Semin. Arthritis Rheum. 18, 282–296.

Zaneveld, L.J., Goldsmith, A., 1984. Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception 30, 161–167.

Zeiger, E., 1998. Identification of rodent carcinogens and noncarcinogens using genetic toxicity tests: premises, promises, and performance. Regul. Toxicol. Pharmacol. 28, 85–95. http://dx.doi.org/10.1006/rtph.1998.1234.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ. Mol. Mutagen. 11 (Suppl. 12), 1–157.

Zipper, J.A., Stachetti, E., Medel, M., 1970. Human fertility control by transvaginal application of quinacrine on the fallopian tube. Fertil. Steril. 21, 581–589.

Journal of Reproductive Immunology 97 (2013) 159–166

Contents lists available at SciVerse ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jreprimm

Review

Quinacrine-induced occlusive fibrosis in the human fallopian tube is due to a unique inflammatory response and modification of repair mechanisms

Roger G. Growe[a], Michael I. Luster[b,*], Patricia A. Fail[c], Jack Lippes[d]

[a] *International Federation for Family Health, Chapel Hill, NC, USA*
[b] *M.I. Luster Associates, Morgantown, WV, USA*
[c] *Patricia Fail Associates, Iola, KS, USA*
[d] *University of Buffalo, 31 Hampton Hill Dr., Buffalo, NY, USA*

ARTICLE INFO

Article history:
Received 2 October 2012
Received in revised form
11 December 2012
Accepted 13 December 2012

Keywords:
Quinacrine
Fallopian tube occlusion
Contraception
Uterotubal junction
Pro-inflammatory cytokines
Acute inflammation
Fibrotic response
Acetylcholine receptors
Cell adhesion
Neisseria gonorrhoeae
Chlamydia trachomatis

ABSTRACT

Quinacrine has been widely used in treatment of parasitic diseases such as malaria and giardiasis, and in the treatment of autoimmune diseases. Quinacrine has also been used as an effective substitute for surgical contraception by causing occlusion of the fallopian tube. This minimally invasive treatment protocol involves intrauterine insertion of the drug in the form of pellets and has been studied in humans in a number of countries, including the United States. Despite its development in the 1970s, the cellular and molecular events induced by quinacrine in the human fallopian tube have not been described. Here we describe a plausible mechanism for quinacrine action in the fallopian tube. This is manifested as an acute pro-inflammatory response in the uterus and fallopian tube, characterized by loss of epithelial cell adhesion. This response relies on properties of gated channels found on the surface of epithelial cells in the reproductive tract. While the uterus returns to normal, the inflammatory response affects the uterotubal junction and transmural segment of the human fallopian tube, and initiates formation of mature collagen in the lumen of the fallopian tube, resulting in its permanent occlusion. The response within the fallopian tube appears similar to the protective mechanisms that have evolved in women to minimize the likelihood of systemic infection from *Neisseria gonorrhoeae*, and to some extent from *Chlamydia trachomatis*. This review could assist in development of experimental models used in investigating the mechanisms of fibrotic responses in humans as well as development of techniques for permanent non-surgical female contraception.

1. Introduction

Quinacrine hydrochloride (quinacrine, QC), when formulated into pellets and inserted into the uterus of women, causes fibrotic occlusion of the fallopian tubes and can be used as a substitute for surgical contraception. The currently recommended clinical protocol for this permanent female contraceptive method is two insertions, one month apart, of 252 mg of quinacrine hydrochloride in the form of seven pellets. Except for occlusion of the fallopian tubes, the reproductive organs return to normal (Merchant et al., 1995). Efficacy after one year is >99% and compares favorably to other reported efficacy rates for approved contraceptive methods (Hatcher et al., 2012). By 1996, over 100 000 women globally had undergone this procedure (Kessel, 1996) and its use has continued in many countries. Long-term follow-up studies suggest that the method is

* Corresponding author at: M.I. Luster Associates, 39 Quail Road, Morgantown, WV 26508, USA. Tel.: +1 304 216 5516; fax: +1 304 212 4701.
E-mail address: miklus22@comcast.net (M.I. Luster).

0165-0378/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jri.2012.12.003

safe (Sokal et al., 2008, 2010) and effective (Alpizar, 2003; Bilgrami and Shah, 2003). In over 150 000 women who have undergone the procedure, only two have reported a severe allergic response (both cases successfully treated) with no other serious adverse events reported. Ectopic pregnancies following quinacrine have been reported to range from 0.26 to 0.60 per 1000 individuals (Sokal et al., 2000; Hieu and Luong, 2003; Zipper and Trujillo, 2003), which is similar to the ectopic pregnancy rates among women who use intrauterine devices or tubal ligation for contraception. All three interventions result in ectopic pregnancy rates considerably lower than in women using no contraceptive method.

In addition to quinacrine (Zipper et al., 1973), a number of drugs have been screened for their potential use as a minimally invasive, nonsurgical procedure for tubal closure because of their effectiveness as a sclerosant. Studies in animal models with tetracycline (Dubin et al., 1984a,b), erythromycin (Fail et al., 2000), and polidocanol (Jensen et al., 2004) have shown promise. However, studies conducted with tetracycline and erythromycin have shown that the failure rate following intrauterine administration is high, exceeding 50% in the case of tetracycline (Mullick et al., 1987), and 36% for erythromycin (Bairagy and Mullick, 2004).

Laboratory studies to identify sclerosing agents that produce tubal occlusion have been limited by lack of experimental models that clearly mimic the response that occurs in humans, as suggested by studies in rats, pigs and monkeys (King et al., 1983; Dubin et al., 1982; Zaneveld and Goldsmith, 1984; Fail et al., 2000; Jensen et al., 2004; Cancel et al., 2010). Many of these sclerosing agents produce histological changes but do not produce tubal occlusion. In Cynomolgus monkeys, intrauterine administration of tetracycline or doxycycline, like quinacrine, produces morphologic damage of the uterine lining and intramural section of the tube, including necrosis, inflammation and fibrosis (Dubin et al., 1982, 1984b). The latter is consistent with the type of damage which may lead to tubal closure, but does not necessarily mean that closure will occur. In a recent 2-year rat bioassay where rats received intrauterine quinacrine administration (Cancel et al., 2010), uterine horns were specifically examined for fibrosis and lumen closure, and no dose-related increase in fibrosis was found nor lumen closure reported; the oviduct appeared unaffected.

While the mechanisms of action of several uses of quinacrine have recently been reported (Gurova, 2009), and the extensive use of quinacrine has made it one of the most widely studied drugs in humans (Ehsanian et al., 2011), little is known regarding its mechanism of action in the fallopian tube. Recent cellular and molecular studies have provided insights into this process. This review, which summarizes our current understanding of the mechanism of action of quinacrine in the human fallopian tube, may help resolve some of the questions raised during the development of this drug for nonsurgical sterilization. In brief, the composite studies suggest that quinacrine induces a species- and tissue-specific response in the uterotubal junction and transmural segment of the human fallopian tube, causing disruption of cell adhesion and an acute pro-inflammatory and pro-fibrotic cytokine cascade. This is followed by a higher order primate-specific and tissue-specific modification in the healing mechanisms that produces tubal occlusion by replacing the lumen with mature collagen, using the same mechanisms that have evolved in protecting women from systemic infection from *Neisseria gonorrhoeae* and, to some degree, *Chlamydia trachomatis*.

2. Quinacrine response in the human fallopian tube

In women, quinacrine is administered *via* the uterus (4 mg/kg body weight), and the target organ (fallopian tube) is exposed to only a small percentage of the administered dose (estimated at <5% of the total administered dose). The result is the formation of mature collagenous fibrotic material replacing the lumen and limited to the uterotubal junction and transmural segment of the fallopian tube (Fig. 1A). After one year, ≈90% of cases, a single application of ∼250 mg quinacrine hydrochloride pellets in the human uterus results in complete occlusion of both fallopian tubes and >99% following a second administration.

While acute inflammation is associated with this process in the uterus, the pathology is quickly resolved without any loss of organ function. The sequence of histopathological changes following intrauterine administration of quinacrine in women has been described in detail by el-Kady et al. (1991); within 10 days, necrosis of the epithelial lining of the fallopian tube occurs, along with an acute inflammatory reaction. This is followed by absorption of the inflammatory cellular exudate, progressive fibrosis with partial or almost complete occlusion of the lumen, and failure of regeneration of the epithelial lining. Occlusion is characterized by obliteration of the lumen by mature fibrous material and the absence of epithelium. The occlusion of the fallopian tube lumen with dense collagenous material is easily visualized by hysteroscopic video, as seen in the photograph taken of the uterotubal junction in Fig. 1B (Lu et al., 2003) and by ultra-sonography (Ferreira et al., 2003). Except for tubal occlusion, all other macro and microscopic effects are reversed.

The changes following exposure of the fallopian tube to quinacrine show similarities to observations reported in women who underwent surgical procedures for infertility and were found to have uterotubal obstruction (Fortier and Haney, 1985). Of 42 women studied, the most frequent lesion encountered was obliterative fibrosis (38.1%), characterized by complete obliteration of the tubal lumen with no evidence of other pathology. The lumen was replaced by densely collagenous connective tissue with no epithelium visible. Fibrosis was medial to the inner longitudinal muscle layer with minimal involvement of the muscle directly. The obstruction involved the entire transmural segment uniformly (including the uterotubal junction). Fortier and Haney further observed that in almost all instances the obstructing lesion began within the transmural portion of the oviduct and extended a variable distance into the isthmic segment but not beyond the ampullary–isthmic junction. These findings suggested that the process is initiated in the uterus, and fibrosis represents a response to injury of the transmural and isthmic segments of the tube.

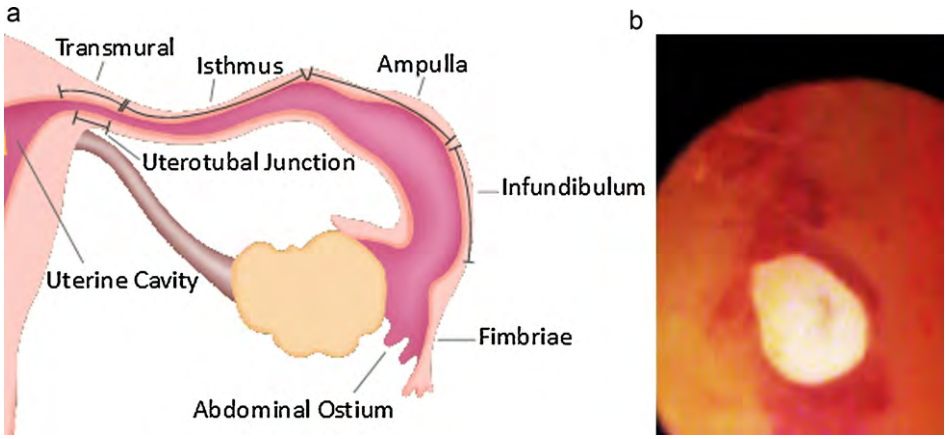


Fig. 1. (A) Fallopian tube. (B) Still photo of an occluded uterotubal junction taken from the perspective of the uterine cavity using a video camera attached to a hysteroscope.
Reprinted from Lu et al. (2003), Copyright 2003; with permission from Elsevier.

Merchant et al. (1995) studied 33 women awaiting hysterectomy for nonmalignant conditions who had received intrauterine quinacrine at doses of either 252 mg ($n = 10$) or 324 mg ($n = 23$), at least 6 weeks prior to surgery but not longer than 20 weeks prior. The key findings were that tubal closures were most directly related to quinacrine dose and to a lesser extent the time interval between insertion and hysterectomy. Only 55% of intramural tubal segments showed evidence of closure at the low dose, compared to 100% at the high dose. Histological changes were confined to the fallopian tube and sections through the regenerated endometrium, cervix and myometrium of the uterus were normal, confirming that the chemical has no lasting effect on these structures. No adhesions or other abnormal changes (including fibrosis) were detected in the uterus or cervix.

3. The fibrotic response within the fallopian tube

Wound healing is a dynamic process consisting of hemostasis, inflammation, proliferation, and remodeling. Remodeling of damaged tissues, as occurs with quinacrine, requires that each phase must occur in a precise and regulated manner. The events involved in tubal closure by quinacrine are initially associated with epithelial cell damage and an acute inflammatory response in the specialized tissue of the transmural portion of the fallopian tube. These processes damage the epithelium as well as the underlying stromal tissue. Over approximately three months, this early reaction undergoes a tissue remodeling and repair process resulting in a collagenous connective tissue plug that fills the lumen, and permanently occludes the fallopian tube (Merchant et al., 1995; el-Kady et al., 1991). Successful occlusion of the tube has been predicted to depend on the nature and duration of exposure to the causative agent, on the extent of tissue destruction, and on the type of tissue injured (Eddy and Pauerstein, 1983). Although usually beneficial, the healing process can become pathogenic if it continues unchecked, resulting in substantial remodeling of the extracellular matrix and formation of permanent scar tissue. Chronic fibrosis is associated with several diseases (Wynn, 2007). However, instead of a poorly regulated wound healing response or an incomplete resolution of the healing process, quinacrine produces a self-confined fibrotic response within the fallopian tube.

4. The immune system and the fallopian tube

The human fallopian tube is lined by columnar ciliated cells and secretory cells with microvilli which function as a channel and storage organ for spermatozoa; a collecting vessel for oocytes released from the ovaries; the site of sperm capacitation, fertilization, and zygote formation; and as a means for transporting the early embryo to the uterus. The female reproductive system has evolved to address various threats to survival by developing site-specific immunoregulatory mechanisms. For example, the upper female genital tract has a powerful innate inflammatory response that can rapidly protect the reproductive organs from pathogenic challenge, and prevent a pathogen from ascending the fallopian tube to infect the ovary and the peritoneum while maintaining tissue function and integrity (Quayle, 2002).

Epithelial cells and stromal fibroblasts are the primary sources of inflammatory mediators in the human fallopian tube and have evolved unique, site-specific mechanisms for recognizing viral and bacterial infection. In this respect, each segment, *i.e.* the isthmus, isthmic–ampullary junction (or middle section), ampulla and fimbriae, could be considered anatomically and immunologically distinct (Ochiel et al., 2008). Studies of the combined morphological and ultrastructural features of the epithelial lining along the length of the fallopian tube substantiate the concept of functional differentiation among these segments (Crow et al., 1994).

Human fallopian tube epithelial cells secrete a broad spectrum and unique pattern of proinflammatory cytokines and chemokines from the apical and basolateral compartments. These include, among others, interleukin (IL)-8, IL-6, monocyte chemoattractant protein-1 (MCP-1), granulocyte–macrophage colony-stimulating factor (GM-CSF), TNF-α and macrophage inflammatory peptide-1β

(MIP-1β) (Fahey et al., 2005). IL-1 is also expressed by epithelial cells in the human fallopian tube (Hess et al., 2009). Toll-like receptors (TLRs) and their attendant cooperating receptors, which initiate proinflammatory responses to pathogen-associated molecular patterns (PAMPs) and other agonists, are readily expressed in the reproductive tract (Parker et al., 2007; Fichorova et al., 2002).

In tissues of the human female reproductive tract, quantitative analysis of TLR2 mRNA levels revealed that the highest expression occurs in fallopian tube and cervical tissues, followed by endometrium and ectocervix (Pioli et al., 2004). In contrast to TLR2, TLR4 expression declined progressively along the tract, with highest expression in the upper tissues (fallopian tubes and endometrium), followed by the cervix and ectocervix. In addition to mRNA, protein expression of TLR2 and TLR4 was also documented in these tissues (Pioli et al., 2004). Taken together, these data suggest that TLRs are differentially expressed in distinct segments of the female reproductive tract and that inflammation within the tract is highly regulated. Proinflammatory cytokines are also important for initiating a fibrotic response. For instance, there are many examples showing that TNF-α induces fibroblast proliferation and collagen production, much of which occurs through production of plasminogen activator inhibitor (PAI-1). IL-1 has also been shown to be profibrotic by stimulating TGF-α and fibroblast growth factor (FGF) synthesis production of collagen and fibronectin (Mutsaers et al., 2004).

5. Quinacrine and proinflammatory cytokine secretion

Levels of the proinflammatory cytokines, including TNF-α and IL-1β, increase after quinacrine instillation into the pleural cavity (Agrenius et al., 1994). Within 4 h after a single administration of 150 mg of quinacrine, injected interstitially into C6 glioma cells implanted in the subcutaneous tissue of Wistar rats, a temporal increase in TNF-α can be detected in tumor cell homogenates. Similarly, an increase in proinflammatory cytokines is detected in cell homogenates 24 h after quinacrine injection, independent of cell toxicity (Sotelo et al., 2004). In human endothelial cells, chloroquine (150 μM) increases the production of IL-1α. While LPS (5 μg/ml), by itself, significantly increased the production of IL-1α, when it is combined with chloroquine, a synergistic increase is found. IL-1α production is associated with the direct loss of endothelial cells similar to that observed in the human fallopian tube. After 24 h of exposure, 150 μM of the drug causes significant IL-1α production, as well as the detachment of about 50% of the cells (Potvin et al., 1997).

A number of drugs and agents, including tetracycline, minocycline, *Corynebacterium parvum*, talc, bleomycin, nitrogen mustard, doxorubicin, radioactive colloid gold and quinacrine, have been used to decrease or prevent fluid accumulation in the pleural cavity for treatment of malignant pleural effusion. While each has demonstrated its own unique properties, like quinacrine, in all cases successful treatment entails a robust intrapleural inflammatory reaction, tissue remodeling and fibrin deposition, resulting in the adhesion of the visceral to the parietal pleura and pleurodesis (Kroegel and Antony, 1997). In fact, quinacrine has been used over the last four decades for pleurodesis in Scandinavian countries (Dikensoy and Light, 2005).

6. Similarities between protection from systemic *N. gonorrhoeae* infection and quinacrine administration

Worldwide, fibrotic obstruction of the fallopian tube is a leading cause of infertility in women, and can be attributed, to a large degree, to two pathogens: *N. gonorrhoeae*, and *C. trachomatis*. It has been suggested that to protect against the ascension of *N. gonorrhoeae* into the abdominal cavity and protect women from systemic infection, the fallopian tube undergoes rapid cell exfoliation (Muenzner et al., 2010) and the induction of an acute pro-inflammatory and pro-fibrotic response culminates in tubal occlusion (Stephens, 2003; McGee et al., 1999). This protective response has similar biological processes to the action of quinacrine.

The response to gonorrhea may have disseminated through positive selection across human populations, and studies indicate that the point in the phylogenic tree at which susceptibility to gonococcal infection commences is between baboons and chimpanzees (or between monkeys and apes) (McGee et al., 1990). Thus, while humans and higher order non-human primates are susceptible to experimental mucosal infection, these pathogens attach very infrequently or not at all to the mucosa of rabbit, porcine, or bovine oviduct, and no histological damage occurs. Taken together, host specificity appears to be determined, at least in part, by the species differences in the ability of the organisms to attach to and damage the genital mucosa (Johnson et al., 1977).

The occlusion of the fallopian tube is the final stage of an elaborate progression of organ-specific pathological and repair mechanisms in protection from systemic infection in the upper reproductive tract. The human fallopian tube opens into the abdominal cavity, making it the most available and susceptible pathway for dissemination of pathogens directly into the peritoneum. Occlusion of the fallopian tube may confer a distinct survival advantage, as fallopian tube occlusion can prevent pathogens from ascending the tube into the peritoneum, thus preventing systemic infection or death. The downside, by comparison, is minimal. Redundancy allows the possibility of the uninfected fallopian tube to maintain fertility. In the worst case, where both fallopian tubes are occluded, mothers can continue to nurture and raise their children to reproductive age.

7. Mechanistic basis for occlusion by *N. gonorrhoeae* and *C. trachomatis*

N. gonorrhoeae and *C. trachomatis* also have developed an extensive repertoire of pathogenic mechanisms by which they resist the immune mechanisms of the human reproductive tract. Rapid epithelial cell exfoliation (cell sloughing) is a survival mechanism used in several organs to effectively clear infected cells and

Gram-negative bacteria from the tissue (Mulvey et al., 2000). In the fallopian tube, *N. gonorrhoeae* blocks the shedding of infected epithelial cells by stimulating integrin activation (Muenzner et al., 2010). By controlling cell adhesion processes, pathogen-infected cells cannot be shed and pathogen colonization is assured. During infection with *N. gonorrhoeae* or *C. trachomatis*, the human fallopian tube undergoes an inflammatory response prior to collagen depositing (Edwards and Apicella, 2004; Patton et al., 1989).

The epithelial layer and the mucosal surface act as physical and biological barriers against microbial invasion which is maintained by tight cell–cell junctions (TJ) and the basement membrane. The pathogen circumvents this barrier by expressing lipooligosaccharide (LOS) which induces epithelial cells to express tumor necrosis factor (TNF)-α that, in turn, causes impaired TJ function in a number of epithelial and endothelial cell lines (Capaldo and Nusrat, 2009). The early response involves cell detachment and a transient but robust inflammatory response characterized by pro-inflammatory cytokine secretion, such as TNF-α and IL-1 (McGee et al., 1999). In organ explant cultures, the levels of TNF-α are directly proportional to the loss of ciliated cells from the epithelium, which closely mimics the progression of gonococcal infection observed *in vivo* (McGee et al., 1999).

Because *C. trachomatis*, *N. gonorrhoeae* and quinacrine can each cause occlusion in the human fallopian tube, a comparison of *C. trachomatis* with *N. gonorrhoeae* is relevant to the mechanism of action of quinacrine proposed here. The differences are significant and instructive. Like *N. gonorrhoeae* (and quinacrine) the tissue damage induced by *C. trachomatis* infection occurs as an immune response to infection. In the case of *C. trachomatis*, the cytokine IL-1, induced by the presence of *C. trachomatis* has been shown to be the initiator of tissue damage and inflammation as well as the induction of the secondary cytokine IL-8, a potent neutrophil chemoattractant (Hvid et al., 2007). In *N. gonorrhoeae* both TNF-α and IL-1 are active initiators of tissue damage. Multiple infections of *C. trachomatis* are required for tubal scarring to occur (Paavonen and Eggert-Kruse, 1999). In *N. gonorrhoeae* a single untreated infection is sufficient. One study of *C. trachomatis* involving 1844 women concluded that, following primary infection, each reinfection of *C. trachomatis* roughly doubled the risk of tubal occlusion (Haggerty et al., 2010). *C. trachomatis* causes cell–cell attachment disruption of epithelial cells but not desquamation (Prozialeck et al., 2002). The response to *N. gonorrhoeae* is complete disruption of cell attachment and desquamation of the epithelium. *C. trachomatis* infection of the oviduct has been successfully studied in several species susceptible to the pathogen including pigs (Vanrompay et al., 2006), guinea pigs, mice (Su et al., 1997), and macaques (Patton et al., 1989, 1990, 1997). Conversely, like *Haemophilus influenzae*, *Moraxella catarrhalis*, and *N. meningitidis*, *N. gonorrhoeae* is a human-specific pathogen (Schmitter et al., 2004; Muenzner et al., 2010) and the chimpanzee (*Pan troglodytes*) is the only animal species other than humans in which localized urethral infections of 3–6 weeks in duration have been established (Arko, 1989).

8. Quinacrine disrupts cell adhesion

In most tissues, cell disruption with loss of adhesion properties occurs in response to cytotoxic chemicals or inflammation. In the bladder urothelium, procedures that efficiently induce cell removal are associated with an inflammatory response and prolonged cell desquamation, resulting in epithelial hyperplasia (Veranic et al., 2009). In the model for tubal closure by quinacrine proposed here, one of the earliest events following intrauterine quinacrine administration is sloughing of surface epithelial cells. *In vitro* studies with quinacrine in different cell models have shown that the drug commonly causes disruption of cell adhesion. For example, culturing rat hepatocytes with quinacrine at concentrations as low as 50 μM rapidly results in cell detachment (Leduc et al., 1981). Quinacrine at 10 μM also causes cell rounding, reduced cell size, blebbing and detachment in head and neck squamous cell carcinoma cells (Friedman et al., 2007). Quinacrine also induces cell detachment in porcine aortic endothelial cells. Prior to detachment, quinacrine causes the loss of monolayer integrity and the formation of intercellular gaps (Stuhlmeier, 2000).

The mechanism by which quinacrine disrupts cell adhesion may rely on properties of gated channels found on the cell surface of epithelial cells in the reproductive tract. In addition to neurons (Gotti and Clementi, 2004; Arias et al., 2006), acetylcholine receptors (AChRs), members of the Cys-loop superfamily of ligand-gated ion channels, are also expressed on the surface of endothelial, epithelial and immune cells (Wessler and Kirkpatrick, 2008). One of the important biological functions of non-neuronal AChRs is to allow for cell adhesion. The downstream targets of these AChRs include intercellular adhesion molecules, such as classical and desmosomal cadherins, and integrins, mediating keratinocyte adhesion to a substrate (Grando, 2006). Quinacrine can act as a noncompetitive inhibitor (NCI) for both the muscarinic acetylcholine receptor (mAChR) and the nicotinic acetylcholine receptor (nAChR). Yu et al. (2003) mapped the binding site for quinacrine in the open channel of the non-neuronal ACh receptor in cysteine-substituted mutants of the α subunit expressed with wild-type β, γ, and δ subunits. In an analysis of the mechanistic basis for the noncompetitive action of quinacrine and the kinetic changes in nAChRs at both the single-channel and macroscopic current levels, the main effect of quinacrine was a profound concentration-dependent decrease in both the frequency of opening events and the duration of clusters elicited by high acetylcholine concentrations (Spitzmaul et al., 2001).

Results from studies with smooth muscle cells isolated from guinea pig vas deferens and urinary bladder showed that quinacrine is also a potent Ca^{2+} channel blocker (Nagano et al., 1996), which regulates cell adhesion as well. The IC_{50} for quinacrine is about 1.2 μM, apparently lower than that reported for the inhibition of high-threshold voltage-dependent Ca^{2+} channel current in rat hippocampal neurons (30 μM), and slightly lower than that in guinea pig ventricular myocytes (6 μM). The inhibition of A-type K^+ current in melanotrophs and other membrane currents or channels in various cells requires higher concentrations

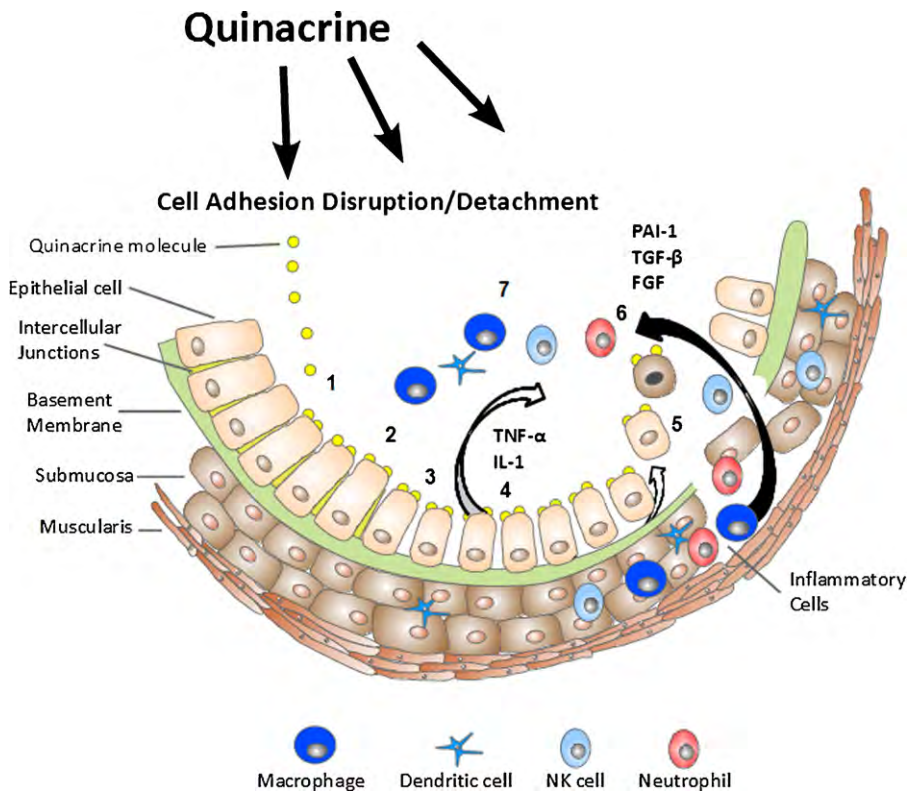


Fig. 2. Proposed mode of action for quinacrine in the fallopian tube. Cross-section of the fallopian tube and lumen showing the proposed mode of action of quinacrine-induced inflammatory response. (1) Dissolved, positively charged molecules of quinacrine bind to the extracellular domain and open channel of acetylcholine receptors on the surface of epithelial cells. (2) Quinacrine-bound acetylcholine receptors disrupt cell adhesion. (3) Epithelial cells shrink, round up and intercellular and cell matrix adhesion is disrupted. (4) Pro-inflammatory cytokines (TNF-α and IL-1) are expressed from the apical portion of the epithelial cells. (5) TNF-α and IL-1 induce epithelial cell sloughing and cell death through apoptosis. (6) Inflammatory cells and cytokines are released from the submucosa into the lumen, leading to the release of superoxides. (7) This response destroys mucosal cells, which leads to fibrosis and collagen formation. *Abbreviations*: PAI-1 = plasminogen activator inhibitor-1; TGF-β = transforming growth factor-β; FGF = fibroblast growth factors.

of quinacrine. The effect of quinacrine is apparently due to direct block of L-type Ca^{2+} channels from the outside. Not only Ca^{2+} channels, but also many other channels, including ligand-operated channels, are directly blocked by quinacrine, suggesting nonspecific effects of quinacrine on ion channels. Since internally applied quinacrine cannot reach the binding site in the Ca^{2+} channel, only protonated quinacrine in external solution can bind to the site from the outside (Nagano et al., 1996).

9. Summary

As depicted in Fig. 2, the events invoked in tubal closure by quinacrine are postulated to occur through disruption of cell adhesion and detachment of epithelial cells in the reproductive tract which, in turn, may rely on the ability of quinacrine to affect gated channels found on the cell surface. This event leads to an acute inflammatory response in the specialized tissue of the transmural portion of the fallopian tube, which damages the epithelium as well as the underlying stromal tissue. Over approximately three months, the tissue undergoes a remodeling and repair process, forming a collagenous connective tissue plug that fills the lumen and permanently occludes the fallopian tube. Successful occlusion of the tube can depend on the nature and duration of exposure, on the extent of tissue destruction and on the type of tissue injured. This model is based on the human response that prevents sexually transmitted infections, such as *N. gonorrhoeae* and *C. trachomatis*, from becoming systemic. Available data suggest that the effect on the fallopian tube is both tissue-specific and species-specific, at least for humans and certain higher order primates. The identification of a species/tissue-specific immune/inflammatory mechanism of quinacrine-induced fibrotic occlusion of the human fallopian tube answers many questions posed by investigators and healthcare providers, and challenges the basis for the assumptions used to rationalize dose selection and animal/organ model choices in studies of quinacrine in non-human species.

The authors hope this review will assist in the development of experimental models used in investigating the mechanisms of fibrotic responses in the human body as well as the development of techniques for permanent non-surgical female contraception.

Conflict of interest

The authors serve as scientific consultants for International Services Assistance Fund (ISAF). The authors have no financial or personal relationships with ISAF or other

organizations that inappropriately influenced (biased) their contribution to this work. The authors alone are responsible for the content and writing of this paper.

Authors' contribution

RGG and MIL initiated and designed the review, and drafted and revised the manuscript. PAF and JL reviewed and edited the manuscript.

Acknowledgements

The authors thank Ernest E. McConnell, DVM, MS (Path), DACVP, DABT, and Stephen D. Mumford, DrPH, for their advice and comments on the manuscript. R. Grant Steen, PhD, and Margaret Miller Growe are gratefully acknowledged for their editorial assistance in its preparation.

References

Agrenius, V., Gustafsson, L.E., Widström, O., 1994. Tumor necrosis factor-α and nitric oxide, determined as nitrite, in malignant pleural effusion. Respir. Med. 88, 743–748.

Alpizar, F., 2003. Quinacrine sterilization (QS) in Costa Rica: 694 cases. Int. J. Gynecol. Obstet. 83 (S2), S141–S145.

Arias, H.R., Bhumireddy, P., Bouzat, C., 2006. Molecular mechanisms and binding site locations for noncompetitive antagonists of nicotinic acetylcholine receptors. Int. J. Biochem. Cell Biol. 38, 1254–1276.

Arko, R.J., 1989. Animal models for pathogenic *Neisseria* species. Clin. Microbiol. Rev. 2 (Suppl.), S56–S59.

Bairagy, N.R., Mullick, B.C., 2004. Use of erythromycin for non-surgical female sterilization in West Bengal, India: a study of 790 cases. Contraception 69, 47–49.

Bilgrami, M., Shah, L., 2003. Marie Stopes Society, Pakistan: 1000 cases of quinacrine sterilization (QS). Int. J. Gynecol. Obstet. 83 (Suppl. 2), S125–S127.

Cancel, A.M., Dillberger, J.E., Kelly, C.M., Bolte, H.F., Creasy, D.M., Sokal, D.C., 2010. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 156–165.

Capaldo, C.T., Nusrat, A., 2009. Cytokine regulation of tight junctions. Biochim. Biophys. Acta 1788, 864–871.

Crow, J., Amso, N.N., Lewin, J., Shaw, R.W., 1994. Morphology and ultrastructure of fallopian tube epithelium at different stages of the menstrual cycle and menopause. Hum. Reprod. 9, 2224–2233.

Dikensoy, O., Light, R.W., 2005. Alternative widely available, inexpensive agents for pleurodesis. Curr. Opin. Pulm. Med. 11, 340–344.

Dubin, N.H., Parmley, T.H., Ghodgaonkar, R.B., Pharm, B., King, T.M., 1984a. Comparative effects of intrauterine instillation of analogues of quinacrine and tetracycline on uterine morphology in the rat. Contraception 29, 553–559.

Dubin, N.H., Parmley, T.H., Ghodgaonkar, R.B., Pharm, B., Strandberg, J.D., Rosenshein, N.B., King, T.M., 1984b. Effect of intrauterine administration of tetracycline on cynomolgus monkeys. Contraception 29, 561–571.

Dubin, N.H., Strandberg, J.D., Craft, C.F., Parmley, T.H., Blake, D.A., King, T.M., 1982. Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry, and hematology in cynomolgus monkeys. Fertil. Steril. 38, 741–747.

Eddy, C.A., Pauerstein, C.J., 1983. Anatomic and physiologic factors affecting the development of transcervical sterilization techniques. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 7–23.

Edwards, J.L., Apicella, M.A., 2004. The molecular mechanisms used by *Neisseria gonorrhoeae* to initiate infection differ between men and women. Clin. Microbiol. Rev. 17, 965–981.

Ehsanian, R., van Waes, C., Feller, S.M., 2011. Beyond DNA binding – a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. Cell Commun. Signal. 9, 13.

el-Kady, A.A., Mansy, M.M., Nagib, H.S., Kessel, E., 1991. Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. Adv. Contracept. 7, 1–9.

Fahey, J.V., Schaefer, T.M., Channon, J.Y., Wira, C.R., 2005. Secretion of cytokines and chemokines by polarized human epithelial cells from the female reproductive tract. Hum. Reprod. 20, 1439–1446.

Fail, P.A., Martin, P., Sokal, D., 2000. Comparative effects of quinacrine and erythromycin in adult female rats: a non-surgical sterilization study. Fertil. Steril. 73, 387–394.

Ferreira, C.R., Magalhães, D.R., Ferreira, D.C., Hanan, M.Z., Camargos, A.F., 2003. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women. Int. J. Gynecol. Obstet. 83 (Suppl. 2), S59–S66.

Fichorova, R.N., Cronin, A.O., Lien, E., Anderson, D.J., Ingalls, R.R., 2002. Response to *Neisseria gonorrhoeae* by cervicovaginal epithelial cells occurs in the absence of toll-like receptor 4-mediated signaling. J. Immunol. 168, 2424–2432.

Fortier, K.J., Haney, A.F., 1985. The pathologic spectrum of uterotubal junction obstruction. Obstet. Gynecol. 65, 93–98.

Friedman, J., Nottingham, L., Duggal, P., Pernas, F.G., Yan, B., Yang, X.P., Chen, Z., van Waes, C., 2007. Deficient TP53 expression, function, and cisplatin sensitivity are restored by quinacrine in head and neck cancer. Clin. Cancer Res. 13, 6568–6578.

Gotti, C., Clementi, F., 2004. Neuronal nicotinic receptors: from structure to pathology. Prog. Neurobiol. 74, 363–396.

Grando, S.A., 2006. Cholinergic control of epidermal cohesion. Exp. Dermatol. 15, 265–282.

Gurova, K., 2009. New hopes from old drugs: revisiting DNA-binding small molecules as anticancer agents. Future Oncol. 5, 1685–1704.

Haggerty, C.L., Gottlieb, S.L., Taylor, B.D., Low, N., Xu, F., Ness, R.B., 2010. Risk of sequelae after *Chlamydia trachomatis* genital infection in women. J. Infect. Dis. 201 (S2), S134–S155.

Hatcher, R.A., Trussell, J.S., Nelson, A.L., Cates, W., Kowal, D., Policar, M., 2012. Contraceptive Technology, 20th ed. Ardent Media, Inc., Beverly, MA.

Hess, A.P., Baston-Buest, D.M., Schanz, A., Hirchenhain, J., Bielfeld, P., Kruessel, J.S., 2009. Interleukin-1 system in the human fallopian tube – no spatial but a temporal regulation of mRNA and protein expression. Mol. Cell. Endocrinol. 303, 7–12.

Hieu, D.T., Luong, T., 2003. The rate of ectopic pregnancy for 24,589 quinacrine sterilization users compared to users of other methods and no methods in Vietnam. Int. J. Gynecol. Obstet. 83 (S2), S34–S35.

Hvid, M., Baczynska, A., Deleuran, B., Fedder, J., Knudsen, H.J., Christiansen, G., Birkelund, S., 2007. Interleukin-1 is the initiator of fallopian tube destruction during *Chlamydia trachomatis* infection. Cell Microbiol. 9, 2795–2803.

Jensen, J.T., Rodriguez, M.I., Liechtenstein-Zábrák, J., Zalanyi, S., 2004. Transcervical polidocanol as a nonsurgical method of female sterilization: a pilot study. Contraception 70, 111–115.

Johnson, A.P., Taylor-Robinson, D., McGee, Z.A., 1977. Species specificity of attachment and damage to oviduct mucosa by *Neisseria gonorrhoeae*. Infect. Immun. 18, 833–839.

Kessel, E., 1996. 100 000 quinacrine sterilizations. Adv. Contracept. 12, 69–76.

King, T.M., Dubin, N.H., Blake, D.A., Parmley, T.H., 1983. Quinacrine hydrochloride: future research. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 138–140.

Kroegel, C., Antony, V.B., 1997. Immunobiology of pleural inflammation: potential implications for pathogenesis, diagnosis and therapy. Eur. Respir. J. 10, 2411–2418.

Leduc, E.H., Bernhard, W., Viron, A., Fain, J., Puvion, E., 1981. Effect of quinacrine on nuclear structure and RNA synthesis in cultured rat hepatocytes. Cancer Res. 41, 2832–2841.

Lu, W., Zhu, J., Zhong, C., Zhao, Y., 2003. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China. Int. J. Gynecol. Obstet. 83 (S2), S51–S58.

McGee, Z.A., Gregg, C.R., Johnson, A.P., Kalter, S.S., Taylor-Robinson, D., 1990. The evolutionary watershed of susceptibility to gonococcal infection. Microb. Pathog. 9, 131–139.

McGee, Z.A., Jensen, R.L., Clemens, C.M., Taylor-Robinson, D., Johnson, A.P., Gregg, C.R., 1999. Gonococcal infection of human fallopian tube mucosa in organ culture: relationship of mucosal tissue TNFα concentration to sloughing of ciliated cells. Sex. Transm. Dis. 26, 160–165.

Merchant, R.N., Prabhu, S.R., Kessel, E., 1995. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. Int. J. Fertil. 40, 47–54.

Muenzner, P., Bachmann, V., Zimmerman, W., Hentschel, J., Hauck, C.R., 2010. Human-restricted bacterial pathogens block shedding of epithelial cells by stimulating integrin activation. Science 329, 1197–1201.

Mullick, B., Mumford, S.D., Kessel, E., 1987. Studies of quinacrine and of tetracycline for non-surgical female sterilization. Adv. Contracept. 3, 245–254.

Mulvey, M.A., Schilling, J.D., Martinez, J.J., Hultgren, S.J., 2000. Bad bugs and beleaguered bladders: interplay between uropathogenic *Escherichia coli* and innate host defenses. Proc. Natl. Acad. Sci. U.S.A. 97, 8829–8835.

Mutsaers, S.E., Prele, C.M., Brody, A.R., Idell, S., 2004. Pathogenesis of pleural fibrosis. Respirology 9, 428–440.

Nagano, N., Imaizumi, Y., Watanabe, M., 1996. Novel blockade of Ca^{2+} current by quinacrine in smooth muscle cells of the guinea pig. Jpn. J. Pharmacol. 71, 51–60.

Ochiel, D.O., Fahey, J.V., Ghosh, M., Haddad, S.N., Wira, C.R., 2008. Innate immunity in the female reproductive tract: role of sex hormones in regulating uterine epithelial cell protection against pathogens. Curr. Women's Health Rev. 4, 102–117.

Paavonen, J., Eggert-Kruse, W., 1999. *Chlamydia trachomatis*: impact on human reproduction. Hum. Reprod. Update 5, 433–447.

Parker, L.C., Prince, L.R., Sabroe, I., 2007. Translational mini-review series on Toll-like receptors: networks regulated by Toll-like receptors mediate innate and adaptive immunity. Clin. Exp. Immunol. 147, 199–207.

Patton, D.L., Moore, D.E., Spadoni, L.R., Soules, M.R., Halbert, S.A., Wang, S.P., 1989. A comparison of the fallopian tube's response to overt and silent salpingitis. Obstet. Gynecol. 73, 622–630.

Patton, D.L., Wolner-Hanssen, P., Holmes, K.K., 1990. The effects of *Chlamydia trachomatis* on the female reproductive tract of the *Macaca nemestrina* after a single tubal challenge following repeated cervical inoculations. Obstet. Gynecol. 76, 643–650.

Patton, D.L., Sweeney, Y.C., Bohannon, N.J., Clark, A.M., Hughes, J.P., Cappuccio, A., Campbell, L.A., Stamm, W.E., 1997. Effects of doxycycline and anti-inflammatory agents on experimentally induced chlamydial upper genital tract infection in female macaques. J. Infect. Dis. 175, 648–654.

Pioli, P.A., Amiel, E., Schaefer, T.M., Connolly, J.E., Wira, C.R., Guyre, P.M., 2004. Differential expression of Toll-like receptors 2 and 4 in tissues of the human female reproductive tract. Infect. Immun. 72, 5799–5806.

Potvin, F., Petitclerc, E., Marceau, F., Poubelle, P.E., 1997. Mechanisms of action of anti-malarials in inflammation: induction of apoptosis in human endothelial cells. J. Immunol. 158, 1872–1879.

Prozialeck, W.C., Fay, M.J., Lamar, P.C., Pearson, C.A., Sigar, I., Ramsey, K.H., 2002. *Chlamydia trachomatis* disrupts N-cadherin-dependent cell–cell junctions and sequesters beta-catenin in human cervical epithelial cells. Infect. Immun. 70, 2605–2613.

Quayle, A.J., 2002. The innate and early immune response to pathogen challenge in the female genital tract and the pivotal role of epithelial cells. J. Reprod. Immunol. 57, 61–79.

Schmitter, T., Agerer, F., Peterson, L., Münzner, P., Hauck, C.R., 2004. Granulocyte CEACAM3 is a phagocytic receptor of the innate immune system that mediates recognition and elimination of human-specific pathogens. J. Exp. Med. 199, 35–46.

Sokal, D., Hieu, D.T., Weiner, D., Vinh, D., Vach, T., Hanenburg, R., 2000. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: Interim safety analysis. Fertil. Steril. 77, 1065–1068.

Sokal, D.C., Hieu, D.T., Loan, N.D., Hubacher, D., Nanda, K., Weiner, D.H., Vach, T.H., 2008. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. Contraception 78, 66–72.

Sokal, D.C., Vach, T.H., Nanda, K., McCann, M.F., Weiner, D.H., Drobnes, C., Rochanawutanon, M., Duc, N.B., Loan, N.D., 2010. Quinacrine sterilization and gynecologic cancers: a case–control study in northern Vietnam. Epidemiology 21, 164–171.

Sotelo, J., Guevara, P., Pineda, B., Diaz, C., 2004. Interstitial quinacrine activates a distinctive immune response effective for tumor immunotherapy. Surgery 136, 700–707.

Spitzmaul, G., Dilger, J.P., Bouzat, C., 2001. The noncompetitive inhibitor quinacrine modifies the desensitization kinetics of muscle acetylcholine receptors. Mol. Pharmacol. 60, 235–243.

Stephens, R.S., 2003. The cellular paradigm of chlamydial pathogenesis. Trends Microbiol. 11, 44–51.

Stuhlmeier, K.M., 2000. Effects of quinacrine on endothelial cell morphology and transcription factor–DNA interactions. Biochim. Biophys. Acta 1524, 57–65.

Su, H., Feilzer, K., Caldwell, H.D., Morrison, R.P., 1997. *Chlamydia trachomatis* genital tract infection of antibody-deficient gene knockout mice. Infect. Immun. 65, 1993–1999.

Vanrompay, D., Lyons, J.M., Morré, S.A., 2006. Animal models for the study of *Chlamydia trachomatis* infections in the female genital infection. Drugs Today (Barc.) 42 (Suppl. A), 55–63.

Veranic, P., Erman, A., Kerec-Kos, M., Bogataj, M., Mrhar, A., Jezernik, K., 2009. Rapid differentiation of superficial urothelial cells after chitosan-induced desquamation. Histochem. Cell Biol. 131, 129–139.

Wessler, I., Kirkpatrick, C.J., 2008. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. Br. J. Pharmacol. 154, 1558–1571.

Wynn, T.A., 2007. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J. Clin. Invest. 117, 524–529.

Yu, Y., Shi, L., Karlin, A., 2003. Structural effects of quinacrine binding in the open channel of the acetylcholine receptor. Proc. Natl. Acad. Sci. U.S.A. 100, 3907–3912.

Zaneveld, L.J., Goldsmith, A., 1984. Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception 30, 161–167.

Zipper, J.A., Prager, R., Medel, M., 1973. Biologic changes induced by unilateral intrauterine instillation of quinacrine in the rat and their reversal by either estradiol or progesterone. Fertil. Steril. 24, 48–53.

Zipper, J., Trujillo, V., 2003. 25 years of quinacrine sterilization experience in Chile: review of 2592 cases. Int. J. Gynecol. Obstet. 83 (S2), S23–S29.

Contraception

Contraception 92 (2015) 91 – 95

Review article

Quinacrine sterilization (QS): time for reconsideration☆

Jack Lippes*

State University of New York at Buffalo, School of Medicine, 31 Hampton Hill Drive, Buffalo, NY 14221

Received 28 October 2014; revised 1 June 2015; accepted 4 June 2015

Abstract

Dr. Jaime Zipper, the Chilean inventor of the quinacrine method of nonsurgical permanent contraception, was aware that when chest surgeons injected quinacrine into the pleural cavity to treat and prevent reoccurrence of pleural effusion, it resulted in the formation of fibrous adhesions between the lung and costal pleura. Zipper thought that a similar scarring effect could occur in the fallopian tubes if quinacrine was instilled into the uterine cavity. A series of refinements of the methodology culminated in the use of a modified Copper T intrauterine device inserter tube as a delivery system to introduce seven quinacrine pellets into the uterus. This approach with quinacrine sterilization (QS) was introduced into clinical practice in several countries, and a national clinical trial of over 50,000 women was conducted in Vietnam. However, in 1993, the World Health Organization raised concerns that quinacrine might be carcinogenic. This resulted in abandonment of QS in Vietnam and other countries. Subsequent epidemiologic data from extensive human studies do not support an increase in cancer risk. This paper reviews the history, limitations and clinical potential of QS.

Keywords: Quinacrine; Nonsurgical; Permanent contraception; Epidemiology

1. Introduction

Quinacrine was discovered, synthesized and patented in 1928 in Germany [1]. The Winthrop Pharmaceutical Company acquired the patent. Winthrop published a bibliography of 121 references on quinacrine in 1942 [2]. Included were human data as well as data on the use of nine different animal species. Quinacrine is known to be safe and effective in the treatment of a variety of parasitic infections, including malaria, giardia and tapeworm. Quinacrine also was effective for collagenous tissue diseases, such as lupus erythematosus, and rheumatoid arthritis. It remains one of the most thoroughly studied drugs of all time [3].

Where did the idea of using quinacrine as a contraceptive originate? Quinacrine is known to be effective treating a collapsed lung, which may be a consequence of a pleural effusion. When the pleural fluid is drained and replaced by quinacrine, the instilled quinacrine stimulates production of fibrous tissue causing the visceral pleura and parietal pleura to adhere, a process known as pleurodesis [4]. Pleurodesis eliminates the cavity in the chest, which allows the lungs to expand, and the patient is made more comfortable. Dr. Jaime Zipper, who first used quinacrine as a method for permanent contraception, postulated that a similar reaction would occur, when quinacrine was placed in the uterine cavity, and cause sclerosis of the lumen of the human oviduct (fallopian tube). His hypothesis turned out to be true. Dr. Zipper's initial approach was to instill 1500 mg of quinacrine into the uterine cavity as a slurry [5]. The 1500-mg slurry was discovered to have significant toxicity, including at least one death. The slurry technique was abandoned. Subsequently a refinement of the quinacrine sterilization (QS) formulation was made. Quinacrine was administered as seven 36-mg pellets for a total dose of 252 mg. The pellets dissolve slowly, and quinacrine interacts with the fallopian tube epithelium, replacing the epithelium with fibrous tissue. This effectively occludes the oviductal lumen [6]. Hysterectomy/Salpingectomy specimens and pelvic sonography have identified scar tissue (2–4 mm) in the intramural portion of the fallopian tube following QS [6,7].

☆ Conflict of Interest Statement: Dr. Lippes has received no pay from any source, including the International Services Assistance Fund (ISAF). ISAF, the sponsor of this work, is a nonprofit and nongovernmental organization.

* Tel.:+1-716-633-6663, +1-716-390-4482 (mobile).
E-mail address: jacklippes90@gmail.com.

http://dx.doi.org/10.1016/j.contraception.2015.06.005

2. QS technique

Subsequently QS was extensively used in developing countries as a nonsurgical method of female sterilization. The method offers a particular advantage in settings where surgery is difficult to access or unsafe. Seven pellets of quinacrine are loaded into an inserter similar to the one used to insert the Copper T intrauterine device (IUD). The health worker, nurse, nurse practitioner or physician deposits the seven 36-mg pellets of quinacrine to the fundus of the uterine cavity. Insertion of quinacrine is done at the end of menses when quinacrine easily scleroses the lumen of the oviduct. The insertion is repeated 4 weeks later. It is necessary to protect the patient against pregnancy for 3 months to be certain that the oviductal lumen is occluded. Diaphragms, condoms and/or injected Depo-Provera are recommended for the 3-month period.

Dr. Do Trong Hieu described the importance of technique when inserting the pellets of quinacrine [8]. While using the Copper T inserter, there is the expectation that as the operator pulls back the barrel of the inserter, it leaves the pellets in a straight line. This is known as the "Copper T IUD technique" of insertion. Hieu found that failure or pregnancy rates were much lower if the operator held the barrel of the inserter steady and gently applied pressure to the push rod, thereby depositing all pellets at the very top of the uterine cavity and not in a straight line. This is known as the "Hieu technique" (see Fig. 1).

3. Efficacy

A pregnancy rate of 12.1% was reported by Sokal [9]. But in that article he wrote, "…various insertion techniques may have contributed to the relatively high failure rate." Feldblum reported that the cumulative 10-year pregnancy probability for two insertions was 9%, but commented that "The variety of pellet regimens combined in this analysis makes it difficult to compare pregnancy rates…." [10]. Moreover, these failure estimates reflect the use of the Copper T IUD technique, which was abandoned 21 years ago and replaced by the more effective Hieu technique.

Two treatments also reduce the risk of failure. In a study of QS sponsored by the Indonesian government to compare single insertion versus two insertions, the pregnancy rate within 8 years of treatment was 14.3% among 70 patients receiving a single insertion of quinacrine, and there were zero pregnancies among 30 women who received 2 insertions [11].

Efficacy results using the more advanced Hieu method for placing quinacrine at the top of the uterine fundus can be seen in Table 1. The Lu et al. paper described in Table 1 reports on a Chinese clinical trial of 589 patients that compared pregnancy rates of 289 QS patients versus 300 women who had a surgical tubal ligation. Patients were matched by age, parity and other variables. There were no serious adverse events (SAEs) attributed to QS. With QS, the cumulative life table revealed a 1.2% failure rate per 100 women at 24 months compared to 0.7% for tubal ligation patients [12]. Further study is needed to confirm the advantage of the Hieu technique.

4. Human safety data

Quinacrine has been used extensively to treat malaria. It was the only effective synthetic antimalarial available during the Second World War. Three million American soldiers took 100 mg of quinacrine daily while serving in the South Pacific during WWII. These millions of service men and women suffered few SAEs from quinacrine [22]. Side effects from the chronic daily use of quinacrine include gastrointestinal upset and yellowing of the sclera and skin in a small percentage of patients. Rare cases of aplastic anemia were reported after long-term use [23]. For the treatment of

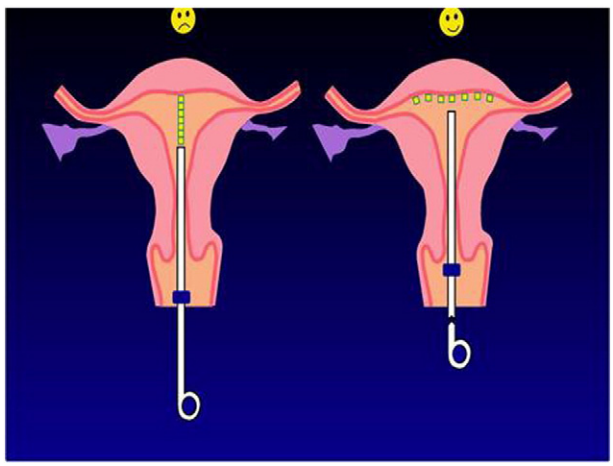


Fig. 1. Copper T IUD technique (left) vs. Hieu technique (right) of quinacrine intrauterine insertion for permanent contraception.

Table 1
QS failure rate using current protocol, i.e., employing the Hieu technique.

Investigators	No. cases	Follow-up years	Crude pregnancy rate (%)
Lu, et. al. [12]	265	2	1.2
Bashir, Bashir [13]	885	5	1.1
Sarin, Sarin [14]	134	7.2	0
Roy [15]	122	3.5	0.8
Soroodi-Moghaddam [16]	85	0.5–5	2.6
El Mahaishi [17]	66	3	0
	80	2	0
	54	1	0
Alfonso, Albano [18]	36	42.9 woman–years	0
Bilgrami [19]	1000	4	2
Agoestina [11]	30	8	0
Garabedian [20]	297	0.5–2	0.3 (ectopic)
Alpizar [21]	694	0.5–5	2.5
Ferreira [7]	128	0–4	1.6

malaria, quinacrine was replaced by chloroquine in 1946 because it was both more effective and less toxic [24]. Before chloroquine, in malarial endemic areas, people ingested 100 mg of quinacrine daily for many years, even as long as a decade or more. A daily dose of 100 mg a year equals 36,500 mg/year or 365,000 mg over 10 years. By comparison, to provide QS, the clinician installs quinacrine into the uterine cavity in two split doses of 252 mg each, 1 month apart, for a total lifetime dose of 504 mg. Long-term oral exposure during World War II was associated with the development of a cutaneous lichenoid eruption called *atabrine dermatitis*, and some patients with this condition subsequently developed squamous cell carcinoma of the skin [25]. No other evidence for human carcinogenicity exists.

In 1993, Hieu et al. reported results on 31,781 women who had chosen QS [26]. This article, published in The Lancet, provided evidence for the safety of quinacrine-induced tubal sclerosis. The authors estimated that because 31,781 women had received QS, 242 maternal deaths had been averted. Although this study provided reassuring human safety data, the World Health Organization (WHO)[1] issued a statement in 1993, declaring that quinacrine should not be used for permanent contraception. Presumably, the WHO decision was based on a positive Ames test for mutagenicity. However, Ames recognized that his test often gives false positives [27]. Nevertheless, the WHO statement caused the clinical trial of QS in Vietnam to be discontinued and inhibited other countries from pursuing QS trials. In 1994, the editors of The Lancet published an editorial entitled, *Death of a study, WHO, what and why*, calling these actions of WHO "reprehensible" [28].

Several epidemiology studies published between 1995 and 2012 evaluated whether QS causes cancer [29–33]. A study of all gynecologic cancers in 12 Vietnamese provinces during the period 2001–2006 found no increased risk with QS [31], and similar results were seen in a separate study from Chile [30]. When the number of individuals in each study is small the consistency of the results of these studies supports the conclusion of no effect of QS on cancer risk.

During this period, Dr. Claudia Ferreira and her colleagues at Minas Gerais University Hospital in Belo Horizonte, Brazil, made two significant contributions for understanding and improving QS. First, they provided QS to HIV+ women at a time when other physicians were fearful of treating these patients [34]. Second, they performed sonography on patients at 1-, 3-, 6- and 12-month intervals after receiving QS. This revealed that the endometrium returned to normal height within 2 to 4 weeks following a QS procedure suggesting normalization of the endometrium and no chronic inflammation [7]. Definitive evidence revealing no chronic inflammation was provided by biopsies taken by Dr. Lu in her examination of QS patients in Guizhou Province, China [12]. These observations are important because chronic inflammation is a known promoter of cancer [35].

In 2000, a Food and Drug Administration (FDA) Phase 1 study of QS was initiated at the Women and Children's Hospital of Buffalo, a teaching hospital affiliated with the State University of New York at Buffalo School of Medicine [36]. The hospital's investigational review board approved the clinical trial. Ten women who desired sterilization volunteered for QS and agreed to participate in the trial. This study was completed in 2003. There were no SAEs reported in this Phase 1 trial.

In October of 2003, the International Federation of Gynecology and Obstetrics (FIGO) devoted a half-day seminar to QS at its biannual international meeting in Santiago, Chile. Most of the presentations were published in a special supplemental issue of FIGO's journal, the International Journal of Gynecology & Obstetrics [37]. Twenty-five articles from 15 countries, covering 40,252 cases of QS, updated the QS literature. This collection of articles provides evidence for the safety of this method. All published clinical studies to date show that QS is not associated with an increased risk of reproductive tract cancer.

In 2001, Potts and Benagiano wrote, in an article entitled, *Quinacrine sterilization: a middle road*, "…we both wish to help broaden the range of fertility control options available, especially for low income women around the world. …. It always takes a decade or two to gather empiric evidence of safety, based on large-scale actual use." [38].

5. Animal safety studies

The WHO comments on quinacrine-prompted Family Health International to conduct animal (mouse and rat) studies to evaluate a possible risk of cancer from QS. These animal studies were initiated in the early 2000s. Quinacrine demonstrated no genotoxicity in a neonatal mouse assay, published in 2006 [39]. A 2-year rat carcinogenicity study (CaBio) used varying doses of quinacrine, which were placed in the rat uterus in an attempt to "mimic" the action of QS in the human situation [40]. However, for the following four reasons, the rat study did not mimic the human QS experience: (a) quinacrine was administered to rats in a slurry formulation while in women quinacrine is placed in the uterus in the form of solid pellets (use of the slurry formulation in women was abandoned in 1975 due to excessive toxicity); (b) methylcellulose (MC), a known tissue irritant that causes chronic inflammation [41], was added to the slurry of quinacrine (MC is not part of the quinacrine formulation administered to women); (c) the rats developed rare cancers that were preceded by chronic inflammation, and chronic inflammation is a known tumor promoter in cancer induction [35] (chronic inflammation has not been reported in women who received QS); and (d)

[1] Letter, Frank Webb, of the WHO Human Reproduction Programme, to Linda Demers, UNFPA representative for Vietnam, Dec. 7, 1993.

cancers in the rats developed only when doses of quinacrine exceeded the maximum tolerated dose (MTD). However, FDA/international conference on harmonization guidance states that the MTD in a study should be one that is minimally toxic and one that is tolerated without chronic dysfunction or pathological changes that would interfere with the interpretation and, therefore, the validity of the study [42].

These differences in formulation and dosing undermine the rat CaBio study's usefulness for an assessment of carcinogenicity with QS. One published interpretation of this rat CaBio concludes that quinacrine is not carcinogenic in rats at doses that do not exceed the MTD [43].

6. Comparison of QS to alternative methods of permanent contraception

Some critics of QS have proffered that alternative methods of contraception, like IUDs, might serve the same purpose as QS. While acceptance of long-acting reversible methods is growing in the United States, continuation rates may be lower in developing nations. Four IUDs were studied in a randomized controlled trial of 1905 women by the Indian Council of Medical Research. After 3 years, continuation of the levonorgestrel IUD was 38.8%, and the Cu T 200 IUD ranged from 45.4% to 50.4% [44]. Sterilization is the only method where the continuation rate approaches 100%. Essure™ (Bayer Healthcare), a device that is placed into the openings of the fallopian tubes using hysteroscopic guidance has been advanced as a minimally invasive method that is safer and more effective than traditional surgery. However, the technique still requires surgical facilities. Considerable surgical training is required, as failure of bilateral placement as high as 23% have been reported [45]. This is due to various reasons, including poor visualization, sclerosis and scarring of the oviduct. Due to these placement problems, and failure of some women to complete active follow up to confirm tubal occlusion, the failure rate for hysteroscopic sterilization may be higher than laparoscopy [46].

7. Conclusion

Like all methods of family planning and especially permanent methods, QS should always be offered in human rights frameworks of fully informed consent. Much is now known about QS. It is nonsurgical, there is no need for anesthesia, and studies have shown that it is safe. With the improved Hieu insertion technique, and two treatments, QS effectiveness (failure rate of 1.2% after 2 years) compares favorably, with surgical tubal ligation (0.7% at 2 years). The cost is low, and QS can be performed by nonphysicians [12]. It is time to reexamine the epidemiological and clinical data on the use of QS and reconsider its use in both developed and developing countries.

Acknowledgements

The author acknowledges with gratitude the invaluable assistance of Mrs. Margaret Mille Growe for assistance with preparation of the manuscript.

References

[1] Mauss H, Mietzsch F. Atabrin, ein neues Heilmittel gegen Malaria. Klin Wochenschr 1932;12:1276–8.
[2] Annotated biblography chemistry and phamacology atabrine dihydochloride. Library Winthrop Chemical Co.; 1942
[3] Ehsanian R, Van Waes C, Feller SM. Beyond DNA binding - a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. Cell Commun Signal 2011;9:1.
[4] Hickman LA, Jones MC. Treatment of neoplastic pleural effusions with local instillations of quinacrine hydrochloride. Thorax 1970;25(2):226–9.
[5] Zipper J, Kessel E. Quinacrine sterilization: a retrospective. Int J Gynaecol Obstet 2003;83(Suppl 2):S7–11.
[6] Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM. Quinacrine-induced pathologic changes in the fallopian tube. Fertil Steril 1980;33(6):666–7.
[7] Ferreria CRC, Magalhaes DC, Ferreria MZ, Hanan CF, Camargos AF. Quinacrine female non- surgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women. Int J Gynecol Obstet 2003;83(Suppl 2):S59–66.
[8] Hieu DT, Tan TT, Tan DN, Nguyet PJ, Than P, Vinh DQ. Author reply to letter to editor: non-surgical female sterilisation. Lancet 1993;342:869–70 [author reply 870–1].
[9] Sokal DC, Hieu DT, Loan ND, Hubacher D, Nanda K, Weiner DH, et al. Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam. Contraception 2008;78:61–5.
[10] Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 2000;61:379–84.
[11] Agoestina T. 8-Year follow-up in a randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization in Indonesia. Int J Gynecol Obstet 2003;83(Suppl2):S129–31.
[12] Lu W, Zhu J, Zhong C, Zhao Y. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province China. Int J Gynecol Obstet 2003;83(Suppl 2):S51–6.
[13] Bashir A, Bashir M, Afzal S. The effect of special training for quinacrine sterilization (QS) in Faisalabad, Pakistan: a report on an 1833-women subset of 11,000 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S67–71.
[14] Sarin AR, Sarin RK. Quinacrine sterilization (QS) among high-risk women: a study of 134 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S73–6.
[15] Roy A. A 22-year experience with quinacrine sterilization in a rural private clinic in Midnapore, India: a report on 5 protocols and 1838 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S87–91.
[16] Soroodi-Moghaddam S. Quinacrine sterilization (QS) in Iran and the use of HSG as a measure of success. Int J Gynecol Obstet 2003;83(Suppl 2):S93–6.
[17] El Mahaishi MS, Azzidani AM. Quinacrine sterilization in Libya: 200 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S113–5.
[18] Alfonso LA, Albano HA. Quinacrine sterilization (QS) experience in the Philippines: a preliminary report. Int J Gynecol Obstet 2003;83(Suppl 2):S121–3.

[19] Bilgrami M, Shah L. Marie Stopes Society, Pakistan: 1000 cases of quinacrine sterilization (QS). Int J Gynecol Obstet 2003;83(Suppl 2):S125–7.
[20] Garabedian V. Quinacrine sterilization (QS) in Syria: a preliminary report on 297 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S133–5.
[21] Alpizar F. Quinacrine sterilization (QS) in Costa Rica: 694 cases. Int J Gynecol Obstet 2003;83(Suppl 2):S141–5.
[22] Joy RT. Malaria in American troops in South Southwest Pacific in World War II. Med Hist 1999;43(2):192–207.
[23] Custer RP. Aplastic anemia in soldiers treated with Atabrine(Quinacrine). Am J Med Sci 1946 Aug;212(2):211–24.
[24] Coatney GR. Pitfalls in a discovery: the chronicle of Chloroquin. Am J Trop Med Hyg 1963 Mar;12:121–8.
[25] Bauer F. Quinacrine hydrochloride drug eruption. Its early and late sequelae and its malignant potential: a review. J Am Acad Dermatol 1981;4(2):239–48.
[26] Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong JQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. Lancet 1993;342:213–7.
[27] Forman D. "Ames", the Ames test, and the causes of cancer. BMJ 1991;303:428–9.
[28] Editors of The Lancet. Death of a study, WHO, what and why. Lancet 1994;343:987–8.
[29] Zipper J, Trujillo V. 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases. Int J Gynaecol Obstet 2003;83(Suppl 2):S23–9.
[30] Sokal DC, Trujillo V, Guzmán SC, Guzman-Serani R, Wheeless A, Hubacher D. Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort. Contraception 2010;81(1):75–8.
[31] Sokal DC, Hieu do T, Loan ND, Hubacher D, Nanda K, Weiner DH, et al. Safety of quinacrine contraceptive pellets: results from 10-year follow- up in Vietnam. Contraception 2008;78(1):66–72.
[32] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril 2000;74(1):169–71.
[33] Dabancens A, Sokal DC, Pruyas M, Rivera M, Zipper J. Prevalence and standardized incidence rates of preclinical cervical pathology among 1,061 women sterilized with transcervical quinacrine hydrochloride pellets. Fertil Steril 1995;64(2):444–6.
[34] Magalhaes DR, de Carvalho Ferreria CR, Barbosa Magalhaes E, Camargos AF, Lippes J, Carvalho Ferreria D. Quinacrine sterilization for human immunodeficiency virus-positive women. Fertil Steril 2009;92(1):108–15.
[35] Balkwill F, Mantovanni A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
[36] Lippes J, Brar M, Gerbracht K, Neff P, Kokkinakis S. An FDA Phase 1 clinical trial of quinacrine sterilization (QS). Int J Gynecol Obstet 2003;83(Suppl 2):S4–9.
[37] Lippes J (guest editor). Quinacrine Sterilization: reports on 40,252 cases. Int J Gynaecol Obstet 2003; 83(Suppl 2):S1-S147.
[38] Potts M, Benagiano G. Quinacrine sterilization: a middle road. Contraception 2001;64:275–6.
[39] Cancel AM, Smith T, Rehkemper U, Dillberger JE, Sokal D, McClain RM. A one-year neonatal mouse carcinogenesis study of quinacrine dihydrochloride. Int J Toxicol 2006;25:109–18.
[40] Cancel AM, Dillberger JE, Kelly CM, Bolte HF, Creasy DM, Sokal DC. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol 2010;56(2):156–65.
[41] Haseman JK, Growe RG, Zeiger E, McConnell EE, Luster MI, Lippes J. A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat cancer bioassay and its implications for human clinical use. Regul Toxicol Pharmacol 2015;71:371–8.
[42] International Conference on Harmonisation. European Medicines Agency, Note for Guidance on dose selection for carcinogenicity studies of pharmaceuticals, ICH Expert Working Group, Topic S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals. 7 Westferry Circus, Canary Wharf, London, E14 4HB, United Kingdom; 2008.
[43] McConnell EE, Lippes J, Growe RG, Fail P, Luster M, Zeiger E. An alternative interpretation of "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol 2010;56(2):166–73.
[44] Indian Council of Medical Research Task Force on IUD. Randomized clinical trial with intrauterine devices (levonorgestrel intrauterine device (LNG), CuT 380Ag, CuT 220C and CuT 200B). A 36-month study 1996.
[45] Jenss JA, Pattij TO, Eijkemans MJ, Broelmans FJ, Veersema S, Shreuder HW. Learning curve of hysteroscopic placement of tubal sterilization microinserts in 15 gynecologists in Netherlands. Fertil Steril 2013;100(3):755–60.
[46] Gariepy AM, Creinin MD, Smith KJ, Xu X. Probability of pregnancy after sterilization: a comparison of hysteroscopic versus laparoscopic sterilization. Contraception 2014;90:174–81.

Clinical Study on Female Non-Surgical Sterilization with Quinacrine *

Lu Weiqun, Zhu Jiang, Zou Suping, Liu Guanghua, Hou Yonghua, Yang Zhengpin, Xiao Shiwen, An Wenshi, Tian Yingmei

[Abstract] **Objective**: To study the safety, reliability, and acceptability of large-scale clinical use of non-surgical sterilization (QS) of women with quinacrine. **Methods**: From March 2007 to July 2010, 6,000 women who voluntarily received QS were recruited in Guizhou Province, namely: 7 (252 mg) quinacrine pellets were placed in the modified T-copper IUD placer, and then the quinacrine pellets placed into the uterus at 3 days to 7 days after menstruation ends, or 6 weeks after childbirth, or induced abortion. The second application was completed after at 4 weeks. Follow-up was performed at 3, 6, 12, and 24 months. **Results**: 5,780 follow-up forms and 88 pregnancy forms were recovered with the longest follow-up time of 1,248 days. The main adverse reactions were yellow vaginal discharge, dizziness, fatigue, and irregular menstruation, etc. No serious adverse reactions were found. The effective rate of sterilization was 98.5%, and the drug application status and the number of times of application affect the success rate. **Conclusion**: QS is low cost, easy to be operated, non-invasive, painless, less adverse reactions, and more accepted by women with voluntary sterilization intention and clinicians. Preoperative physical examination excluded contraindications, applied at 6 weeks postpartum or 3 – 7 days after menstruation, 2 doses of medication, patients were instructed to lie down for 2 hours after the QS procedure, and 3 months of postoperative contraception are beneficial to improve the success rate of QS. The promotion of QS has a positive effect on improving the acceptance offemale sterilization and reducing the cost of family planning surgery.

[Keywords]: Sterilization, Reproductive Tract; Female (Female) Sex; Quinacrine; and Non-Surgical Sterilization

Clinical Study of Quinacrine Female Voluntary Non-Surgical Sterilization LU Wei –qun, ZHU Jiang, ZOU Su-ping, LIU Guang-hua, HOU Yong-hua, YANG Zheng-pin, XIAO Shi-wen, AN Wen-shi, TIAN Ying-mei. Center for Research on Population, Guizhou University, Guiyang 550025, China (LU Wei-qun); Guizhou Provincial Research Institue for Family Planning, Guiyang 550004, China (ZHU Jiang); Huaxi Health Care Service Center of Maternal and Child, Guiyang 550025，China (ZOU Su -ping); Nanming Family Planning Station, Guiyang 550001, China (LIU Guang -hua); Rongjiang County Family Planning Station, Rongjiang County 557200, Guizhou Province, China (HOU Yong-hua); Liping County Family Planning Station, Liping County 557300, Guizhou Province, China (YANG Zheng-pin); Zunyi County Health Care Service Center of Maternal and Child, Zunyi County 563100，Guizhou Province, China (XIAO Shi-wen); Fenggang County Health Care Service Center of Maternal and Child, Fenggang County 564200, Guizhou Province, China (AN Wen-shi); Yuqing County Health Care Service Center of Maternal and Child, Yuqing County564400, Guizhou Province, China (TIAN Ying-mei)
Corresponding author: ZHU Jiang, E-mail: zhujianggy@yahoo.com.cn

* Fund Project: Special Fund Project of the Governor of Guizhou Province for Outstanding Scientific and Technological Education Talents [QSZHZ (2006) No. 2], Social Development Project of Guizhou Provincial Department of Science and Technology [QKHNY Zi (2006) 3052]
Authors' Units: 550025 Population Study Center of Guizhou University (Lu Weiqun); Guizhou Population and Family Planning Study Institute (Zhu Jiang); Family Planning Maternal and Child Health Care Services Center in Huaxi District (Zou Suping); Nanming Family Planning Publicity and Guidance Station of Guiyang (Liu Guanghua); Rongjiang Family Planning Publicity Technology Station (Hou Yonghua); Liping Family Planning Publicity and Technical Guidance Station (Yang Zhengpin); Zunyi Maternal and Child Health Center for Population and Family Planning (Xiao Shiwen); Fenggang Family Planning Maternal and Child Health Care Station (An Wenshi); Yuqing Family Planning and Reproductive Maternal and Child Health Care Center (Tian Yingmei)

△Corresponding Author: Zhu Jiang, E-mail zhujianggy@yahoo.com.cn

Quinacrine, also known as atabrine, mepacrine, used as an antimalarial specific medicine in World War II, which had saved the lives of millions of soldiers, and has also been used for treating cancerous pleural ascites in recent years. Study on its use in female sterilization was began by Chilean doctor Zipper in 1970. The quinacrine pellet method used in this study is the same procedure recommended since 1976. In the early 1990s, nearly 100,000 subjects in 14 countries around the world, including Chile, Vietnam, India, Egypt, Iran, and China, underwent quinacrine non-surgical female sterilization (QS). At the same time, with the increased usage of QS, the failure rate will decrease further [1-2]. The purpose of this study is to study the safety, reliability, and acceptability of QS in large-scale clinical use.

1. Subjects and methods

1.1 **Subjects**: According to the needs of the study and the arrangement of the Family Planning Administration Department of Guizhou Province, experimental sites were established in seven district / county-level family planning stations in Huaxi District, Guiyang City, Nanming District, Zunyi County, Rongjiang County, Fenggang County, Yuqing County and Liping County of Guizhou Province. From March 2007 to July 2010, for those women who voluntarily accepted QS and met the study conditions, it was agreed that women who participated in 4 follow-up visits after operation shall undergo QS operation. General physical examination before operation, such as blood pressure, blood routine, urine pregnancy test, ultrasound, and other examinations, to exclude serious systemic diseases and pregnancy; Meanwhile, general gynecological examinations such as double diagnosis shall be performed to exclude unexplained reproductive system diseases such as vaginal bleeding, pelvic inflammation, salpingitis, cervicitis, genital tract malformation and tumor. Furthermore, women with a history of ectopic pregnancy and mental illness were excluded. All the selected subjects signed the Informed Consent Form of QS study, a total of 5,917 cases. The age was 19 - 47 years old, with an average of 30.7 years old. Nearly 90% of the subjects were from rural areas, with an average of 2.35 surviving children, and the vast majority of the subjects have more than two children. The youngest child of more than 80% of the objects is under 1 year old.

1.2 Methods: At 3 - 7 days after menstruation ended, or six weeks after delivery, or induced abortion, 7 quinacrine pellets with a total of 252 mg were placed into the modified t-copper IUD placer and then applied into the uterus, and the drug was placed again at an interval after 1 month (4 weeks). After the first dose, the subjects were instructed to use alternative contraceptives (such as condoms) for 3 months. After each application, the doctor shall carefully fill in the Drug Application Form, and conduct follow-up at 3, 6, 12, and24 months after the first drug placement (includingoutpatient, home visit, telephone interview and other forms), and fill in the Follow-Up Form at the same time. If the subjects were pregnant, they were considered as failing and the PregnancyForm shall be filled in.

1.3 Statistical Methods The Recovery Form was reviewed by two persons and entered into the computer. The data were analyzed by SPSS, and the influencing factors of QS failure rate were analyzed by chi-square test in cross tabs.

2. Results

2.1 Follow-up: 5,780 follow-up tables, including 88 pregnancy tables, were recovered in this study. The total recovery rate was 97.7% (5,780 / 5,917). The table recovery conditions, follow-up rate and failure rate of the seven test points are shown in Table 1. The main reason why the follow-up form could not be recovered was that the subjects were less than 90 days after QS. It can be seen from Table 1 that Zunyi County has the most cases, Yuqing County has the least, Fenggang County and Yuqing County have the highest

follow-up rate, while Liping County has the lowest follow-up rate, less than 90%; The failure rate is also just corresponding. Fenggang County and Yuqing County are the most and Liping County is the least. The number of QS cases completed in each county is related to the number of women of childbearing age in the county; The follow-up rate was related to the start time of QS. The QS study was only performed in Liping County in 2010. As of the end of the survey, many QS were still performed. Nearly 10% of the subjects did not arrive at the first follow-up time and did not fill in the Follow-up Form, so the follow-up rate was the lowest. The average menstrual cycle of women was 29.7 days, with an average of 29.1 days. The longest follow-up object in this study was 1,248 days, about 42 female months; The shortest is 91 days, about 3 female months (excluding losers); The average follow-up was 614.2 days, about 20 female months. The total follow-up time was 3,549,816 days, about 118,327 female months. 321 cases (about 5.5%) of the follow-up objects only bought medicine once because of going out to work and being troublesome.

Table 1: Report of "Medication Form, Follow-up Form, Pregnancy Form"

Test Site	N (Proportion)	Number of follow ups (follow-up rate)	Number of pregnant female (failure rate)
Nanming District	975 (16.5%)	970 (99.5%)	10(1.0%)
Huaxi District	976 (16.5%)	969 (99.3%)	17(1.8%)
Zunyi County	1334(22.5%)	1330 (99.7%)	18(1.4%)
Rongjiang County	898(15.2%)	854(95.1%)	17(2.0%)
Fenggang County	799(13.5%)	799(100.0%)	19(2.4%)
Liping County	728(12.3%)	651(89.4%)	2(0.3%)
Yuqing County	207(3.5%)	207(100.0%)	5(2.4%)
Total	5917(100%)	5780(97.7%)	88 (1.5%)

2.2 Adverse reactions: Among the 5,780 follow-up forms received, 1,172 lacked "feelings after QS", and 86.8% of the 4,608 filled in answered that there was no discomfort. The main adverse reactions were vaginal yellow secretion, dizziness, fatigue, irregular menstruation, abnormal menstruation, etc., as shown in Table 2. These adverse reactions generally do not need special treatment and disappear naturally after 1 day and 2 days (except irregular menstruation).

2.3 Failure: 88 pregnancy tables were received in this study, i.e. 88 cases failed, and the failure rate was 1.50% (88 / 5,780), including 4 cases of ectopic pregnancy. The average age of the failed subjects was 30.1 years old, which was lower than the average age of all subjects. The time between failure (pregnancy) and QS was 39 - 848 days, and the longest was about 28 months; The average is 366.4 days, about 12 female months. Therewere 5, 14, 29, 25 and 5 cases for the time between failure (pregnancy) and QS <90 days, 90- 180 days, 180-360 days, 360-720 days. The constituent ratios were 5.7%, 15.9%, 32.9%, 39.8% and 5.7%, respectively. Failure (pregnancy) occurs within
0.5 – 2 years at most. Five cases were pregnant within 90 days after QS. There are 5 cases after QS of pregnancy within 90 days.

Table 2: Adverse Reactions after Application

Adverse reactions	Number of cases	Percentage (%)
None	4,001	86.9
Uterine perforation	0	0.0
Dizziness	63	1.4
Severe abdominal pain	1	0.0
Cervical adhesions	2	0.0
Fatigue	40	0.9
Decreased quality of sex life	3	0.1
Increased menstrual flow	21	0.5
Decreased menstrual flow	75	1.6
Intermenstrual bleeding	54	1.2
Irregular menstruation	38	0.8
Lower abdominal pain	74	1.6
Back pain	75	1.6
Yellow discharge	127	2.8
Other	30	0.7
Total	4,608	100.0

2.4 Effective rate: The effective rate expressed as a percentage was 98.5%. Pearl index, which is closer to the concept of natural fertility than percentage, is the most widely used measure of contraceptive effect in the world. Pearl index is an actual risk rate, which is usually expressed as

the number of pregnancies due to contraceptive failure per 100 women using contraceptives for one year. The calculation formula is "the number of all unintended pregnancies during the application of contraceptives divided by the total number of people and months of female using contraception and multiplied by 1200"[3]. According to this definition, the Pearl index of this study is 88 x 1,200 / 118,327 = 0.8924. Life Table is widely used in "Time Decline" analysis. Using life table to judge the effectiveness of contraceptives is also more and more accepted by people. Calculated by SPSS, the cumulative effective rate of 5780 cases of QS life table analysis was 97.54%.

2.5 Analysis of the failure reasons: Analysis of failure causes this study found that the failure rate of rural group (1.57%) was slightly higher than that of urban group (1.45%); The failure rate of the group with lower education level is higher. The failure rate of the group with higher education level is junior middle school and above (1.68%), primary school group (1.55%), illiterate group (1.09%) and missing group (0.99%). "Drug application status" and "drug application times" are the influencing factors (P about 0.05). The results are shown in Table 3. The failure rate of "postpartum", especially "after IUD removal", is significantly higher than that of "after menstruation"; The failure rate of "one application" is significantly higher than that of "two applications".

Table 3: Factors Influencing Failure Rates

Factor	Follow-ups	Number of Pregnant female	Failure rate (%)	x^2	P
Drug status				40.83	0
Postpartum	3,183	55	1.73		
After menstruation	2,481	24	0.97		
After taking the ring	53	6	11.33		
Missing	63	3	4.76		
Number of doses				5.75	0.016
1 time	321	10	3.12		
2 times	5,459	78	1.43		

3. Discussion: As a new type of non-invasive sterilization, QS has a short history, and there are few clinical follow-up reports of thousands of cases at home and abroad. In 1998, 572 cases of QS clinical studies were reported in Jiangsu Province and Guizhou Province of China [4] with the failure rate of 3.13%. 31,871 QS clinical studies around 1995 were reported in Vietnam. Some experts suggested that, the practice of clinical follow-up test was not standardized, and questioned the results (including safety and reliability)[5]. Furthermore, hundreds or thousands of QS clinical studies have also been reported in India, Pakistan, Costa Rica, Indonesia, and Syria [6-10], with a failure rate of 0 - 15% and scattered results. Various family planning operations were affected by the external environment, such as study location, personnel and objects, and the results were different. At present, only 2,592 cases (4 batches) in Chile have been followed up for 25 years, which has attracted the attention of the International Family Planning Study Community [2]. The follow-up survey of QS in Chile and some data of IUD birth control and tubal ligation sterilization performed in China before the 1990s [11] show that the QS failure rate of this study (1.5%) is lower than that reported by the International (Chile) (4.6%), which is equivalent to IUD (0.3% -3.7%) and tuballigation (0.18% - 2.01%). Its Pearl Index (0.89) was higher than that of International (0.41), but lower than that of IUD (2.7 - 5.3%). The incidence of abnormal menstruation in this study was 3.3%, which was lower than that of IUD (3.9% - 17.3%) and tubal ligation (10% - 20%). The incidence of ectopic pregnancy (0.07%) was lower than that of IUD (0.6%), which was equivalent to that of tubal ligation (0.06% - 0.3%). It can beseen that as a newly developed sterilization method, the failure rate of QS in this study is not high compared with the failure rate of early clinical use of IUD and tubal ligation (TL). Of course, with the expansion of clinical use, the effective rate of IUD and TL has made great progress compared with the early use. It is

believed that with the continuous accumulation of clinical experience, the effective rate of QS will also be greatly improved. Studies have shown that quinacrine is the most effective drug in blocking the confluence of the oviduct and the oviduct [12]. For those with thicker stroma, the risk of sterilization failure will increase; during endometrial hyperplasia, drugs are not easy to act on the myometrium to cause inflammation, and the risk of failure increases; Scar formation takes time, generally more than 30d, during which the risk of failure will increase. According to the study and training, lie flat for 2h after operation to melt the medicine and flow into the fallopian tube; It is required to apply the drug twice within one month to increase the depth of drug action. Meanwhile, doctors shall explain to the object that condoms and other alternative contraceptive methods must be used for three months after the first medication. The study and training also stipulates that the medicine shall be applied within 6 months postpartum or 3 – 7 days after menstruation to avoid postpartum and IUD removal, to avoid the failure caused by QS's own defects risk. In this study, one case was found pregnant 39 days after the first administration of medicine and had been pregnant for 6 weeks. This case is very likely to have been pregnant before QS and was not found during preoperative physical examination. Failure occurred within 90 days in 5 cases, accounting for 5.7% of the total failures. These subjects are likely to fail to take alternative contraceptives as required. More than 50% of the patients were treated postpartum, and the failure rate was significantly higher than that after menstruation. It can be seen that standardizing surgical operation is an important link to improve the success rate of QS.

Since the International Conference on population and development was held in Cairo in 1994, while paying attention to family planning and population control continuously, China has strengthened its understanding of population, family planning and health issues, and carried out high-quality family planning services, i.e., people-oriented, all-round human development as the center and people's needs as the starting point, so as to comprehensively improve the quality of family planning services, Promote the all-round development of population and society, and meet the needs of people of childbearing age for diversified contraceptive methods. In China, with the continuous improvement of people's living standards, most urban people can have a variety of contraceptive methods to choose from. However, about two-thirds of women still live in rural areas and have poor access to effective contraceptives. Sterilization is often the most effective method available to them. Many working women are unwilling to accept "ligation" for reasons such as worrying about their physical strength, and are afraid of the pain of ligation. The improvement of sterilization methods is of great significance to the implementation of China's family planning policy, improving the acceptability of sterilization, and improving the quality of life of women undergoing sterilization. It is found in this study that many voluntary sterilization women prefer to pay for QS rather than enjoy free "ligation". According to their words: "QS women only need to lie in bed for 2 hours and can work in the field when return home; they don't dare to work in the field for 1 week after being ligation, and she has to eat chicken to supplement nutrition". The results of this study show that QS has less adverse reactions than surgical female sterilization. It is a female sterilization method welcomed by women who choose sterilization voluntarily. The study and promotion of QS plays a positive role in improving the acceptance of sterilization, people's satisfaction and reducing the cost of family planning surgery.

References

[1] Lu Weiqun, Zhu Jiang. 300 cases of non-surgical female sterilization with Adiping suppository A retrospective study on safety[J]. Reproduction and Contraception, 2001, 21(4): 249-252.

[2] Zipper J., Kessel E. Quinacrine sterilization: a retrospective[J]. Int J Gynecol Obstet, 2003 83 (Suppl 2):S7-11.

[3] Gao Ersheng, editor-in-chief. Family Planning Statistics and Evaluation [M]. Beijing: China Population Publishing House, 1992.

[4] Ding Juhong, Lu Weiqun, Ding Wanhua, et al. Non-surgical female sterilization with Adiping suppository Review of efficacy and safety[J]. Reproduction and Contraception, 2001, 21(2): 110- 115.

[5] Hieu DT, Tan TT, Tan DN, et al. 31781 cases of non -surgical female sterilization with quinacrine pellets in Vietnam[J]. Lancet, 1993, 342(8865): 213-227.

[6] Bhatt RV. Quinacrine nonsurgical female sterilization in Baroda, India: 23 years of follow -up of 84 female [J]. Int J Gynecol Obstet, 2003, 83(Suppl 2): S31-33.

[7] Bashir A, Bashir M, Afzal S. The effect of special training for quinacrine sterilization (QS) in Faisalabadm Pakistan: a report on an 1833-female subset of 11 000 cases [J]. Int J Gynecol Obstet, 2003, 83 (Suppl 2): S67-71.

[8] Alpizar F. Quinacrine sterilization (QS) in Costa Rica: 694 cases [J]. Int J Gynecol Obstet, 2003, 83(Suppl 2): S141-145.

[9] Agoestina T. 8 -Year follow -up in a randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization in Indonesia [J]. Int J Gynecol Obstet, 2003, 83(Suppl 2): S129- 131.

[10] Garabedian V. Quinacrine sterilization (QS) in Syria: a preliminary report on 297 cases [J]. Int J Gynaecol Obstet, 2003, 83(Suppl 2): S133-135.

[11] Lu Zilan, editor-in-chief. Family Planning Theory and Practice [M]. Guangzhou: Guangdong Science and Technology Press, 1988.

[12] Lu Weiqun, Zhu Jiang, Pan Qinrui, et al. Pathological study on occlusion of fallopian tubes by quinacrine in mice and rabbits [J]. Reproduction and Contraception, 1998, 18(4): 239-241.

(Received date: 2011-05-17) [Editor of this article Li Shujie]

ELSEVIER

Contraception 86 (2012) 106 – 109

Contraception

Original research article

Pelvic surgery and hospitalization among Chilean women after nonsurgical sterilization with quinacrine pellets between 1977 and 1989

Paul J. Feldblum[a], Angie Wheeless[a], Valentin Trujillo[b], Sergio Guzman[c], Vera Halpern[a], David C. Sokal[a,*]

[a]*FHI 360, P.O. Box 13950, Research Triangle Park, NC 27709, USA*
[b]*Sótero del Río Hospital-Clínica Bicentenario, 4850 Santiago, Chile*
[c]*Escuela de Medicina, Universidad Austral de Chile, 5090000 Valdivia, Chile*

Received 25 March 2011; revised 24 October 2011; accepted 29 November 2011

Abstract

Background: Concern about quinacrine lingers because of its carcinogenic effects in rats. We describe results of long-term follow-up of women who underwent quinacrine pellet sterilization in Chile between 1977 and 1989 (*N*=1492).
Methods: We interviewed the women or relatives in five rounds of data collection between 1991–1993 and 2006–2007, and reviewed hospital records. Median follow-up was 18.5 years; total person-time was 23,894 woman-years. This analysis focuses on pelvic and abdominal surgeries and conditions. We used survival analysis to estimate the 15-year cumulative probability of hysterectomy, other pelvic surgical procedures and relevant adverse events.
Results: Uterine fibroids were by far the most common gynecologic condition, reported by 11% of the cohort. Surgical procedures were recorded for 15% of the cohort; hysterectomy was the most frequent procedure (10%), followed by salpingectomy (2%). The 15-year probability of any pelvic or abdominal procedure was 14.7 per 100 women (95% confidence interval 12.4–16.9). The probability of hysterectomy was 9.3 per 100 women (95% confidence interval 7.4–11.1). Number of quinacrine insertions had little impact on the probabilities.
Conclusion: During long-term follow-up of women who received quinacrine pellets for nonsurgical sterilization, the incidence of noncancer adverse outcomes was not unusually high, and no alarming patterns emerged.

Keywords: Quinacrine; Tubal sterilization; Pelvic surgery; Hysterectomy; Contraceptive safety; Cohort study

1. Introduction

Although quinacrine has not been approved for transcervical use by the US Food and Drug Administration or other regulatory authorities, tens of thousands of women around the world have received it as a method of nonsurgical tubal occlusion. Quinacrine in the endometrial cavity was first used for sterilization in Chile, and various formulations and doses have been tested [1]. The most commonly used regimen was seven 36-mg pellets of quinacrine hydrochloride introduced into the endometrial cavity by modified intrauterine device (IUD) inserter at two separate insertions 1 month apart (252 mg per insertion) [1].

Concern about quinacrine lingers because of a preclinical study in rats that found increased cancers after high intrauterine doses [2]. Long-term safety and effectiveness issues following sterilization with intrauterine quinacrine have been studied in Vietnam [3-5] and in Chile [6–9], including pregnancy, cancer and other sequelae. Results of the studies showed no increased risk of cancer in women. In this article, we describe gynecologic and lower abdominal health problems and surgical procedures that might be related to intrauterine effects or to transfallopian tube peritoneal spill of quinacrine.

2. Materials and methods

2.1. Identification of cohort

The cohort comprises 1492 Chilean women who underwent nonsurgical sterilization with intrauterine quinacrine at

* Corresponding author.
E-mail address: dsokal@fhi360.org (D.C. Sokal).

0010-7824/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2011.11.072

two hospitals between 1977 and 1989, including 1341 women in Santiago and 151 women in Valdivia [1]. The quinacrine regimens varied: women received from one to four insertions of quinacrine; most pellets had an in vitro dissolution time of 10 min; several adjuvants were tested including pentothal, dipyrone and diclofenac; and doses of quinacrine ranged from 180 to 375 mg per insertion. The cohort has been followed to collect long-term safety and effectiveness data, with methods approved by the Family Health International (now FHI 360) Protection of Human Subjects Committee.

2.2. Data collection

We initially contacted the women in 1991–1993, completed interviews with 54% of the 1492 quinacrine recipients (or family members of deceased women) and conducted hospital record reviews at the two hospitals. We collected similar data in four additional rounds: 1994–1996, 1999–2001, 2003–2005 and 2006–2007, again contacting and interviewing the women or family members and reviewing hospital records. During interviews, women were asked "Have you had any major health problems?" During record reviews, all surgeries were abstracted from hospital files. At least one interview has been completed for 86.0% of women at the Santiago site and 95.4% of women in Valdivia [9], although increasing numbers are becoming lost to follow-up, particularly in Santiago. The median age of the women in 2006–2007 was 51 years, with median follow-up of 18.5 years for a total follow-up time of 23,894 woman-years (w-y).

This analysis focuses on pelvic and lower abdominal surgeries and conditions occurring through 2007. All health events in this study were coded using the Medical Dictionary for Regulatory Activities (MedDRA) V5.0 (the internationally accepted system for coding medical information including adverse events). We reviewed surgical events in a two-step process to minimize the chance of missing a relevant event. First, in collaboration with the study statistician, we compiled a list of codes that might be associated with pelvic surgery, e.g., fibroids, pelvic pain, ovarian cyst, etc. Based on the relevant code list, the statistician provided a list of cases for data abstraction and further review of the case report forms. Second, one clinician (V.H.) conducted a primary review of two thirds of the cases, and another clinician (D.S.) conducted primary review of one third of the cases. The second clinician (D.S.) then reviewed the abstracted data and performed a second review of selected cases (N=85), including all cases that were marked "needs additional review." FHI clinicians then reviewed the hard copies of the case report forms of ambiguous cases.

In the case of discrepancies across forms or interview rounds regarding dates for the same apparent event, dates of events reported in the hospital records took precedence over dates reported during the personal interview, and dates reported earlier took precedence over dates that were reported later.

2.3. Outcomes

We tabulated adverse events comprising nonsurgical pelvic or abdominal diagnoses, conditions and complaints that might conceivably be considered potential sequelae of uterine or pelvic peritoneal exposure to quinacrine, echoing methods in the Vietnam quinacrine safety study [4].

We established a priori inclusion/exclusion criteria for the pelvic surgery cases. We excluded surgeries related to pregnancy outcomes, e.g., ectopic pregnancy or C-section, because earlier pregnancy data have been reported [8] and updated pregnancy data are being analyzed separately (manuscript in preparation). We also excluded pelvic surgery due to gynecologic cancers as those have been reported separately [9]. We excluded gall bladder surgeries because they are upper abdominal and unlikely to be related to pelvic spill of quinacrine. We also excluded surgical sterilization procedures. We found many surgeries related to urinary incontinence, and excluded those cases as well unless there was an indication of intraperitoneal surgery. These exclusion criteria are similar to the criteria used for identifying relevant pelvic surgeries in the Vietnam long-term safety study [4]. All remaining pelvic or abdominal surgeries that involved entry into the lower peritoneal cavity were included.

Within the aggregated pelvic surgeries, the event of primary interest was hysterectomy by any approach, with or without oophorectomy (excluding hysterectomy due to pregnancy complications). A second specific surgical outcome was intestinal obstruction, in light of concerns raised by US Food and Drug Administration staff regarding use of sclerosing agents for fallopian tube occlusion.

2.4. Analysis methods

Baseline characteristics of the cohort have been presented in previous publications and are not repeated here [6,7,9]. We computed frequencies and percentages for each gynecologic or abdominal endpoint. For all percentages, the numerator is the number of women who ever reported the specific problem being analyzed, and the denominator is the 1492 women in the cohort. If a participant had more than one problem in a given System Organ Class (e.g., gynecologic disorder), she is counted only once in that category. But multiple outcomes could be recorded for each woman if she reported more than one unrelated pelvic/abdominal surgery or health problem.

We used survival analysis to estimate the cumulative probability of surgical endpoints. We calculated cumulative 5-, 10- and 15-year Kaplan–Meier probabilities and their 95% confidence intervals (CIs). The first day in each analysis was the date of the first quinacrine insertion; the last day was the date of the first qualifying pelvic or abdominal surgery event, or the earliest censoring date. The two censoring

Table 1
Selected adverse events by system organ class and lower level term[a] (number and percent)

System organ class/lower level term	Number of participants	Percent of all participants
Selected gynecologic and lower abdominal disorders	334	22.4
Uterine fibroids	159	10.7
Pelvic pain	62	4.2
Benign ovarian neoplasm	55	3.7
Genital prolapse	47	3.2
Appendicitis	22	1.5
Adenomyosis	20	1.3
Benign cervix uteri neoplasm	10	0.7
Pelvic inflammatory disease	8	0.5
Uterine synechiae	5	0.3
Gastrointestinal obstruction	3	0.2
Peritonitis	3	0.2
Fallopian tube cyst	3	0.2
Hydrosalpinx	2	0.1
Uterine cyst	1	0.1

[a] Most specific level of diagnostic codes in the MedDRA system.

events were death and the last known date of follow-up (including proxy interviews for women who have died). We examined potential differences in surgery probabilities due to age at time of insertion (expressed dichotomously as <35 vs. ≥35) and number of insertions received (2 vs. 3).

3. Results

There were 490 relevant gastrointestinal or abdominal disorders recorded for 334 participants (22% of women; Table 1). Fibroids were the most common problem (11% of women); pelvic pain, benign neoplasms and prolapse followed (Table 1).

We found 230 relevant surgical and medical procedures recorded for 224 participants (15% of the analysis population; Table 2). Hysterectomy was the most frequent procedure (10% of the cohort), mostly due to fibroids or genital prolapse, followed by salpingectomy (2%).

The 15-year cumulative probability of any pelvic or lower abdominal surgical procedure was 14.7 per 100 women (95% CI 12.4–16.9; Table 3). The probability was higher among women aged 35 years or older at quinacrine insertion (16.4 per 100; 12.7–20.0) than women younger than 35 years at insertion (13.4 per 100; 10.6–16.3; data not shown). Similarly, the probability was slightly higher among women who received three insertions (14.9 per 100; 12.1–17.6) than women who received two insertions (13.2 per 100; 9.3–17.2; data not shown).

Table 2
Pelvic and abdominal surgeries by system organ class and lower level term[a] (number and percent)

System organ class/lower level term	Number of participants	Percent of participants
Surgical and medical procedures	224	15.0
Hysterectomy	143	9.6
Salpingectomy	26	1.7
Appendectomy	22	1.5
Prolapse repair	17	1.1
Other[b]	15	1.0

[a] Most specific level of diagnostic codes in the MedDRA system.
[b] Includes adhesiolysis, fallopian tube reconstruction, myomectomy, oophorectomy, ovarian cystectomy and unspecified pelvic surgery.

Table 3
Cumulative pelvic surgery probabilities and 95% confidence bounds through 15-year follow-up

All pelvic and abdominal surgeries				
Interval	No. at risk	Surgery probability[a]	Lower 95% bound	Upper 95% bound
Thru 5 years	1243	3.8	2.7	4.8
10 years	989	9.9	8.2	11.7
15 years	811	14.7	12.4	16.9

[a] Per 100 women.

The 15-year probability of hysterectomy was 9.3 per 100 women (95% CI 7.4–11.1; Table 4). The probability was higher among women aged 35 years or older at insertion (11.4 per 100; 8.3–14.6) than women younger than 35 years at insertion (7.7 per 100; 5.4–9.9; data not shown). The probability was slightly lower among women who received three insertions (8.9 per 100; 6.7–11.1) than women who received two insertions (9.7 per 100; 6.3–13.2; data not shown).

Three women had gastrointestinal obstructions (0.3%) after quinacrine insertion, two of whom required surgical intervention. The 15-year cumulative probability of intestinal obstruction was 0.2 per 100 women (0.0–0.6; data not shown). All three women with obstructions had a surgical intervention (cholecystectomy) that preceded the obstruction, and one woman also reported prior pancreatitis.

4. Discussion

Hysterectomy rates in this cohort of Chilean quinacrine users were higher than for overall US women through 2006 [10]. But the probability of hysterectomy in the Chilean quinacrine cohort (9 per 100 women at 15 years) was lower than that reported in the US Collaborative Review of Sterilization (CREST) study (17 per 100 procedures at 14 years) among US women who had had

Table 4
Cumulative hysterectomy probabilities and 95% confidence bounds through 15-year follow-up

Interval	No. at risk	Surgery probability[a]	Lower 95% bound	Upper 95% bound
Thru 5 years	1267	2.0	1.3	2.8
10 years	1034	5.8	4.4	7.1
15 years	859	9.3	7.4	11.1

[a] Per 100 women.

surgical sterilization [11]. In both the Chilean and US cohorts, older women had higher probabilities of hysterectomy than younger women.

Long-term follow-up has been done for one other large cohort of quinacrine recipients, in Vietnam [4]. That study had the added feature of a comparison group of IUD users. The probabilities of hysterectomy and rates of other pelvic/abdominal surgery were slightly but not significantly higher in quinacrine users compared with IUD users [4]. Access to surgery differs in Vietnam and Chile. During follow-up of Vietnamese quinacrine users, the hysterectomy incidence rate was 0.13 per 100 w-y [4], compared with 0.60 per 100 w-y in the Chile cohort. The incidence of all pelvic/abdominal surgeries in Vietnam was 0.27 per 100 w-y, compared with 0.95 per 100 w-y in Chile.

Our study features notable strengths. The follow-up period is remarkably long, and the stable cohort and accessible hospital records result in considerable person-time, relatively complete ascertainment of adverse events and substantial numbers of adverse events for analysis.

The main limitation of this study is the absence of an internal comparison group with which to compare our surgery and hysterectomy probabilities. But these data complement the long-term follow-up data on the Vietnam quinacrine cohort and its IUD control group, as well as the CREST study participants followed in the United States. Beyond that, the greatest threat to the validity of our results is loss during the lengthy follow-up, particularly at the Santiago site. Yet the follow-up rate here is better than that achieved by the CREST study in the United States, which reported follow-up of 58% of eligible surgically sterilized women at 8–14 years after the procedure [11]. Earlier analysis of the Chile cohort revealed that interviewed women were broadly similar to those not interviewed, although those interviewed were slightly older than those lost [6]. Arguably, women with problems would be more likely to generate hospitalization data and thus remain in the cohort, which would tend to increase the observed adverse event rates. Also, many women in the Santiago cohort continue to attend the hospital where the quinacrine insertions were conducted.

The short-term safety of nonsurgical quinacrine sterilization (deaths, immediate serious complications) has been demonstrated [3]. The carcinogenic potential of quinacrine has been evaluated in Chile [7,9] and in Vietnam [4,5], with reassuring results. In this study, the hysterectomy rates were unremarkable, adhesions and obstructions were rare, and the pattern of adverse events was not alarming nor did their probability increase with a higher number of quinacrine insertions. We found no compelling evidence of elevated rates of noncancer pelvic/abdominal surgeries or other adverse events in women who received quinacrine pellets for nonsurgical sterilization.

Acknowledgments

The authors are grateful to Dr. Jaime Zipper, inventor of the Quinacrine Pellet Method of Sterilization, for his mentoring and guidance over many years, and we are saddened to note that he died in March 2011. This project also owes much to the careful long-term follow-up work conducted in Valdivia by Dr. Rene Guzman-Serani, who died in April 2009. This study was supported in part by FHI 360 with funds from an anonymous foundation. The views expressed in this article do not necessarily reflect those of the authors' institutions. FHI 360 is an international not-for-profit organization that supports public health interventions and conducts research to improve health in developing countries.

References

[1] Zipper J, Trujillo V. 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases. Int J Gynaecol Obstet 2003;83(Suppl 2): s23–9.
[2] Cancel AM, Dillberger JE, Kelly CM, Bolte HF, Creasy DM, Sokal DC. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol 2010;56:156–65.
[3] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. Lancet 1993;342:213–7.
[4] Sokal DC, Hieu DT, Loan ND, et al. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. Contraception 2008;78:66–72.
[5] Sokal DC, Vach TH, Nanda K, et al. Quinacrine sterilization and gynecologic cancers: a case–control study in northern Vietnam. Epidemiology 2010;21:164–71.
[6] Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril 1995;64:325–34.
[7] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril 2000;74:169–71.
[8] Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 2000;61:379–84.
[9] Sokal DC, Trujillo V, Guzman SC, Guzman-Serani R, Wheeless A, Hubacher D. Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort. Contraception 2010;81:75–8.
[10] Merrill RM, Layman AB, Oderda G, Asche C. Risk estimates of hysterectomy and selected conditions commonly treated with hysterectomy. Ann Epidemiol 2008;18:253–60.
[11] Hillis SD, Marchbanks PA, Tylor LR, Peterson HB, for the U.S. Collaborative Review of Sterilization Working Group. Tubal sterilization and long-term risk of hysterectomy: findings from the U.S. Collaborative Review of Sterilization. Obstet Gynecol 1997;89: 609–14.

CELL COMMUNICATION & SIGNALING

REVIEW Open Access

Beyond DNA binding - a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers

Reza Ehsanian[1,2,3*], Carter Van Waes[1] and Stephan M Feller [3]

Abstract

This is an in-depth review of the history of quinacrine as well as its pharmacokinetic properties and established record of safety as an FDA-approved drug. The potential uses of quinacrine as an anti-cancer agent are discussed with particular attention to its actions on nuclear proteins, the arachidonic acid pathway, and multi-drug resistance, as well as its actions on signaling proteins in the cytoplasm. In particular, quinacrine's role on the NF-κB, p53, and AKT pathways are summarized.

Nomenclature and chemical grouping

Quinacrine (IUPAC name 4-N-(6-chloro-2-methoxyacridin-9-yl)-1-N,1-N-diethylpentane-1,4-diamine) is a heterocyclic three-ring compound (Figure 1A), and an acridine (Figure 1B) derivative (9-aminoacridine). It is readily available as quinacrine dihydrochloride, the dihydrochloride salt of quinacrine, for clinical use. The interest in quinacrine stems from its long history of therapeutic uses, as will be discussed in the following sections, and in particular its potential antineoplastic activities.

Quinacrine formulations and isomers are known by numerous designations some of which are: acrichine, Atabrine®, atebrine, atebrin, mepacrine, quinacrine dihydrochloride, quinacrine dihydrochloride dihydrate, quinacrine dihyrochloride (R)-isomer, quinacrine dihyrochloride (S)-isomer, quinacrine dimesylate, quinacrine hydrochloride, quinacrine monoacetate, quinacrine monohydrochloride, quinacrine monomesylate, quinacrine (R)-isomer, quinacrine (S)-isomer, and 6-chloro-9-[[4-(diethylamino)-1 methylbutyl]amino]-2-methoxyacridine. The most commonly used designations for quinacrine are mepacrine, quinacrine hydrochloride, quinacrine dihydrochloride, and the registered name Atabrine®. Quinacrine is one of several known aminoacridines which include, for example, acridine orange, acriflavine, aminacrin, amsacrine, ethacridine, nitracrine, proflavine and tacrine and which have a range of biological and therapeutic applications. Table 1 summarizes some of the key biological and therapeutic applications of these compounds.

History of quinacrine

Originally developed as pigments and dyes, the pharmalogical properties of acridine compounds were first investigated by Ehrlich and Benda in 1912, as antiprotozoal agents that act upon trypanosome parasites and developed further by Carl Browning as antibacterial agents [1-3]. The use of acridines as antibacterial agents fell out of favor in the 1940's after the discovery and wide spread availability of penicillin to combat bacterial infections. However, from the 1940's to the present day acridines have found wide use as antimalarial agents with Atabrine® (quinacrine) being one of the acridine derivatives successfully used to combat the disease. Atabrine® was discovered as part of an intensive antimicrobial research program broadly based on biologically active dyes carried out in 1930's in the German laboratories of I.G. Farbenindustrie. The program covered the preparation and trial of over 12,000 compounds leading

* Correspondence: rezae@stanford.edu
[1]Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA
Full list of author information is available at the end of the article

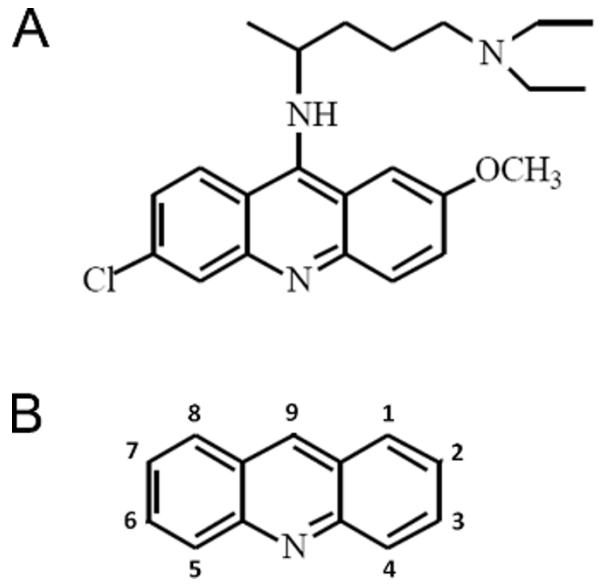


Figure 1 Structures of acridine and the acridine family member quinacrine. (A) Chemical structure of the acridine family member quinacrine. (B) Chemical structure of acridine.

to the identification of pamaquine and quinacrine as potential therapeutic agents [4].

Quinacrine was re-discovered in American laboratories as "American Atabrine" during the Second World War when an alternative to quinine was needed for the treatment of malaria [4]. The outcomes from the use of quinacrine in the armed forces demonstrated it to be superior to quinine and made it the official medicine for the treatment of malaria [5] until 1945 when it was substituted by chloroquine [6]. Before the substitution, millions of military personal took Atabrine® for prophylaxis. This allowed physicians in the US armed forces to conduct extensive follow-up studies and provide health professionals with detailed information on the side effects and toxicity of quinacrine, making it among the best studied drugs ever introduced. Three million soldiers took the drug for up to four years in the controlled setting of the military service where arguably compliance and follow up rates are much better than in a typical study in the civilian population [7-9].

Throughout the years, the use of quinacrine has continued attaining FDA-approval for the treatment of diseases such as malaria, giardiasis [10-13] and tapeworm infection [14-16]. Its therapeutic effectiveness has also been demonstrated in controlled studies in combating refractory lupus erythematosus [17-22], rheumatoid arthritis [21,23], and as an adjuvant cancer therapy [24,25]. In addition, quinacrine has been used as an intrapleural sclerosing agent to prevent recurrence of pleural effusion or pneumothorax in patients at high risk of recurrence, resulting in painless pleurodesis and remission of fluid and/or air collections [26-30]. Quinacrine has also been used for regional cancer therapy of pericardial and abdominal effusions with an ~25-50% responses rate [31]. Due to its effectiveness as a sclerosing agent, quinacrine has also been utilized for contraceptive purposes. It produces an asymptomatic fibrosis and occlusion of the fallopian canal [32-35]. It should be noted that for some of these conditions quinacrine has been superseded by other agents, however the use of quinacrine has to date not become contraindicated due to safety concerns. Quinacrine is currently being clinically tested in the treatment of Creutzfeldt-Jakob disease through the National Institute of Aging (NIA) [ClinicalTrials.gov Identifier: NCT00183092] and

Table 1 Selected aminoacridines and their typical applications

Acridine orange	A cationic cytochemical stain specific for cell nuclei, especially DNA. It is used as a supravital stain and in fluorescence cytochemistry. It may cause mutations in microorganisms.
Acriflavine	3,6-Diamino-10-methylacridinium chloride mixture. with 3,6-acridinediamine. Fluorescent dye used as a local antiseptic and also as a biological stain. It intercalates into nucleic acids thereby inhibiting bacterial and viral replication.
Aminacrine	A highly fluorescent anti-infective dye used clinically as a topical antiseptic and experimentally as a mutagen, due to its interaction with DNA. It is also used as an intracellular pH indicator.
Amsacrine	Aminoacridine derivative that is a potent intercalating antineoplastic agent. It is effective in the treatment of acute leukemias and malignant lymphomas, but has poor activity in the treatment of solid tumors. It is frequently used in combination with other antineoplastic agents in chemotherapy protocols. It produces consistent but acceptable myelosuppression and cardiotoxic effects.
Ethacridine	A topically applied anti-infective agent.
Nitracrine	Acridine antineoplastic agent used in mammary and ovarian tumors. It inhibits RNA synthesis.
Proflavine	3,6-Diaminoacridine. Topical antiseptic used mainly in wound dressings.
Tacrine	A cholinesterase inhibitor that crosses the blood-brain barrier. Tacrine has been used to counter the effects of muscle relaxants, as a respiratory stimulant, and in the treatment of Alzheimer's disease and other central nervous system disorders.
Quinacrine	An acridine derivative formerly widely used as an antimalarial but superseded by chloroquine in recent years. It has also been used as an anthelmintic and in the treatment of giardiasis and malignant effusions as well as a form of contraception/sterilization. It is used in cell biological experiments as an inhibitor of phospholipase A2.

Modified from National Library of Medicine - Medical Subject Headings; 2009 MeSH; MeSH Descriptor Data. http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Aminoacridines&field=entry#TreeD03.494.046.250; retrieved July 2010.

through the Medical Research Council, in the PRION-1 trial, [ClinicalTrials.gov Identifier: NCT00104663]. In addition, a trial has recently been completed in the treatment of androgen-independent prostate cancer through the University of Chicago and Cleveland Biolabs [ClinicalTrials.gov Identifier: NCT00417274].

Pharmacokinetics of quinacrine

The typical route of quinacrine administration is orally with water after a meal [36]. The drug can also be administered intralesionally/paralesionally [21,25,37,38], intramuscularly, rectally, intravenously [21], transcervically [34], and interstitially [26-30,39].

It is rapidly absorbed from the gastrointestinal tract following oral administration [40] with plasma levels increasing 2-4 hours after administration and reaching a peak in 8-12 hours [7,21]. Plasma concentration increases rapidly during the first week and equilibrates (94%) by the fourth week. Quinacrine is also rapidly absorbed and distributed after intrapleural, intralesion/paralesion, and intrauterine administration [41,42]. The plasma levels of quinacrine remain low in comparison to tissue concentrations. Peak plasma concentrations of up to 140 ng/ml (0.32 μM) for quinacrine have been documented on a standard malaria regimen [8]. It is distributed throughout the body and its liberation from different tissue compartments is slow. The highest concentrations are found in the liver, spleen, lungs and adrenal glands, with liver concentrations reaching 20,000 times that of plasma. The lowest concentrations of the drug are found in the brain, heart and skeletal muscle [6,8]. Quinacrine is also heavily deposited in the skin, fingernails and hair [21]. Spinal fluid concentrations are 1-5% of plasma levels. 80-90% of the drug is bound to plasma proteins when given at therapeutic doses and the half life of the drug is five to fourteen days depending on the dosing regimen [41,43]. Although small amounts are excreted in bile, sweat, and saliva [21,40], the major route of quinacrine elimination is via the renal system which may be enhanced by acidification and reduced by alkalinization [6,7].

Reported quinacrine toxicity

Quinacrine has the advantage of a long history of clinical use in the treatment of malaria, so that human tolerances are well known. In addition quinacrine has displayed tissue specificity making its toxicity tolerable in different therapeutic situations [21,44-46]. The following sections give an overview of the toxicity of quinacrine as it is applicable in the clinical setting.

General toxicity

Mostly minor or reversible adverse reactions include transient symptoms of mild headache, dizziness, or gastrointestinal symptoms (diarrhea, anorexia, nausea, abdominal cramps) which decrease with a reduction in dosage [21]. These symptoms occur in half of the patient population receiving 100 mg of quinacrine daily while almost all patients treated with higher doses experience some sort of adverse reaction. Some infrequent serious side effects of quinacrine have been reported and will be covered in the following sections.

Gastroenterological and hepatic toxicity

Persistent abdominal cramping or diarrhea has been reported for patients receiving the drug. These symptoms are readily dealt with by co-administration of bismuth-containing suspensions or antispasmodic agents. Long-term high-dose malarial suppressive therapy was occasionally associated with reversible hepatitis presumably due to quinacrine's tendency to concentrate in the liver. Transient lupus associated quinacrine hepatitis and peritonitis have also been reported, although these symptoms are attributed to doses three times that of the recommended dose [47,48].

Ophthalmologic and central nervous system toxicity

Quinacrine has very low risk of retinal toxicity [49,50]. At doses over 500 mg the drug has the potential to induce in rare cases a hypersensitivity reaction resulting in corneal edema, which is reversible [51,52]. Cortical stimulatory effects of quinacrine were documented in a study of a group of healthy volunteers given doses of quinacrine ranging between 200 to 1,200 mg daily for ten days [53]. At higher doses symptoms may include restlessness, vertigo, insomnia, nightmares, hyperirritability, psychosis and convulsions. Although toxic psychosis following quinacrine administration has been reported [54-56], large scale studies reveal this to be a rare and quickly reversible event. However it must be noted that a study of over 7,500 US soldiers given quinacrine (100 mg/day) in World War II revealed a 0.4% incidence of toxic psychosis [57]. Further investigations revealed twenty eight (0.1%) CNS-toxic cases among 30,000 treated for malaria [58].

Hematologic toxicity

The most serious potential toxicity of quinacrine is aplastic anemia. The incidence of aplastic anemia in World War II soldiers increased after the drugs introduction, but still remained quite low (0.003%) [59]. Reported cases of aplastic anemia have been associated with patients receiving more than the recommended daily dose and long treatment periods without having blood counts checked [60-65]. In considering this toxicity it is important to note that the potential lethality of aplastic anemia is readily preventable due to the early

signs of skin rash. Moreover, hypoplastic anemia can be identified with frequent routine blood tests [60]. In the more modern clinical setting 300 mg/day of quinacrine has been administered and found to be reasonably tolerated with no reported incidence of hematologic toxicity [66].

Dermatologic toxicity

In a study of 120,000 Australian soldiers serving during the Second World War only 1.6 percent developed rashes from quinacrine treatment. Eighty percent were eczematous and twenty percent were lichenoid or exfoliative [67]. Lichen planus was observed in 1 of 2,000 soldiers given 100 mg/day and in 1 of 500 given 200 mg/day. The dermatitis quickly resolved upon cessation of drug administration. Quinacrine can produce a yellow stain in the skin as well as areas of discoloration appearing like "black and blue marks" or bruises presumably due to melanin binding [67-69]. Slate-colored pigmentation of the palate and subungual areas were described in soldiers treated with quinacrine hydrochloride by Lippard and Kauer [69]. Hyperpigmentation of the oral mucosa, typically restricted to the hard palate has since been reported by many others [70]. These marks consist of membrane bound intracellular granules of quinacrine that contain large amounts of iron and some sulphur [67,71-76]. At the doses currently used, approximately half of the patients receiving the drug develop increased pigmentation and in half of these patients, an asymptomatic yellow stain is evident, which is reversible upon reduction to an average daily dose of <50 mg of the drug [21].

Carcinogenicity/Tumorigenicity

There have been no studies conducted to investigate the tumorigenicity of orally administered quinacrine in humans. The data that exist document the use of quinacrine in female sterilization. Retrospective analysis revealed that patients administered with intrauterine quinacrine had a slight but not statistically significant increase in the incidence of cancer compared to a control population. However, the studies concluded that there was no evidence for an excess risk of cancer development [34,77-79].

Conflicting tumorigenicity data have been reported in short term (up to 30 days) animal studies. Studies in female mice and rats have shown that quinacrine (at doses of 30 mg/kg and 22.5 mg/kg, respectively) enhanced growth of implanted tumor cells and decreased survival [80,81]. However, other studies in male mice have shown that quinacrine at doses between 20-25 mg/kg suppress the growth of transplanted tumors and increase the rate of survival [82-84]. These inconsistencies may be explained by a recent study that reveals that dosing schemes in mice that are not equivalent to that used in humans lead to tumor formation [10]. While tumor formation in mice receiving dosages that are equivalent to those currently used in the clinic are equivalent to that of control animals [10].

LD50 established in animal studies

The LD50 of quinacrine hydrochloride for rats is 900 mg/kg by oral administration [85,86]. The LD50 for the i.p. route for rats has not been estimated, but the experiments of Keeler and Richardson [87] suggest that it is approximately 250 mg/kg.

Mechanisms of quinacrine as an anti-cancer agent

Most of the efforts in anti-cancer drug discovery have so far been focused on identifying drugs which target a single protein. Currently there is an increasing recognition for the need of rationally designed drugs that act on several different proteins and pathways [88-90]. Hence "polypharmacology", the term used for drugs that bind to and modulate multiple targets, thereby eliciting several clinical effects, is an exciting and developing area of cancer research [91]. The anti-cancer mechanism of quinacrine is complex, with many potential cellular targets. This "shotgun" nature of the drug is what may make it attractive in the treatment of some cancers. The following sections describe the different anti-cancer mechanisms elicited and signaling pathways modulated by quinacrine.

Quinacrine intercalates into DNA

DNA is generally considered to be one of the biological targets for acridine anticancer compounds. There are three general modes of binding that characterize the compound interactions with double-stranded DNA: intercalation, groove binding and covalent binding [92-94]. Synthetic or natural acridine drugs display varying chemical and biological properties but they share the common property of DNA intercalation. This is due to the presence of an acridine "backbone" that confers a planar structure to the molecules, allowing them to intercalate into DNA by stacking between base pairs. The intercalation of several acridines has been demonstrated whereby the flat polyaromatic chromophore inserts between the base pairs of double-helical DNA. This process is driven by stacking and charge-transfer interactions between the aromatic systems of the acridine compounds and the DNA bases, resulting in unwinding of the helix [95,96]. The acridine derivative quinacrine is no exception, it also binds to DNA by intercalation [95,97-109]. It should be noted that intercalation is not the only type of interaction quinacrine has with DNA, another involves the diaminobutyl side chain which interacts with the minor groove of the

DNA and is involved in the stabilization of the double helix against thermal strand separation [110,111].

Parameters such as fluorescence quantum yield (i.e. absorption/emission spectra), binding constant, and flexibility in the quinacrine/polynucleotides complexes have been found to strongly depend on the DNA sequence [102,112,113]. In general, a clear difference has been found between the fluorescence quenching of quinacrine when comparing adenine (A)-thymine (T) rich polynucleotides to guanine (G)-cytosine (C) containing ones. Fluorescence emission is enhanced in AT polymers, and a marked quenching observed in GC polymers [98,100,101,103, 106-108,114]. Fluorescence-assayed preferential binding studies of quinacrine to DNA reveal that the neighbor base sequences influence the binding of quinacrine. In particular the sites where a GC base pair is involved were found to display high affinities [115]. The high affinity of quinacrine for DNA via intercalation can be hampered by denaturation or depurination [114,116].

Acridine interaction with nuclear enzymes - potential mechanisms for anti-tumor effects

It has been demonstrated that DNA intercalation is necessary but not sufficient for the antitumor activities of acridines [109,117,118]. Although the chemotherapeutic potency of acridines is partly determined by the strength of DNA binding [117,119-121], the antitumor properties of acridines are not solely due to their DNA binding, but also stem from specific interactions with certain enzymes. Hence the toxicities of acridines are not largely due to an unspecific toxicity associated with DNA damage or binding.

Telomerases as acridine targets

The two major classes of enzymes which have been considered as targets for these intercalating anticancer drugs are telomerases [122-126] and topoisomerases [127-131]. Topoisomerases have been well described as the target of many DNA-binding anti-cancer drugs while telomerases have more recently been the center of attention.

Telomerases are not active in normal somatic cells after birth. However, perhaps as many as 80-90% of cancer cells have reactivated telomerase [132]. Turning on this enzyme complex prevents or reverses telomere degradation and contributes to the growth of a malignant clone [133]. The inhibition of telomerase in cancer cells leads to growth arrest and ultimately cell death [132-134]. Acridines have been shown to help form or stabilize four-stranded intramolecular quadruplex structures (G-quadruplexes or G-quartets) from the guanine-rich DNA sequences of telomeres, which inhibit telomerase activity [123,126]. The formation of G-quadruplexes in telomeric DNA and the subsequent inhibition of telomerase make these conformations important as anti-cancer targets, and the drugs that help to form or stabilize them candidates for chemotherapeutic agents [135,136].

Topoisomerases as acridine targets

Tumor cells are thought to over-express topoisomerase enzymes to enhance cellular proliferation. As the degree of topoisomerase poisoning and inhibition is a function of the amount of the enzyme present, this mechanism provides a potentially selective mode for killing of tumor cells [130,137]. By inhibiting the re-ligation activity of topoisomerase enzymes, acridines convert topoisomerases into DNA damaging agents leading to cellular toxicity and death [117,127-131].

Quinacrine and telomerases

The mechanism of action of quinacrine on telomerase activity is not well described. Dominick et al. found that purified *E. aediculatus*, *T. thermophila*, and human telomerase was inhibited by quinacrine [138]. The banding patterns of the telomerase products generated in the presence of quinacrine were, however, not consistent with typical quadruplex stabilizing compounds which tend to cause enrichment of products associated with four repeats of the telomeric sequence [138,139]. Hence the exact process of quinacrine-induced inhibition of telomerase remains unclear. It should be noted that a 50 μM concentration of quinacrine was used to achieve telomerase inhibition, a dose well above the concentration needed to see the cytotoxic effects of quinacrine.

Quinacrine and topoisomerase

Quinacrine is suggested to be a topoisomerase inhibitor as it displays intercalative activity and structural similarity to other acridines. Furthermore, quinacrine, like topoisomerase poisons, inhibits DNA repair [140-142]. It also inhibits excision repair processes in *E. coli* [143,144] and in human fibroblasts exposed to ultraviolet light [142,145-147]. In addition, quinacrine also sensitizes cultured HA1 cells (a sub-line of Chinese hamster ovary cells) to killing by X-rays and it prevents the repair of single strand breaks [148]. It has further been shown to sensitize cells when applied at the time of irradiation or shortly beforehand and to prevent the enzymatic rejoining of single strand breaks [148]. Hence it has been postulated that the observed radiosensitization is attributable to its capacity to inhibit such repair processes, in which topoisomerases are implicated [141,142,147,149]. It has also been hypothesized [142,146,147] that densely packed chromatin structures must be transiently loosened by topoisomerase to render the DNA damage sites accessible to excision repair enzymes, particularly for access of repair endonuleases that excise the damaged site [150-152].

It must be noted that the majority of reports which suggest that quinacrine is a topoisomerase inhibitor do not provide direct experimental evidence supporting the topoisomerase inhibitory activity of quinacrine. In one set of studies the effect of quinacrine on topoisomerase is assumed from experiments where quinacrine inhibits UV-induced DNA repair with a Kd of 38.1 μM for reparative DNA synthesis [142] and 781 μM for inhibition of DNA incision [146]. Hence in many studies the effect of quinacrine on topoisomerase is assumed to be due to the effect on DNA repair and when quinacrine is shown to inhibit this nuclear enzyme, the concentration required to induce this effect is quite high.

Although relatively few research reports exist that study the direct role of quinacrine in topoisomerase inhibition, a recent report revealed a lack of detectable topoisomerase interaction for quinacrine at doses up to 11 μM [109]. In another study, an indirect measure of topoisomerase activity, the P4 DNA unknotting assay, revealed that a concentration of 50 μM quinacrine was required to inhibit topoisomerase II P4 unknotting activity. However, in the same study the lowest IC_{50} for growth inhibition was attained in a cell line where drug resistance should have been encountered if the mechanism of action was due to topoisomerase inhibition [153]. Also in the same investigation, no DNA breakage and no DNA-protein binding was observed at lower doses of quinacrine which were observed to have an inhibitory effect on *in vitro* growth [153]. The notion that relatively high amounts of quinacrine are needed to interfere topoisomerase was shown by dose-dependent inhibition of topoisomerase enzyme activity, with 30-40% inhibition at 20 μM and 80-90% inhibition at 100 μM [141]. In addition, the high (>700 μM) concentration of quinacrine needed to induce DNA incision observed by Thielmann et al. [146] hints that enzymes involved in DNA repolymerization and not topoisomerase may be involved. Taken together these finding indeed support the role of other nuclear enzymes in the anti-tumor effect observed by quinacrine. From the body of evidence in the literature it is valid to assume that the stifled DNA repair observed with quinacrine is mediated by the inhibition of other enzymes, for instance repair-specific UV endonucleases, DNA helicases [154], or DNA polymerases [147], but not topoisomerases. One can also assume that at lower doses the effect of quinacrine may not be attributed to its interaction with the DNA and inhibition of nuclear enzymes as detailed further in later section of this review.

Quinacrine effects on DNA and RNA polymerases

The literature describing the mechanism of quinacrine's anti-tumor effect suggests that two candidate families of nuclear enzymes, DNA polymerase and to a less extent RNA polymerase, may be involved in the mechanism of quinacrine's radiosensitizing ability. Effective nucleotide excision repair requires DNA gaps be filled by reparative DNA synthesis. In principle, all DNA polymerases found in the nucleus may play a role in this gap-filling. The effects of quinacrine on DNA and RNA polymerase reactions *in vitro* shed light on how quinacrine may inhibit enzymatic polymerization reactions *in vivo* and induce anti-tumor effects.

Early experiments have hinted at a mechanism of quinacrine preventing the action of DNA and RNA polymerase [155,156]. van Dyke et al. [155] demonstrated that quinacrine inhibits the incorporation of tritiated adenosine triphosphate primarily into RNA and DNA of the erythrocyte-free malaria parasite. In *Tetrahymena*, 32 μM quinacrine inhibits the synthesis of DNA (almost completely), RNA (70%), and protein (50%), and almost completely blocks the incorporation of labeled acetate into lipid components [156]. Evidence of quinacrine inhibition of DNA and RNA polymerase has also been obtained in *E. coli* K12, with RNA polymerase inhibition being less sensitive than DNA polymerase to quinacrine inhibition [110,111]. A K_d in excess of 10 μM is reported by O'Brien *et al*. [110] and Hahn *et al*. [111]. More recent work revealed that when normal rat liver and Novikoff hepatoma DNA polymerases α, δ, and ε were treated with a dose range of 0.1 μM to 200 μM quinacrine, the drug preferentially inhibited the DNA polymerases from the malignant cells [157]. The IC_{50} values of quinacrine inhibition were 15.2 μM, 22.6 μM, and 11.4 μM for DNA polymerase α, δ, and ε, respectively, that were isolated from hepatoma, compared to that of 92.5, 200, and 146 μM for DNA polymerase α, δ, and ε isolated from normal rat liver [157]. The observed differences in DNA polymerase inhibition most likely reflects differences in the weakening effect on DNA-protein interactions [157], which in turn suggest a specific change in the DNA-binding domains of the individual polymerase enzymes. This hypothesis has been supported by the discovery of sequence changes of these DNA-binding domains for human and yeast DNA polymerases [158,159].

It should be noted that inhibition of DNA polymerases in other experiments is achieved at much higher concentrations of quinacrine. Inhibition of Hepatitis B virus DNA polymerase by quinacrine was only achieved at over 700 μM [160]. This agrees with the results of Thielmann *et al*. [146] where approximately the same concentration of quinacrine was needed to induce DNA incision in human fibroblasts. It should also be noted that using a different system to analyze the inhibitory effect of quinacrine on Hepatitis B virus DNA polymerase Hess et al. [161] found quinacrine only to be effective in the 20 to 50 mM range. Hence

the cytotoxicity and anti-tumor effect of quinacrine achieved at lower dose well below those needed to generally inhibit polymerase activity must be attributed to other cellular mechanisms.

Interaction with and inhibition of proteins involved in multidrug resistance

Multidrug resistance (MDR) is a major obstacle to the effective treatment of cancer, as MDR proteins aid in the active transport of a broad range of anticancer drugs out of the cancer cells. This export is ATP-dependent, allowing efflux against concentration gradients. An important set of proteins involved in this export is the ATP-binding cassette transporter family, which includes P-glycoprotein (P-gp). P-gp is encoded by the MDR1 gene and its overexpression is one of the major underlying mechanisms of MDR. The upregulation of P-gp in cancer cells has made it an attractive therapeutic target for combating MDR. One hypothesis supposes that P-gp allows cells to achieve MDR by actively pumping the chemotherapeutic agent out of the cells, thereby reducing the toxic effect [162,163]. The interaction of acridine-based chemotherapeutics with P-gp thus inhibits not only their own efflux but may also the efflux of co-administered chemotherapeutics, as well as increasing uptake into cells [164-168]. The interaction of acridine derivatives with proteins involved in MDR is not related to their DNA intercalation capabilities and appears to be an exciting new strategy for chemotherapy [162,167,169].

Quinacrine is implicated in the reversal of the MDR phenotype from several studies. It has been shown to reverse drug resistance to vincristine in a MDR subclone of K562 cells (a human chronic myelogenous leukemia cell line) starting at 5 μM [170]. Furthermore, it has been demonstrated to induce cytotoxicity, but the exact mechanism of cell death was not investigated [170]. The effect of quinacrine in reversing the MDR phenotype in leukemia cell lines *in vitro* was also supported by other investigators who used approximately 6 μM of quinacrine to increase cellular uptake of vincristine. They observed a cytotoxic effect with approximately 1aμM of quinacrine treatment, reducing cell growth by 82% when used alone, and almost completely inhibiting growth when combined with vincristine [171]. These same investigators then went on to conduct *in vivo* experiments showing the reversal of vincristine resistance with addition of 50 or 80 mg/kg/day of quinacrine [171].

The only direct test of the role of quinacrine as an inhibitor of P-gp has been conducted by using a multidrug resistant human T-cell leukemic cell line which expresses P-gp as a doublet that can be photaffinitty labeled by the analog of vinblastine, N(p-azido-[3-^{125}I] salicyl)-N'-β- amlnoethylvindesine ([^{125}I]NASV) [172]. [^{125}I]NASV specifically binds to P-gp and the inhibition of its binding was used as a read out for the affinity of quinacrine for P-gp. In this study the binding affinity of quinacrine to P-gp was correlated to its ability to increase vinblastine sensitivity. It is, however, noteworthy that, although in an earlier investigation published by the same authors quinacrine increased the toxicity of vinblastine (12-fold) and vincristine (15-fold) at 5 μM and had an IC_{50} of 14 μM when administered alone [173], in this subsequent study a 50 μM dose only partially reduced [^{125}I]NASV labeled P-gp [172].

The study of quinacrine's role in MDR has not been limited to leukemia but it has also been analyzed in MDR cells from the ovary and prostate cancer. Quinacrine was reported to affect MDR Chinese hamster ovary (CHO) cells at 6 μM in studies measuring the uptake of labeled palmitoyl carnitine and palmitoyl lysophosphatidyicholine. They were more rapidly taken up by the MDR cells and this uptake was reversed after quinacrine treatment back to the rates observed with the parental cell line, hence implicating quinacrine in reversing the MDR [174]. It also enhanced the activity of paclitaxel in hormone-refractory prostate cancer cells both *in vitro* and *in vivo* [175]. Quinacrine itself displayed IC_{50} values of 3.1 μM for PC-3, of 4.7 μM for PC-3M (a MDR sub-clone of the cell line) and of 3.5 μM for DU145 cells. Combination therapy of quinacrine and paclitaxel were determined to be synergistic in both, *in vitro* and *in vivo* (mouse xenografts) experiments. The exact mechanism of this synergistic effect was not studied however, the authors attributed to quinacrine's effect on phospholipase A_2 (PLA_2)[175].

Disruption of the arachidonic acid pathway

Manipulations of the arachidonic acid pathway (Figure 2) have received considerable attention in the chemoprevention of cancer [176-180]. Agents which inhibit this pathway have been demonstrated to hold promise in the chemoprevention of prostate, gastrointestinal, lung as well as esophageal cancer [177,181-184]. Although cyclooxygenase has been the focus of many anti-neoplastic agents targeting the arachidonic acid pathway [185], other components of the pathway could potentially also be promising targets. One such putative target, PLA_2, hydrolyzes the sn-2-acyl bond of membrane phospholipids to produce arachidonic acid (Figure 2), which has been implicated in a variety of signal transduction events, including those regulating malignant cell proliferation [186,187]. Histological studies suggest that membrane phospholipase A_2 expression levels are associated with tumor aggressiveness in gastric [188] and breast cancers [189].

Disruption of the arachidonic acid pathway by quinacrine via inhibition of PLA_2, leads to a wide array of

effects. The inhibition of PLA_2 [190-193] occurs via quinacrine's binding to membrane phospholipids (primarily phosphatidylethanolamine), and subsequent intercalation into the membrane [194-198] and inhibition of PLA_2 membrane binding and activity [190-193,199]. The decrease in arachidonic acid due to PLA_2 inhibition [199] in turn results in the inhibition of leukotrienes (LOX activity) and prostanoids (COX activity), as well as eicosanoids (MOX/CYP450 activity) [193,194, 200-210]. This is of interest since recent reports implicate an enhanced activity of arachidonic acid pathway proteins in preventing apoptosis and promoting tumor progression in head and neck cancer [211-222].

In platelets, the conversion of arachidonic acid to thromboxane is suppressed by quinacrine [21,206, 210,223]. Thromboxane is a major factor in blocking the release of arachidonic acid from cellular phospholipases. In addition, thromboxane is involved in angiogenesis and the development of tumor metastasis [224-226]. Quinacrine also decreases prostaglandin E2 (PGE_2)

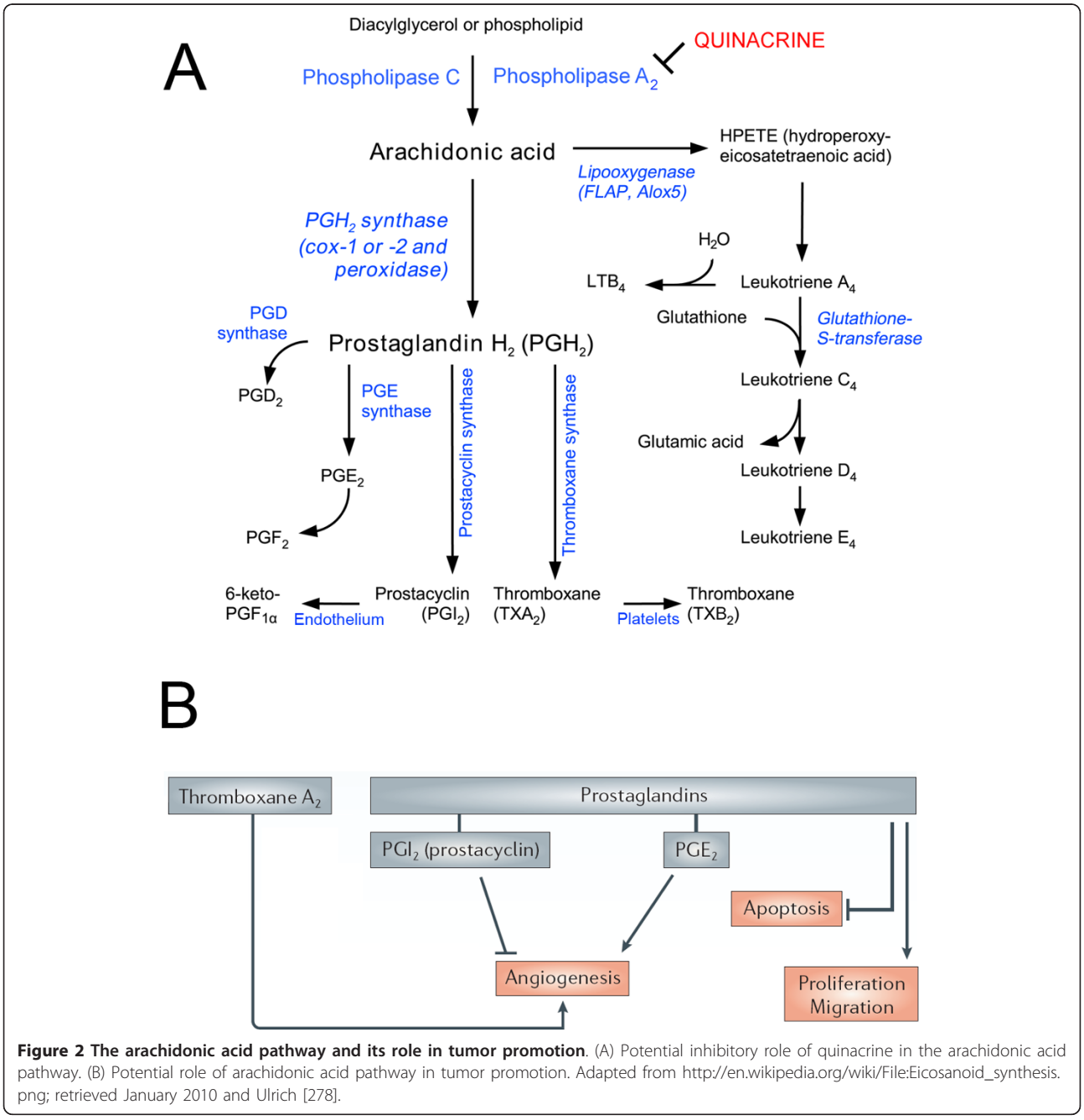


Figure 2 The arachidonic acid pathway and its role in tumor promotion. (A) Potential inhibitory role of quinacrine in the arachidonic acid pathway. (B) Potential role of arachidonic acid pathway in tumor promotion. Adapted from http://en.wikipedia.org/wiki/File:Eicosanoid_synthesis.png; retrieved January 2010 and Ulrich [278].

production in a dose-dependent manner. Prostaglandin, PGE_2 and the COX2-PGE_2 pathway/arachidonic acid pathway play an important role in the induction of the pro-inflammatory response and ultimately tumorigenesis [227-229]. PGE_2 levels have been implicated in angiogenesis, tumor growth and invasion, apoptosis resistance and suppression of anti-tumor immunity via suppression of T and NK cells, and amplifying T_{reg} [227,230-232]. The upregulation and pro-oncogenic actions of PGE_2 have been demonstrated in head and neck cancer [222,233-237].

Quinacrine as an inducer of p53 and inhibitor of the NF-κB and AKT pathways

The deleterious roles of p53 inactivation [238,239] and nuclear factor-kB (NF-κB) hyperactivation [240,241] have been well established in human cancers. They lead to inhibition of cell death and promotion of oncogenesis. Cross talk between these two pathways has been identified and studied (Figure 3). It has been reported that p53 and NF-κB repress each other's activity by competing for transcriptional proteins such as p300 and CREB-binding protein (CBP) [242]. One signaling protein known to influence this competition is IKKα [243,244]. In particular, IKKα has been implicated in phosphorylating and directing CBP to participate in either the p53 or NF-κB pathway [243,244]. Another well studied signaling protein, AKT, can both activate IKKs as well as phosphorylate and enhance the transcriptional activity of p65 (NF-κB complex protein) [245-247]. In addition it has been demonstrated that AKT-mediated phosphorylation of MDM2 inhibits p53 stabilization [248]. Hence, it is likely that inhibitors of AKT activation could be utilized as anti-cancer agents for the inactivation of p53 and the inhibition NF-κB signaling.

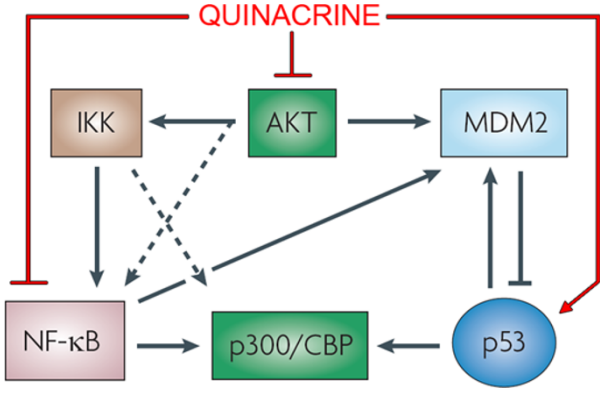


Figure 3 Cross talk between NF-κB and p53. There are many lines of crosstalk between the p53 and NF-κB pathways. A few of these are highlighted, such as AKT and the transcriptional co-activator proteins CREB-binding protein (CBP) and the related p300 protein. AKT can activate both IκB kinases (IKKs) and phosphorylate p65. AKT-mediated MDM2 phosphorylation can also inhibit p53 stabilization. Due to competition for the limited pool of CBP/p300, this protein also plays a crucial role in determining which pathway dominates in terms of cellular outcome. In addition, NF-κB has been shown to directly upregulate the levels of MDM2 mRNA and hence the protein. One promising aspect of quinacrine is its simultaneous ability to inhibit AKT, to induce the p53 pathway, and to inhibit the NF-κB pathway. Adapted from Dey et al. [279].

Besides the development of AKT inhibitors, there has been no concerted effort to rationally design drugs that can simultaneously activate p53 and inhibit NF-κB. The opposing nature of these pathways suggests that a drug which activates p53 and simultaneously inhibits NF-κB would have significant clinical potential due to the fact that it is concomitantly modulating two critical cancer targets. In addition, a drug capable of affecting both of these pathways would also be a useful tool to study the interactions between the opposing p53 and NF-κB pathways. The literature [249] and further unpublished work from members of the Tumor Biology Group of NIDCD at NIH point to quinacrine as being such a drug (Van-Waes et al., unpublished data).

Quinacrine and p53

Several recent investigations support the notion that quinacrine-induced cell death is caused by a mechanism that is independent of DNA damage [250-252]. Quinacrine has been demonstrated to stabilize p53 in a manner that differs from that of DNA-damage induced p53 stabilization [250,251]. Wang *et al*. have reported the ability of quinacrine and other acridine derivatives to activate wild-type p53 transcription in ovarian cancer, non-small cell-lung carcinoma and colon adenocarcinoma cell lines, independent of DNA damage and MDM2 [251]. This DNA damage- and MDM2-independent effect of quinacrine in activating wild-type p53 in a diverse set of cell lines was supported by Gurova *et al*. when they found that quinacrine activates p53 in renal cell carcinomas, non-small cell lung carcinoma, colon and breast carcinomas, prostate adenocarcinomas, and fibrosarcomas [250]. Friedman et al. extended these findings to reveal that quinacrine activates p53 in several different head and neck squamous cell carcinoma cell lines with wild-type p53 [249]. The cell death induced after quinacrine treatment was not only p53 dependent [250], but also involved Bcl-2-associated X protein (BAX) [251], thereby indicating an important role of the mitochondrial apoptosis pathway. This suggests that other signaling proteins may also be involved in the cell death induction by quinacrine. The mechanism of p53 activation by quinacrine and its ability to modulate other signaling proteins may minimize the toxic side effects seen with treatments using DNA-binding platinum agents, making it potentially a desirable anticancer agent.

Quinacrine and NF-κB

The unique mechanism of p53 upregulation which differs from the genotoxic upregulation of p53 was not investigated by Wang *et al*. [251], but Gurova *et al*. [250], found the induction of p53 to be linked to the inhibition of NF-κB. These results were later extended using a skin inflammation mouse model where the contact hypersensitivity (CHS) response to chemical allergen sensitization was evaluated [253]. In this mouse model the authors identified NF-κB to be critical in the development of the contact hypersensitivity response and demonstrated that quinacrine reduced CHS by inhibiting NF-κB activation and as well as cytokines (TNFα, IL-1β, and CCL21) that are dependent on NF-κB activation [253].

NF-κB is also a key regulator of cytokine-induced expression of endothelial cellular adhesion molecules (CAMs) [254,255]. The inhibitory effect of quinacrine on NF-κB in this context was supported in experiments where $NiCl_2$- and $CoCl_2$-induced cellular activation of ICAM-1 was inhibited by quinacrine [256]. The effect was attributed to PLA_2 because the enzyme causes the generation of platelet activation factor and eicosanoids [257], which are thought to play a role in the activation of NF-κB [256].

NF-κB has been recently shown to also depend on arachidonic acid metabolites [258] and upstream inhibition by quinacrine has been proposed to inhibit the activation of NF-κB due to its inhibitory effects on PLA_2 [259]. In a study evaluating the effect of lysophosphatidic acid (LPA) on endothelial cell activation, quinacrine blocked LPA-stimulated activation of NF-κB as well as the increase in expression of genes known to be dependent on the activation of the NF-κB transcription factor: E-selectin, ICAM-1, IL-8, and MCP-1 [260].

Another interesting line of investigation further revealed that reactive oxygen intermediates (ROI) are implicated in UVB-induced expression of TNFα in keratinocytes and that COX products and, more importantly, LOX products, also known as eicosanoids, which are themselves products of an oxidative metabolism, are the main ROI implicated in this induction [261]. The investigators hypothesize that eicosanoids likely exert their function through activation of NF-κB [261]. They also attributed the reduction of TNFα mRNA after quinacrine administration to the inhibitory activity of quinacrine on PLA_2, based on reports showing that UVB can induce PLA_2 in keratinocytes [262-264]. Another study investigating the source of oxygen radicals which activate Kupffer cell NF-κB after co-culture with AH70 cells attributed the attenuation of oxidative NF-κB activation to the PLA_2 inhibitory activity of quinacrine [265].

However, because many studies do not directly implicate PLA_2 inhibition by quinacrine as the mechanism of NF-κB inhibition and in light of more recent investigations challenging the notion that quinacrine acts primarily as an inhibitor of PLA_2 [200,253,266], quinacrine's effect is presumably, at least partially, due to NF-κB inactivation via a mechanism other than PLA_2 inhibition. Pupe et al. [261] present another intriguing mechanism for NF-κB inactivation as their experiments revealed quinacrine to inhibit UVB-induced IκBα degradation. However, this type of inhibition may be tumor-specific since another mechanism of NF-κB inhibition, nuclear translocation and sequestration of an inactive complex, has been well documented.

Unlike other NF-κB inhibitors, quinacrine does not inhibit the NF-κB pathway via cytoplasmic sequestration of p65. Instead, published experiments indicate a mechanism involving confinement of the p65 complex in the nucleus in an inactive state [250]. The increased presence of NF-κB in the nucleus after quinacrine exposure was supported by experiments revealing increased DNA binding of NF-κB after quinacrine treatment alone or in combination with TNFα [267]. These experiments also revealed that quinacrine plus TNFα induced greater NF-κB DNA binding than TNFα treatment alone. The lack of DNA binding inhibition of NF-κB after quinacrine treatment was also confirmed in a report by Fabbri *et al*. [268].

Down-regulation of p65 Ser536 phosphorylation by IKKα has been suggested as the primary mechanism of action for quinacrine [250]. The physiological importance of this inhibition was recently confirmed in the skin inflammation mouse model described in a previous section [253]. Further support of this mechanism was attained by Na *et al*. when hydrogen peroxide-induced phosphorylation of the p65 subunit of NF-κB was partially inhibited by quinacrine [269]. The effects of quinacrine on NF-κB are in line with its uses in the treatment of inflammatory diseases as a single agent or in combination with other medications [21]. As discussed further below, first hints of the mechanism by which quinacrine may inhibit the NF-κB pathway and promote the p53 pathway have come from studies with 9-aminoacridine (9AA), which implicated AKT and mTOR as targets for quinacrine [270].

Quinacrine and AKT

As shown in Figure 3, AKT is involved in the NF-κB and p53 signaling pathways [245,271,272]. AKT phosphorylates the p65 subunit of NF-κB at Ser536, ultimately stimulating NF-κB transcriptional activity [272,273]. In addition, AKT phosphorylates MDM2 on Ser166 [271]. AKT phosphorylation of MDM2 induces translocation of MDM2 into the nucleus and targets p53 for destruction [271]. Phosphorylated MDM2 also transports p53 from the nucleus to the cytoplasm where

it is involved in the induction of p53 degradation through the proteasome. Therefore, AKT is a critical signaling protein involved in the suppression of p53 activity. This hypothesis has been supported by experiments demonstrating a correlation between AKT kinase activity and inhibition of p53 [272].

Guo *et al*. demonstrated that 9AA inhibits AKT activity and its phosphorylation at Ser473 [270]. They went on to show that this inhibition was not a direct effect of reduced PI3K activity and implicated mTOR in this inhibition. Hence, it seems that acridines like quinacrine may be involved in stopping a positive feedback loop between AKT and mTOR [270]. The inhibition of AKT activity by 9AA has also been confirmed by other investigators in a model of human T-cell leukemia virus-transformed cells [274]. Furthermore, in a study of the role of arachidonic acid metabolism and epidermal growth factor (EGF) receptor in neurotensin-induced prostate cancer cell growth, quinacrine's activity as an inhibitor of AKT was reaffirmed. These experiments revealed quinacrine to inhibit neurotensin-, and to a lesser degree EGF-stimulated phosphorylation of AKT [275].

The multiple actions of quinacrine and its established history of safety make it an attractive anti-neoplastic chemotherapeutic agent

Since its discovery as a potent antimalarial compound, quinacrine has been effective not only in the treatment, but also as a prophylaxis for malaria as well as a medication for a wide range of other disorders. Due to its anti-inflammatory activity in patients with autoimmune disorders quinacrine has been used to treat lupus erythematosus, rheumatoid arthritis, bronchial asthma and other inflammatory diseases. The safety of and bioavailability of quinacrine has been demonstrated as patients with these diseases used quinacrine for months at a time to control their symptoms. The pharmacokinetics and safety of quinacrine has been extensively studied as it was administered as a protective measure to millions of US soldiers in the Pacific region during World War II.

Some of the more serious side effects of quinacrine are mild in comparison to other anti-cancer chemotherapeutics and most of the conditions can be easily reversed after treatment cessation or dose reduction. Many of quinacrine's side effects develop gradually, starting from minor lesions in the case dermatitis or a slight decrease in blood counts in the development of anemia, and have been found to be completely and easily reversible, if quinacrine use is discontinued at this early stage [21,49,64,276]. Indeed some of the side effects exhibited due to quinacrine treatment can be used in the clinical setting to confirm proper dosing of the drug in the treatment of cancer patients. The yellow discoloration of the skin due to the accumulation of the bright yellow compound would indicate to the clinician that the drug has reached the equilibrium and as in the case of squamous cell carcinomas, has potentially reached areas where tumor has developed.

Furthermore, the polypharmacology of quinacrine make it an attractive drug in the use of different cancer types. In addition, as inflammation is now being considered the seventh hallmark of cancer [277], quinacrine's anti-inflammatory effects would seem to increase its potential utility as a anti-cancer drug. As more research is being conducted into quinacrine's mechanisms of action, investigators have begun to realize that its interactions extend beyond mere DNA binding and effects on nuclear proteins. Quinacrine has thus been shown to bind and inhibit proteins involved in multidrug resistance, to disrupt the arachidonic acid pathway, as well as affecting the p53, NF-κB and AKT pathway. Its effects on multiple key signaling pathways, implicated in the malignant progression of numerous cancer types, make quinacrine an exciting candidate as a chemotherapeutic agent in new types of combination treatments. Continued research into the mechanisms of this drug is clearly warranted as it may be used in addition to established therapeutic regimes in hopes of ultimately reducing toxic side effects of drugs, such as DNA damaging agents, currently used in the clinic.

Acknowledgements

The authors would like to thank Zhong Chen, Jay Friedman, and Liesl Nottingham for their input. This work was partially supported by the HeadsUp and CRUK charities. Reza Ehsanian was supported by an NIH-Oxford Fellowship, a Stanford Medscholars Fellowship and HHMI Scholars Fellowship. RE and CVW were supported by NIDCD intramural project ZIA-DC-000016.

Author details

[1]Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, USA. [2]Stanford University School of Medicine, Stanford, CA, USA. [3]Cell Signalling Group, Department of Molecular Oncology, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford University, Headley Way, Oxford OX3 9DS, UK.

Authors' contributions

All authors contributed to the writing of this manuscript and approved the final version.

Competing interests

The authors declare that they have no competing interests.

Received: 5 March 2011 Accepted: 15 May 2011 Published: 15 May 2011

References

1. CH Browning, JB Cohen, R Gaunt, R Gulbransen, Relationships between antiseptic action and chemical consitution with special reference to compounds of the pyridine, quinoline, acridine and phenazine series. Proceedings of the Royal Society. **93**, 329–366 (1922). doi:10.1098/rspb.1922.0025

2. CH Browning, Synthetic dyes as antiseptics and chemotherapeutic agents. Nature. **109**, 750–751 (1922)
3. M Wainwright, Acridine-a neglected antibacterial chromophore. J Antimicrob Chemother. **47**, 1–13 (2001)
4. D Greenwood, Conflicts of interest: the genesis of synthetic antimalarial agents in peace and war. J Antimicrob Chemother. **36**, 857–872 (1995). doi:10.1093/jac/36.5.857
5. Office of the Surgeon General UCln, The drug treament of malaria, suppressive and clinical. J Am Med Assoc. **123**, 205–208 (1943)
6. LS Goodman, A Gilman, (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics. (New Yourk: Macmillian, 1954), 2
7. Joint Report of the Armored Medical Research Laboratory and Commission on Tropical Diseases AEB, Preventative Medicine Service, Office of the Surgen General, US Army, Plasma quinacrine concentration as a function of dosage and enviornment. Arch Intern Med. **78**, 64–107 (1946)
8. JA Shannon, DP Earle, BB Brodie, JV Taggart, RW Berliner, TRSotR Service, The pharmacological basis for the rational use of Atabrine in the treatment of malaria. J Pharmacol Exp Ther. **81**, 307–330 (1944)
9. JW Jailer, Fluorescent microscopic study of the physiological distribution of Atabrine. Science. **102**, 258–259 (1945). doi:10.1126/science.102.2645.258
10. AM Cancel, JE Dillberger, CM Kelly, HF Bolte, DM Creasy, DC Sokal, A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul Toxicol Pharmacol. (2009)
11. RR Babb, Giardiasis. Taming this pervasive parasitic infection. Postgrad Med. **98**, 155–158 (1995)
12. GL Mandell, JE Bennett, R Dolin, Principles and practice of infectious diseases. in *Principles and practice of infectious diseases*, ed. by Mandell GL, Bennett JE, Dolin R (New York: Churchill Livingstone, 1995), pp. 4–69
13. SJ Lerman, RA Walker, Treatment of giardiasis: literature review and recommendations. Clin Pediatr (Phila). **21**, 409–414 (1982). doi:10.1177/000992288202100704
14. PW Pappas, DA Leiby, Competitive, uncompetitive, and mixed inhibitors of the alkaline phosphatase activity associated with the isolated brush border membrane of the tapeworm Hymenolepis diminuta. J Cell Biochem. **40**, 239–248 (1989). doi:10.1002/jcb.240400212
15. AC Cruz, Treatment of human taeniasis in the Philippines: a review. Southeast Asian J Trop Med Public Health. **22**(Suppl):271–274 (1991)
16. PA Koul, A Wahid, MH Bhat, JI Wani, BA Sofi, Mepacrine therapy in niclosamide resistant taeniasis. J Assoc Physicians India. **48**, 402–403 (2000)
17. R Feldmann, D Salomon, JH Saurat, The association of the two antimalarials chloroquine and quinacrine for treatment-resistant chronic and subacute cutaneous lupus erythematosus. Dermatology. **189**, 425–427 (1994). doi:10.1159/000246899
18. V Werth, Current treatment of cutaneous lupus erythematosus. Dermatol Online J. **7**, 2 (2001)
19. S Kalia, JP Dutz, New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther. **20**, 160–174 (2007). doi:10.1111/j.1529-8019.2007.00131.x
20. I Cavazzana, R Sala, C Bazzani, A Ceribelli, C Zane, R Cattaneo, A Tincani, PG Calzavara-Pinton, F Franceschini, Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. Lupus. **18**, 735–739 (2009). doi:10.1177/0961203308101714
21. DJ Wallace, The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. Semin Arthritis Rheum. **18**, 282–296 (1989). doi:10.1016/0049-0172(89)90050-4
22. D Lipsker, JC Piette, P Cacoub, P Godeau, C Frances, Chloroquine-quinacrine association in resistant cutaneous lupus. Dermatology. **190**, 257–258 (1995). doi:10.1159/000246710
23. RI Rynes, Antimalarial drugs in the treatment of rheumatological diseases. Br J Rheumatol. **36**, 799–805 (1997). doi:10.1093/rheumatology/36.7.799
24. WA Denny, BC Baguley, BF Cain, MJ Waring, Antitumor acridines. in *Molecular apects of anticancer drug action*, ed. by Neidle S, Waring MJ (London: Macmillin, 1983), pp. 1–34
25. RI Hiller, A study of quinacrine dihyochloride in the human breast in vitro and in vivo. Am J Surg. **119**, 317–321 (1970). doi:10.1016/0002-9610(70)90058-9
26. SA Taylor, NS Hooton, AM Macarthur, Quinacrine in the management of malignant pleural effusion. Br J Surg. **64**, 52–53 (1977). doi:10.1002/bjs.1800640113
27. S Koldsland, JL Svennevig, G Lehne, E Johnson, Chemical pleurodesis in malignant pleural effusions: a randomised prospective study of mepacrine versus bleomycin. Thorax. **48**, 790–793 (1993). doi:10.1136/thx.48.8.790
28. V Agrenius, V Ukale, O Widstrom, G Kallenius, SB Svenson, Quinacrine-induced pleural inflammation in malignant pleurisy: relation between drainage time of pleural fluid and local interleukin-1 beta levels. Respiration. **60**, 366–372 (1993). doi:10.1159/000196237
29. HM Janzing, A Derom, E Derom, C Eeckhout, F Derom, MT Rosseel, Intrapleural quinacrine instillation for recurrent pneumothorax or persistent air leak. Ann Thorac Surg. **55**, 368–371 (1993). doi:10.1016/0003-4975(93)90999-X
30. AJ Larrieu, GF Tyers, EH Williams, MJ O'Neill, JR Derrick, Intrapleural instillation of quinacrine for treatment of recurrent spontaneous pneumothorax. Ann Thorac Surg. **28**, 146–150 (1979). doi:10.1016/S0003-4975(10)63772-1
31. DA Karnofsky, Cancer Chemotherapeutic Agents. CA Cancer J Clin. **14**, 67–72 (1964). doi:10.3322/canjclin.14.2.67
32. RV Bhatt, A Aparicio, LE Laufe, T Parmley, TM King, Quinacrine-induced pathologic changes in the fallopian tube. Fertil Steril. **33**, 666–667 (1980)
33. DT Hieu, TT Tan, DN Tan, PT Nguyet, P Than, DQ Vinh, 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. Lancet. **342**, 213–217 (1993). doi:10.1016/0140-6736(93)92302-A
34. E Kessel, 100,000 quinacrine sterilizations. Adv Contracept. **12**, 69–76 (1996). doi:10.1007/BF01849629
35. J Zipper, V Trujillo, 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases. Int J Gynaecol Obstet. **83**(Suppl 2):S23–29 (2003)
36. *Physicians' Desk Reference*, 47th edn. (Montavile, NJ: Thomas PDR, 1993)
37. F Ottolenghi-Lodigiani, Treatment of chronic lupus erythematosus, local intradermal infiltration with an acridine preparation. Hautarzt. **6**, 24–27 (1955)
38. W Thies, Recent experience in the treatment of erythematodes chronicus discoides with atebrin and resochin, with special reference to local and combined therapeutic methods. Hautarzt. **6**, 227–232 (1955)
39. TC Bayly, DL Kisner, A Sybert, JS Macdonald, E Tsou, PS Schein, Tetracycline and quinacrine in the control of malignant pleural effusions. A randomized trial. Cancer. **41**, 1188–1192 (1978). doi:10.1002/1097-0142(197803)41:33.0.CO;2-O
40. WC Campbell, The chemotherapy of parasitic infections. J Parasitol. **72**, 45–61 (1986). doi:10.2307/3281795
41. S Bjorkman, LO Elisson, J Gabrielsson, Pharmacokinetics of quinacrine after intrapleural instillation in rabbits and man. J Pharm Pharmacol. **41**, 160–163 (1989)
42. LE Laufe, DC Sokal, LP Cole, D Shoupe, RS Schenken, Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception. **54**, 181–186 (1996). doi:10.1016/S0010-7824(96)00174-6
43. S Looareesuwan, RE Phillips, G Edwards, CL Rodick, P Chanthavanich, W Supanaranond, DA Warrell, Mepacrine accumulation during treatment of chloroquine-resistant falciparum malaria. Ann Trop Med Parasitol. **82**, 107–112 (1988)
44. NB Ackerman, DK Haldorsen, DL Wallace, AJ Madsen, AS McFee, Aminoacridine uptake by experimental tumors. JAMA. **191**, 103–104 (1965)
45. NB Ackerman, A Shemesh, Localization of aminoacridine fluorescence in lung tumors of rats. JAMA. **187**, 832–833 (1964)
46. LJ Anghileri, Uptake of iodine-131-labelled atabrine by Ehrlich ascites tumour and by sarcoma S-180 BALB. Nature. **211**, 878 (1966)
47. W Gibb, DA Isenberg, ML Snaith, Mepacrine induced hepatitis. Ann Rheum Dis. **44**, 861–862 (1985). doi:10.1136/ard.44.12.861
48. SJ Walker, S Montgomery, R Brearley, A Galloway, A case of primary peritonitis possibly related to mepacrine. J R Coll Surg Edinb. **32**, 321–322 (1987)
49. RL Zuehlke, PJ Lillis, A Tice, Antimalarial therapy for lupus erythematosus: an apparent advantage of quinacrine. Int J Dermatol. **20**, 57–61 (1981). doi:10.1111/j.1365-4362.1981.tb05295.x
50. RE Carr, P Henkind, N Rothfield, IM Siegel, Ocular toxicity of antimalarial drugs. Long-term follow-up. Am J Ophthalmol. **66**, 738–744 (1968)
51. VE Ansdell, JD Common, Corneal changes induced by mepacrine. J Trop Med Hyg. **82**, 206–207 (1979)
52. WP Chamberlain, DJ Boles, Edema of cornea precipitated by quinacrine (Atabrine). Arch Ophthalmol. **35**, 120–134 (1946)
53. GL Engel, Quinacrine effects on the central nervous system. JAMA. **197**, 515 (1966). doi:10.1001/jama.197.6.515

54. JP Lindenmayer, P Vargas, Toxic psychosis following use of quinacrine. J Clin Psychiatry. **42**, 162–164 (1981)
55. WQ Ward, WG Walter-Ryan, GM Shehi, Toxic psychosis: a complication of antimalarial therapy. J Am Acad Dermatol. **12**, 863–865 (1985). doi:10.1016/S0190-9622(85)70109-0
56. RL Evans, S Khalid, JL Kinney, Antimalarial psychosis revisited. Arch Dermatol. **120**, 765–767 (1984). doi:10.1001/archderm.120.6.765
57. HS Gaskill, T Fitz-Hugh, Toxic psychosis following Atabrine. Bull US Army Med Dept. **86**, 63–69 (1945)
58. T Lidz, RL Kahn, Toxicity of quinacrine (Atabrine) for the cental nervous system. Arch Neurol. **56**, 284–289 (1946)
59. RP Custer, Aplastic anemia in soldiers treated with Atabrine (quinacrine). Am J Med Sci. **212**, 211–224 (1946)
60. AP Fishman, JM Kinsman, Hypoplastic anemia due to atabrine. Blood. **4**, 970–976 (1949)
61. A Freedman, F Bach, Mepacrine and rheumatoid arthritis. Lancet. **2**, 321 (1952)
62. LG Parmer, A Sawitsky, Fatal aplastic anemia following quinacrine therapy in chronic discoid lupus erythematosus. J Am Med Assoc. **153**, 1172–1174 (1953)
63. MD Paton, MJ Riddell, JA Strong, Aplastic anaemia following mepacrine treatment of lupus erythematosus. Lancet. **268**, 281–282 (1955)
64. L Biro, N Leone, Aplastic anemia induced by quinacrine. Arch Dermatol. **92**, 574–576 (1965). doi:10.1001/archderm.1965.01600170090017
65. I Schmid, C Anasetti, FB Petersen, R Storb, Marrow transplantation for severe aplastic anemia associated with exposure to quinacrine. Blut. **61**, 52–54 (1990). doi:10.1007/BF02076699
66. J Collinge, M Gorham, F Hudson, A Kennedy, G Keogh, S Pal, M Rossor, P Rudge, D Siddique, M Spyer, D Thomas, S Walker, T Webb, S Wroe, J Darbyshire, Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. Lancet Neurol. **8**, 334–344 (2009). doi:10.1016/S1474-4422(09)70049-3
67. F Bauer, Quinacrine hydrochloride drug eruption (tropical lichenoid dermatitis). Its early and late sequelae and its malignant potential: a review. J Am Acad Dermatol. **4**, 239–248 (1981). doi:10.1016/S0190-9622(81)70025-2
68. MA Lerman, N Karimbux, KA Guze, SB Woo, Pigmentation of the hard palate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. **107**, 8–12 (2009). doi:10.1016/j.tripleo.2008.07.022
69. VW Lippard, G Kauer, Pigmentation of the palate and subungual tissue associated with suppressive quinacrine hydrochloride therapy. Am J Tropic Med. **25**, 469–471 (1945)
70. CL Kleinegger, HL Hammond, MW Finkelstein, Oral mucosal hyperpigmentation secondary to antimalarial drug therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. **90**, 189–194 (2000). doi:10.1067/moe.2000.106340
71. MJ Egorin, DL Trump, CW Wainwright, Quinacrine ochronosis and rheumatoid arthritis. JAMA. **236**, 385–386 (1976). doi:10.1001/jama.236.4.385
72. IM Leigh, CT Kennedy, JD Ramsey, WJ Henderson, Mepacrine pigmentation in systemic lupus erythematosus. New data from an ultrastructural, biochemical and analytical electron microscopic investigation. Br J Dermatol. **101**, 147–153 (1979). doi:10.1111/j.1365-2133.1979.tb05599.x
73. RJ Sokol, PK Lichtenstein, MK Farrell, Quinacrine hydrochloride-induced yellow discoloration of the skin in children. Pediatrics. **69**, 232–233 (1982)
74. JL Callaway, Late sequelae of quinacrine dermatitis, a new premalignant entity. J Am Acad Dermatol. **1**, 456 (1979). doi:10.1016/S0190-9622(79)80072-9
75. F Bauer, Late sequelae of atabrine dermatitis–a new pre-malignant entity. Australas J Dermatol. **19**, 9–12 (1978). doi:10.1111/j.1440-0960.1978.tb00178.x
76. DL Tuffanelli, Quinacrine ochronosis. JAMA. **236**, 2491 (1976)
77. A Dabancens, DC Sokal, M Pruyas, M Rivera, J Zipper, Prevalence and standardized incidence rates of preclinical cervical pathology among 1,061 women sterilized with transcervical quinacrine hydrochloride pellets. Fertil Steril. **64**, 444–446 (1995)
78. DC Sokal, J Zipper, R Guzman-Serani, TE Aldrich, Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril. **64**, 325–334 (1995)
79. DC Sokal, A Dabancens, R Guzman-Serani, J Zipper, Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril. **74**, 169–171 (2000). doi:10.1016/S0015-0282(00)00581-1
80. M Castelli, G Baggio, AI Ruberto, A Tampieri, PL Tartoni, T Rossi, MR Bossa, I Galatulas, Influence of antimalarials chloroquine, quinine, primaquine and mepacrine on the evolution of Ehrlich ascites tumour. Anticancer Res. **16**, 2673–2675 (1996)
81. P Dutta, R Karmali, JT Pinto, RS Rivlin, Enhanced growth of mammary adenocarcinoma in rats by chloroquine and quinacrine. Cancer Lett. **76**, 113–119 (1994). doi:10.1016/0304-3835(94)90386-7
82. A Dabancens, J Zipper, A Guerrero, Quinacrine and copper, compounds with anticonceptive and antineoplastic activity. Contraception. **50**, 243–251 (1994). doi:10.1016/0010-7824(94)90070-1
83. JA Zipper, AO Dabancens, AC Guerrero, Opposing effects of quinacrine and chloroquine on the development of TA3 transplanted tumors in mice. Biol Res. **28**, 227–230 (1995)
84. J Zipper, A Dabancens, A Guerrero, V Trujillo, Quinacrine revised. Hum Reprod Update. **1**, 324–342 (1995). doi:10.1093/humupd/1.4.324
85. H Siegel, CW Mushett, Structural changes following administration of quinacrine hydrochloride. Arch Path. **38** (1944)
86. CW Mushett, H Siegel, Hematological changes following the administration of large doses of quinacrine hydrochloride. Blood. **1**, 537–547 (1946)
87. R Keeler, H Richardson, AJ Watson, Enteromegaly and steatorrhea in the rat following intraperitoneal quinacrine (atrabrine). Lab Invest. **15**, 1253–1262 (1966)
88. BL Roth, DJ Sheffler, WK Kroeze, Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov. **3**, 353–359 (2004). doi:10.1038/nrd1346
89. AL Hopkins, JS Mason, JP Overington, Can we rationally design promiscuous drugs? Curr Opin Struct Biol. **16**, 127–136 (2006). doi:10.1016/j.sbi.2006.01.013
90. A Sivachenko, A Kalinin, A Yuryev, Pathway analysis for design of promiscuous drugs and selective drug mixtures. Curr Drug Discov Technol. **3**, 269–277 (2006). doi:10.2174/157016306780368117
91. JP Overington, B Al-Lazikani, AL Hopkins, How many drug targets are there? Nat Rev Drug Discov. **5**, 993–996 (2006). doi:10.1038/nrd2199
92. DR Boer, A Canals, M Coll, DNA-binding drugs caught in action: the latest 3D pictures of drug-DNA complexes. Dalton Trans. 399–414 (2009)
93. U Pindur, M Jansen, T Lemster, Advances in DNA-ligands with groove binding, intercalating and/or alkylating activity: chemistry, DNA-binding and biology. Curr Med Chem. **12**, 2805–2847 (2005). doi:10.2174/092986705774454698
94. L Strekowski, B Wilson, Noncovalent interactions with DNA: an overview. Mutat Res. **623**, 3–13 (2007)
95. LS Lerman, Structural considerations in the interaction of DNA and acridines. J Mol Biol. **3**, 18–30 (1961). doi:10.1016/S0022-2836(61)80004-1
96. MJ Waring, DNA-binding characteristics of acridinylmethanesulphonanilide drugs: comparison with antitumour properties. Eur J Cancer. **12**, 995–1001 (1976)
97. LS Lerman, The structure of the DNA-acridine complex. Proc Natl Acad Sci USA. **49**, 94–102 (1963). doi:10.1073/pnas.49.1.94
98. M Aslanoglu, G Ayne, Voltammetric studies of the interaction of quinacrine with DNA. Anal Bioanal Chem. **380**, 658–663 (2004). doi:10.1007/s00216-004-2797-5
99. SM Doglia, B Albinsson, C Hiort, B Norden, A Graslund, Quinacrine: Spectroscopic properties and interactions with polynucleotides. Biopolymers. **33**, 1431–1442 (1993). doi:10.1002/bip.360330913
100. S Doglia, A Graslund, A Ehrenberg, Specific interactions between quinacrine and self-complementary deoxydinucleotides. Anticancer Res. **6**, 1363–1368 (1986)
101. G Lober, The fluorescence of dye-nucleic acid complexes. J Luminescence. **22**, 221–265 (1981). doi:10.1016/0022-2313(81)90022-3
102. L Rivas, A Murza, S Sanchez-Cortes, JV Garcia-Ramos, Interaction of antimalarial drug quinacrine with nucleic acids of variable sequence studied by spectroscopic methods. J Biomol Struct Dyn. **18**, 371–383 (2000)
103. B Weisblum, PL De Haseth, Quinacrine, a chromosome stain specific for deoxyadenylate-deoxythymidylaterich regions in DNA. Proc Natl Acad Sci USA. **69**, 629–632 (1972). doi:10.1073/pnas.69.3.629
104. M Nastasi, RW Yip, VL Seligy, AG Szabo, RE Williams, Exciton-like splitting in acridine dye-nucleic acid complexes. Nature. **249**, 248–250 (1974). doi:10.1038/249248a0
105. DG Gorenstein, K Lai, 31P NMR spectra of ethidium, quinacrine, and daunomycin complexes with poly(adenylic acid).poly(uridylic acid) RNA duplex and calf thymus DNA. Biochemistry. **28**, 2804–2812 (1989). doi:10.1021/bi00433a010

106. RK Selander, Interaction of quinacrine mustard with mononucleotides and polynucleotides. Biochem J. **131**, 749–755 (1973)
107. A Andreoni, R Cubeddu, S De Silvestri, P Laporta, Time-resolved fluorescence spectrum of quinacrine mustard bound to synthetic polynucleotides. Chemical Physics Letters. **80**, 323–326 (1981). doi:10.1016/0009-2614(81)80118-2
108. JF Constant, P Laugaa, BP Roques, J Lhomme, Heterodimeric molecules including nucleic acid bases and 9-aminoacridine. Spectroscopic studies, conformations, and interactions with DNA. Biochemistry. **27**, 3997–4003 (1988). doi:10.1021/bi00411a016
109. RD Snyder, MR Arnone, Putative identification of functional interactions between DNA intercalating agents and topoisomerase II using the V79 in vitro micronucleus assay. Mutat Res. **503**, 21–35 (2002)
110. RL O'Brien, JG Olenick, FE Hahn, Reactions of quinine, chloroquine, and quinacrine with DNA and their effects on the DNA and RNA polymerase reactions. Proc Natl Acad Sci USA. **55**, 1511–1517 (1966). doi:10.1073/pnas.55.6.1511
111. FE Hahn, RL O'Brien, J Ciak, JL Allison, JG Olenick, Studies on modes of action of chloroquine, quinacrine, and quinine and on chloroquine resistance. Mil Med. **131**(Suppl):1071–1089 (1966)
112. A Kagemoto, A Kunihiro, Y Baba, Thermodynamic studies on interactions between DNA and dye. Thermochimica Acta. **242**, 65–75 (1994)
113. T Haerd, P Fan, D Magde, DR Kearns, On the flexibility of DNA: time-resolved fluorescence polarization of intercalated quinacrine and 9-amino-6-chloro-2-methoxyacridine. The Journal of Physical Chemistry. **93**, 4338–4345 (2002)
114. AT Sumner, Mechanisms of quinacrine binding and fluorescence in nuclei and chromosomes. Histochemistry. **84**, 566–574 (1986). doi:10.1007/BF00482993
115. G Baldini, S Doglia, S Dolci, G Sassi, Fluorescence-determined preferential binding of quinacrine to DNA. Biophys J. **36**, 465–477 (1981). doi:10.1016/S0006-3495(81)84746-7
116. N Xamena, A Creus, A Velazquez, R Marcos, Testing of chloroquine and quinacrine for mutagenicity in Drosophila melanogaster. Mutat Res. **158**, 177–180 (1985). doi:10.1016/0165-1218(85)90081-3
117. WA Denny, DNA-intercalating ligands as anti-cancer drugs: prospects for future design. Anticancer Drug Des. **4**, 241–263 (1989)
118. LF Liu, DNA topoisomerase poisons as antitumor drugs. Annu Rev Biochem. **58**, 351–375 (1989). doi:10.1146/annurev.bi.58.070189.002031
119. JB Le Pecq, X Nguyen Dat, C Gosse, C Paoletti, A new antitumoral agent: 9-hydroxyellipticine. Possibility of a rational design of anticancerous drugs in the series of DNA intercalating drugs. Proc Natl Acad Sci USA. **71**, 5078–5082 (1974). doi:10.1073/pnas.71.12.5078
120. JA Hartley, K Reszka, ET Zuo, WD Wilson, AR Morgan, JW Lown, Characteristics of the interaction of anthrapyrazole anticancer agents with deoxyribonucleic acids: structural requirements for DNA binding, intercalation, and photosensitization. Mol Pharmacol. **33**, 265–271 (1988)
121. L Valentini, V Nicolella, E Vannini, M Menozzi, S Penco, F Arcamone, Association of anthracycline derivatives with DNA: a fluorescence study. Farmaco Sci. **40**, 377–390 (1985)
122. JL Mergny, P Mailliet, F Lavelle, JF Riou, A Laoui, C Helene, The development of telomerase inhibitors: the G-quartet approach. Anticancer Drug Des. **14**, 327–339 (1999)
123. RJ Harrison, SM Gowan, LR Kelland, S Neidle, Human telomerase inhibition by substituted acridine derivatives. Bioorg Med Chem Lett. **9**, 2463–2468 (1999). doi:10.1016/S0960-894X(99)00394-7
124. PJ Perry, TC Jenkins, Recent advances in the development of telomerase inhibitors for the treatment of cancer. Expert Opin Investig Drugs. **8**, 1981–2008 (1999). doi:10.1517/13543784.8.12.1981
125. JE Redman, JM Granadino-Roldan, JA Schouten, S Ladame, AP Reszka, S Neidle, S Balasubramanian, Recognition and discrimination of DNA quadruplexes by acridine-peptide conjugates. Org Biomol Chem. **7**, 76–84 (2009). doi:10.1039/b814682a
126. MA Read, AA Wood, JR Harrison, SM Gowan, LR Kelland, HS Dosanjh, S Neidle, Molecular modeling studies on G-quadruplex complexes of telomerase inhibitors: structure-activity relationships. J Med Chem. **42**, 4538–4546 (1999). doi:10.1021/jm990287e
127. AH Corbett, N Osheroff, When good enzymes go bad: conversion of topoisomerase II to a cellular toxin by antineoplastic drugs. Chem Res Toxicol. **6**, 585–597 (1993). doi:10.1021/tx00035a001
128. MJ Robinson, N Osheroff, Stabilization of the topoisomerase II-DNA cleavage complex by antineoplastic drugs: inhibition of enzyme-mediated DNA religation by 4'-(9-acridinylamino)methanesulfon-m-anisidide. Biochemistry. **29**, 2511–2515 (1990). doi:10.1021/bi00462a012
129. TL Su, Development of DNA topoisomerase II-mediated anticancer agents, 3-(9-acridinylamino)-5-hydroxymethylanilines (AHMAs) and related compounds. Curr Med Chem. **9**, 1677–1688 (2002)
130. WA Denny, BC Baguley, Dual topoisomerase I/II inhibitors in cancer therapy. Curr Top Med Chem. **3**, 339–353 (2003). doi:10.2174/1568026033452555
131. WA Denny, Acridine derivatives as chemotherapeutic agents. Curr Med Chem. **9**, 1655–1665 (2002)
132. CHCM Buys, Telomeres, telomerase, and cancer. N Engl J Med. **342**, 1282–1283 (2000). doi:10.1056/NEJM200004273421710
133. A Satyanarayana, MP Manns, KL Rudolph, Telomeres, telomerase and cancer: an endless search to target the ends. Cell Cycle. **3**, 1138–1150 (2004)
134. MO Robinson, Telomerase and cancer. Genet Eng (N Y). **22**, 209–222 (2000)
135. HM Wong, L Payet, JL Huppert, Function and targeting of G-quadruplexes. Curr Opin Mol Ther. **11**, 146–155 (2009)
136. JH Tan, LQ Gu, JY Wu, Design of selective G-quadruplex ligands as potential anticancer agents. Mini Rev Med Chem. **8**, 1163–1178 (2008). doi:10.2174/138955708785909880
137. YH Hsiang, HY Wu, LF Liu, Topoisomerases: novel therapeutic targets in cancer chemotherapy. Biochem Pharmacol. **37**, 1801–1802 (1988). doi:10.1016/0006-2952(88)90453-4
138. PK Dominick, BR Keppler, JD Legassie, IK Moon, MB Jarstfer, Nucleic acid-binding ligands identify new mechanisms to inhibit telomerase. Bioorg Med Chem Lett. **14**, 3467–3471 (2004). doi:10.1016/j.bmcl.2004.04.055
139. D Sun, B Thompson, BE Cathers, M Salazar, SM Kerwin, JO Trent, TC Jenkins, S Neidle, LH Hurley, Inhibition of human telomerase by a G-quadruplex-interactive compound. J Med Chem. **40**, 2113–2116 (1997). doi:10.1021/jm970199z
140. KA Werbovetz, EK Lehnert, TL Macdonald, RD Pearson, Cytotoxicity of acridine compounds for Leishmania promastigotes in vitro. Antimicrob Agents Chemother. **36**, 495–497 (1992)
141. SW Langer, G Schmidt, M Sorensen, M Sehested, PB Jensen, Inhibitors of topoisomerase II as pH-dependent modulators of etoposide-mediated cytotoxicity. Clin Cancer Res. **5**, 2899–2907 (1999)
142. O Popanda, HW Thielmann, The function of DNA topoisomerases in UV-induced DNA excision repair: studies with specific inhibitors in permeabilized human fibroblasts. Carcinogenesis. **13**, 2321–2328 (1992). doi:10.1093/carcin/13.12.2321
143. AS Sideropoulos, SM Specht, MT Jones, Feasibility of testing DNA repair inhibitors for mutagenicity by a simple method. Mutation Research/Environmental Mutagenesis and Related Subjects. **74**, 95–105 (1980). doi:10.1016/0165-1161(80)90235-6
144. Z Fuks, KC Smith, Effect of quinacrine on x-ray sensitivity and the repair of damaged DNA in Escherichia coli K-12. Radiat Res. **48**, 63–73 (1971). doi:10.2307/3573395
145. JA Skare, TK Wong, Lack of specific inhibition of DNA repair in WI-38 human diploid fibroblasts by sodium saccharin. Cancer Letters. **26**, 191–200 (1985). doi:10.1016/0304-3835(85)90026-6
146. HW Thielmann, O Popanda, H Gersbach, F Gilberg, Various inhibitors of DNA topoisomerases diminish repair-specific DNA incision in UV-irradiated human fibroblasts. Carcinogenesis. **14**, 2341–2351 (1993). doi:10.1093/carcin/14.11.2341
147. O Popanda, HW Thielmann, The function of DNA polymerases in DNA repair synthesis of ultraviolet-irradiated human fibroblasts. Biochim Biophys Acta. **1129**, 155–160 (1992)
148. N Voiculetz, KC Smith, HS Kaplan, Effect of Quinacrine on survival and DNA repair in X-irradiated chinese hamster cells. Cancer Res. **34**, 1038–1044 (1974)
149. CS Downes, RT Johnson, DNA topoisomerases and DNA repair. Bioessays. **8**, 179–184 (1988). doi:10.1002/bies.950080602
150. MW Lieberman, Alterations in chromatin structure during DNA excision repair. Basic Life Sci. **20**, 303–314 (1982)
151. GE Arnold, AK Dunker, MJ Smerdon, Limited nucleosome migration can completely randomize DNA repair patches in intact human cells. J Mol Biol. **196**, 433–436 (1987). doi:10.1016/0022-2836(87)90703-0

152. K Sidik, MJ Smerdon, Rearrangement of nucleosome structure during excision repair in xeroderma pigmentosum (group A) human fibroblasts. Carcinogenesis. **8**, 733–736 (1987). doi:10.1093/carcin/8.5.733
153. E Schneider, SJ Darkin, PA Lawson, LM Ching, RK Ralph, BC Baguley, Cell line selectivity and DNA breakage properties of the antitumour agent N-[2-(dimethylamino)ethyl]acridine-4-carboxamide: role of DNA topoisomerase II. Eur J Cancer Clin Oncol. **24**, 1783–1790 (1988). doi:10.1016/0277-5379(88)90082-X
154. EC Friedberg, Yeast genes involved in DNA-repair processes: new looks on old faces. Mol Microbiol. **5**, 2303–2310 (1991). doi:10.1111/j.1365-2958.1991.tb02074.x
155. K Van Dyke, C Lantz, C Szustkiewicz, Quinacrine: mechanisms of antimalarial action. Science. **169**, 492–493 (1970). doi:10.1126/science.169.3944.492
156. SC Chou, S Ramanathan, Quinacrine: site of inhibition of synchronized cell division in Tetrahymena. Life Sci. **7**, 1053–1062 (1968). doi:10.1016/0024-3205(68)90142-2
157. G Fox, O Popanda, L Edler, HW Thielmann, Preferential inhibition of DNA polymerases alpha, delta, and epsilon from Novikoff hepatoma cells by inhibitors of cell proliferation. J Cancer Res Clin Oncol. **122**, 78–94 (1996). doi:10.1007/BF01226265
158. TS Wang, SW Wong, D Korn, Human DNA polymerase alpha: predicted functional domains and relationships with viral DNA polymerases. FASEB J. **3**, 14–21 (1989)
159. TS Wang, Eukaryotic DNA polymerases. Annu Rev Biochem. **60**, 513–552 (1991). doi:10.1146/annurev.bi.60.070191.002501
160. SZ Hirschman, E Garfinkel, Inhibition of hepatitis B DNA polymerase by intercalating agents. Nature. **271**, 681–683 (1978). doi:10.1038/271681a0
161. G Hess, W Arnold, B Moller, GM Gahl, KH Meyerzum Buschenfelde, Inhibition of hepatitis B virus specific DNA polymerase by intercalating agents. Med Microbiol Immunol. **168**, 25–34 (1980). doi:10.1007/BF02121649
162. K Goda, Z Bacso, G Szabo, Multidrug resistance through the spectacle of P-glycoprotein. Curr Cancer Drug Targets. **9**, 281–297 (2009). doi:10.2174/156800909788166493
163. G Lehne, P-glycoprotein as a drug target in the treatment of multidrug resistant cancer. Curr Drug Targets. **1**, 85–99 (2000). doi:10.2174/1389450003349443
164. F Hyafil, C Vergely, P Du Vignaud, T Grand-Perret, In vitro and in vivo reversal of multidrug resistance by GF120918, an acridonecarboxamide derivative. Cancer Res. **53**, 4595–4602 (1993)
165. P Singh, J Kaur, P Kaur, S Kaur, Search for MDR modulators: design, syntheses and evaluations of N-substituted acridones for interactions with p-glycoprotein and Mg2+. Bioorg Med Chem. **17**, 2423–2427 (2009). doi:10.1016/j.bmc.2009.02.002
166. YC Mayur, GJ Peters, VV Prasad, C Lemo, NK Sathish, Design of new drug molecules to be used in reversing multidrug resistance in cancer cells. Curr Cancer Drug Targets. **9**, 298–306 (2009). doi:10.2174/156800909788166619
167. R Perez-Tomas, Multidrug resistance: retrospect and prospects in anti-cancer drug treatment. Curr Med Chem. **13**, 1859–1876 (2006). doi:10.2174/092986706777585077
168. HC Traunecker, MC Stevens, DJ Kerr, DR Ferry, The acridonecarboxamide GF120918 potently reverses P-glycoprotein-mediated resistance in human sarcoma MES-Dx5 cells. Br J Cancer. **81**, 942–951 (1999). doi:10.1038/sj.bjc.6690791
169. S Nobili, I Landini, B Giglioni, E Mini, Pharmacological strategies for overcoming multidrug resistance. Curr Drug Targets. **7**, 861–879 (2006). doi:10.2174/138945006777709593
170. GW Liang, WL Lu, JW Wu, JH Zhao, HY Hong, C Long, T Li, YT Zhang, H Zhang, JC Wang, X Zhang, Q Zhang, Enhanced therapeutic effects on the multi-drug resistant human leukemia cells in vitro and xenograft in mice using the stealthy liposomal vincristine plus quinacrine. Fundam Clin Pharmacol. **22**, 429–437 (2008). doi:10.1111/j.1472-8206.2008.00613.x
171. M Inaba, E Maruyama, Reversal of resistance to vincristine in P388 leukemia by various polycyclic clinical drugs, with a special emphasis on quinacrine. Cancer Res. **48**, 2064–2067 (1988)
172. WT Beck, MC Cirtain, CJ Glover, RL Felsted, AR Safa, Effects of indole alkaloids on multidrug resistance and labeling of P-glycoprotein by a photoaffinity analog of vinblastine. Biochem Biophys Res Commun. **153**, 959–966 (1988). doi:10.1016/S0006-291X(88)81321-4
173. JM Zamora, HL Pearce, WT Beck, Physical-chemical properties shared by compounds that modulate multidrug resistance in human leukemic cells. Mol Pharmacol. **33**, 454–462 (1988)
174. D Boscoboinik, RM Epand, Increased cellular internalization of amphiphiles in a multidrug-resistant CHO cell line. Biochim Biophys Acta. **1014**, 53–56 (1989). doi:10.1016/0167-4889(89)90239-5
175. PL de Souza, M Castillo, CE Myers, Enhancement of paclitaxel activity against hormone-refractory prostate cancer cells in vitro and in vivo by quinacrine. Br J Cancer. **75**, 1593–1600 (1997). doi:10.1038/bjc.1997.272
176. RA Gupta, RN Dubois, Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat Rev Cancer. **1**, 11–21 (2001). doi:10.1038/35094017
177. JR Mann, RN DuBois, Cyclooxygenase-2 and gastrointestinal cancer. Cancer J. **10**, 145–152 (2004). doi:10.1097/00130404-200405000-00001
178. JM Kurie, RN Dubois, Prostaglandin E synthase: another enzyme in the cyclooxygenase pathway driving epithelial cancer? Clin Cancer Res. **7**, 2608–2610 (2001)
179. PA Bunn Jr, RL Keith, The future of cyclooxygenase-2 inhibitors and other inhibitors of the eicosanoid signal pathway in the prevention and therapy of lung cancer. Clin Lung Cancer **3**, 271–277 (2002). discussion 278. doi:10.3816/CLC.2002.n.012
180. MJ Thun, B Blackard, Pharmacologic effects of NSAIDs and implications for the risks and benefits of long-term prophylactic use of aspirin to prevent cancer. Recent Results Cancer Res. **181**, 215–221 (2009). doi:10.1007/978-3-540-69297-3_20
181. MI Patel, C Kurek, Q Dong, The arachidonic acid pathway and its role in prostate cancer development and progression. J Urol. **179**, 1668–1675 (2008). doi:10.1016/j.juro.2007.12.037
182. RL Keith, YE Miller, Lung cancer: genetics of risk and advances in chemoprevention. Curr Opin Pulm Med. **11**, 265–271 (2005). doi:10.1097/01.mcp.0000166493.77412.2d
183. P Jimenez, A Garcia, S Santander, E Piazuelo, Prevention of cancer in the upper gastrointestinal tract with COX-inhibition. Still an option? Curr Pharm Des. **13**, 2261–2273 (2007)
184. S Mehta, IT Johnson, M Rhodes, Systematic review: the chemoprevention of oesophageal adenocarcinoma. Aliment Pharmacol Ther. **22**, 759–768 (2005). doi:10.1111/j.1365-2036.2005.02667.x
185. E Fosslien, Molecular pathology of cyclooxygenase-2 in neoplasia. Ann Clin Lab Sci. **30**, 3–21 (2000)
186. H Tokumoto, JD Croxtall, Q Choudhury, RJ Flower, Phospholipase A2-induced stimulation of A549 lung adenocarcinoma cell line proliferation. Biochim Biophys Acta. **1169**, 236–242 (1993)
187. K Hanada, E Kinoshita, M Itoh, M Hirata, G Kajiyama, M Sugiyama, Human pancreatic phospholipase A2 stimulates the growth of human pancreatic cancer cell line. FEBS Lett. **373**, 85–87 (1995). doi:10.1016/0014-5793(95)01005-Y
188. S Yamashita, J Yamashita, M Ogawa, Overexpression of group II phospholipase A2 in human breast cancer tissues is closely associated with their malignant potency. Br J Cancer. **69**, 1166–1170 (1994). doi:10.1038/bjc.1994.229
189. K Murata, H Egami, H Kiyohara, S Oshima, T Kurizaki, M Ogawa, Expression of group-II phospholipase A2 in malignant and non-malignant human gastric mucosa. Br J Cancer. **68**, 103–111 (1993). doi:10.1038/bjc.1993.294
190. MK Jain, BZ Yu, J Rogers, GN Ranadive, OG Berg, Interfacial catalysis by phospholipase A2: dissociation constants for calcium, substrate, products, and competitive inhibitors. Biochemistry. **30**, 7306–7317 (1991). doi:10.1021/bi00243a036
191. BM Loffler, E Bohn, B Hesse, H Kunze, Effects of antimalarial drugs on phospholipase A and lysophospholipase activities in plasma membrane, mitochondrial, microsomal and cytosolic subcellular fractions of rat liver. Biochim Biophys Acta. **835**, 448–455 (1985)
192. K Schiess, M Kaszkin, P Jordan, L Seidler, V Kinzel, Mobilization of diacylglycerol in intact HeLa cells by exogenous phospholipase C from Cl. perfringens is accompanied by release of fatty acids including arachidonic acid. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. **1137**, 82–94 (1992). doi:10.1016/0167-4889(92)90104-J
193. A Ahmed, IT Cameron, RA Ferriani, SK Smith, Activation of phospholipase A2 and phospholipase C by endothelin-1 in human endometrium. J Endocrinol. **135**, 383–390 (1992). doi:10.1677/joe.0.1350383
194. DF Horrobin, MS Manku, M Karmazyn, AI Ally, RO Morgan, RA Karmali, Quinacrine is a prostaglandin antagonist. Biochem Biophys Res Commun. **76**, 1188–1193 (1977). doi:10.1016/0006-291X(77)90981-0

195. CA Dise, JW Burch, DB Goodman, Direct interaction of mepacrine with erythrocyte and platelet membrane phospholipid. J Biol Chem. **257**, 4701–4704 (1982)
196. R Zidovetzki, IW Sherman, PA Maguire, H De Boeck, A nuclear magnetic resonance study of the interactions of the antimalarials chloroquine, quinacrine, quinine and mefloquine with lipids extracted from normal human erythrocytes. Mol Biochem Parasitol. **38**, 33–39 (1990). doi:10.1016/0166-6851(90)90202-W
197. AA Abdel-Latif, JP Smith, RA Akhtar, Studies on the mechanism of alteration by propranolol and mepacrine of the metabolism of phosphoinositides and other glycerolipids in the rabbit iris muscle. Biochemical Pharmacology. **32**, 3815–3821 (1983). doi:10.1016/0006-2952(83)90154-5
198. P Mustonen, JYA Lehtonen, PKJ Kinnunen, Binding of quinacrine to acidic phospholipids and pancreatic phospholipase A2. Effects on the catalytic activity of the enzyme. Biochemistry. **37**, 12051–12057 (1998). doi:10.1021/bi980430q
199. K Yamada, Y Okano, K Miura, Y Nozawa, A major role for phospholipase A2 in antigen-induced arachidonic acid release in rat mast cells. Biochem J. **247**, 95–99 (1987)
200. E Bugge, TM Gamst, AC Hegstad, T Andreasen, K Ytrehus, Mepacrine protects the isolated rat heart during hypoxia and reoxygenation–but not by inhibition of phospholipase A2. Basic Res Cardiol. **92**, 17–24 (1997)
201. JK Beckman, SM Borowitz, IM Burr, The role of phospholipase A activity in rat liver microsomal lipid peroxidation. J Biol Chem. **262**, 1479–1484 (1987)
202. PM Evans, DF Lanham, Effects of inhibitors of arachidonic acid metabolism on intercellular adhesion of SV40-3T3 cells. Cell Biol Int Rep. **10**, 693–698 (1986). doi:10.1016/0309-1651(86)90126-8
203. NP Hurst, JK French, AL Bell, G Nuki, ML O'Donnell, WH Betts, LG Cleland, Differential effects of mepacrine, chloroquine and hydroxychloroquine on superoxide anion generation, phospholipid methylation and arachidonic acid release by human blood monocytes. Biochem Pharmacol. **35**, 3083–3089 (1986). doi:10.1016/0006-2952(86)90390-4
204. PC Churchill, MC Churchill, FD McDonald, Quinacrine antagonizes the effects of Na, K-ATPase inhibitors on renal prostaglandin E2 release but not their effects on renin secretion. Life Sci. **36**, 277–282 (1985). doi:10.1016/0024-3205(85)90070-0
205. A Erman, R Azuri, A Raz, Prostaglandin biosynthesis in rabbit kidney: mepacrine inhibits renomedullary cyclooxygenase. Biochem Pharmacol. **33**, 79–82 (1984). doi:10.1016/0006-2952(84)90372-1
206. A Raz, Mepacrine blockade of arachidonate-induced washed platelet aggregation: relationship to mepacrine inhibition of platelet cyclooxygenase. Thromb Haemost. **50**, 784–786 (1983)
207. SL Hofmann, SM Prescott, PW Majerus, The effects of mepacrine and p-bromophenacyl bromide on arachidonic acid release in human platelets. Arch Biochem Biophys. **215**, 237–244 (1982). doi:10.1016/0003-9861(82)90300-9
208. TY Lot, T Bennett, Comparison of the effects of chloroquine quinacrine and quinidine on autonomic neuroeffector mechanisms. Med Biol. **60**, 307–315 (1982)
209. KS Authi, JR Traynor, Stimulation of polymorphonuclear leucocyte phospholipase A2 activity by chloroquine and mepacrine. J Pharm Pharmacol. **34**, 736–738 (1982)
210. JT Flynn, Inhibition of complement-mediated hepatic thromboxane production by mepacrine, a phospholipase inhibitor. Prostaglandins. **33**, 287–299 (1987). doi:10.1016/0090-6980(87)90013-X
211. L Louw, J Claassen, Rationale for adjuvant fatty acid therapy to prevent radiotherapy failure and tumor recurrence during early laryngeal squamous cell carcinoma. Prostaglandins Leukot Essent Fatty Acids. **78**, 21–26 (2008). doi:10.1016/j.plefa.2007.10.007
212. S Itoh, K Matsui, I Furuta, Y Takano, Immunohistochemical study on overexpression of cyclooxygenase-2 in squamous cell carcinoma of the oral cavity: its importance as a prognostic predictor. Oral Oncol. **39**, 829–835 (2003). doi:10.1016/S1368-8375(03)00105-2
213. WC Chen, WH McBride, SM Chen, KF Lee, TZ Hwang, SM Jung, H Shau, SK Liao, JH Hong, MF Chen, Prediction of poor survival by cyclooxygenase-2 in patients with T4 nasopharyngeal cancer treated by radiation therapy: clinical and in vitro studies. Head Neck. **27**, 503–512 (2005). doi:10.1002/hed.20178
214. BW Chang, DH Kim, DP Kowalski, JA Burleson, YH Son, LD Wilson, BG Haffty, Prognostic significance of cyclooxygenase-2 in oropharyngeal squamous cell carcinoma. Clin Cancer Res. **10**, 1678–1684 (2004). doi:10.1158/1078-0432.CCR-03-0354
215. JP Peng, CY Su, HC Chang, CY Chai, WC Hung, Overexpression of cyclo-oxygenase 2 in squamous cell carcinoma of the hypopharynx. Hum Pathol. **33**, 100–104 (2002). doi:10.1053/hupa.2002.30187
216. N Terakado, S Shintani, J Yano, L Chunnan, M Mihara, K Nakashiro, H Hamakawa, Overexpression of cyclooxygenase-2 is associated with radioresistance in oral squamous cell carcinoma. Oral Oncol. **40**, 383–389 (2004). doi:10.1016/j.oraloncology.2003.09.005
217. O Gallo, E Masini, B Bianchi, L Bruschini, M Paglierani, A Franchi, Prognostic significance of cyclooxygenase-2 pathway and angiogenesis in head and neck squamous cell carcinoma. Hum Pathol. **33**, 708–714 (2002). doi:10.1053/hupa.2002.125376
218. EI Cho, DP Kowalski, CT Sasaki, BG Haffty, Tissue microarray analysis reveals prognostic significance of COX-2 expression for local relapse in T1-2N0 larynx cancer treated with primary radiation therapy. Laryngoscope. **114**, 2001–2008 (2004). doi:10.1097/01.mlg.0000147936.67379.e7
219. N Li, S Sood, S Wang, M Fang, P Wang, Z Sun, CS Yang, X Chen, Overexpression of 5-lipoxygenase and cyclooxygenase 2 in hamster and human oral cancer and chemopreventive effects of zileuton and celecoxib. Clin Cancer Res. **11**, 2089–2096 (2005). doi:10.1158/1078-0432.CCR-04-1684
220. L Feng, Z Wang, Chemopreventive effect of celecoxib in oral precancers and cancers. Laryngoscope. **116**, 1842–1845 (2006). doi:10.1097/01.mlg.0000233778.41927.c7
221. M Shibata, I Kodani, M Osaki, K Araki, H Adachi, K Ryoke, H Ito, Cyclo-oxygenase-1 and -2 expression in human oral mucosa, dysplasias and squamous cell carcinomas and their pathological significance. Oral Oncol. **41**, 304–312 (2005). doi:10.1016/j.oraloncology.2004.09.009
222. G Chan, JO Boyle, EK Yang, F Zhang, PG Sacks, JP Shah, D Edelstein, RA Soslow, AT Koki, BM Woerner, JL Masferrer, AJ Dannenberg, Cyclooxygenase-2 expression is up-regulated in squamous cell carcinoma of the head and neck. Cancer Res. **59**, 991–994 (1999)
223. GJ Blackwell, WG Duncombe, RJ Flower, MF Parsons, JR Vane, The distribution and metabolism of arachidonic acid in rabbit platelets during aggregation and its modification by drugs. Br J Pharmacol. **59**, 353–366 (1977)
224. D Nie, M Lamberti, A Zacharek, L Li, K Szekeres, K Tang, Y Chen, KV Honn, Thromboxane A(2) regulation of endothelial cell migration, angiogenesis, and tumor metastasis. Biochem Biophys Res Commun. **267**, 245–251 (2000). doi:10.1006/bbrc.1999.1840
225. N Nakahata, Thromboxane A2: physiology/pathophysiology, cellular signal transduction and pharmacology. Pharmacol Ther. **118**, 18–35 (2008). doi:10.1016/j.pharmthera.2008.01.001
226. J Wei, W Yan, X Li, Y Ding, HH Tai, Thromboxane receptor alpha mediates tumor growth and angiogenesis via induction of vascular endothelial growth factor expression in human lung cancer cells. Lung Cancer. (2009)
227. H Oshima, K Oguma, YC Du, M Oshima, Prostaglandin E2, Wnt, and BMP in gastric tumor mouse models. Cancer Sci. **100**, 1779–1785 (2009). doi:10.1111/j.1349-7006.2009.01258.x
228. D Kamei, M Murakami, Y Nakatani, Y Ishikawa, T Ishii, I Kudo, Potential role of microsomal prostaglandin E synthase-1 in tumorigenesis. J Biol Chem. **278**, 19396–19405 (2003). doi:10.1074/jbc.M213290200
229. K Yoshimatsu, D Golijanin, PB Paty, RA Soslow, PJ Jakobsson, RA DeLellis, K Subbaramaiah, AJ Dannenberg, Inducible microsomal prostaglandin E synthase is overexpressed in colorectal adenomas and cancer. Clin Cancer Res. **7**, 3971–3976 (2001)
230. A Fulton, F Miller, A Weise, WZ Wei, Prospects of controlling breast cancer metastasis by immune intervention. Breast Dis. **26**, 115–127 (2006)
231. K Yoshimatsu, NK Altorki, D Golijanin, F Zhang, PJ Jakobsson, AJ Dannenberg, K Subbaramaiah, Inducible prostaglandin E synthase is overexpressed in non-small cell lung cancer. Clin Cancer Res. **7**, 2669–2674 (2001)
232. HN Jabbour, SA Milne, AR Williams, RA Anderson, SC Boddy, Expression of COX-2 and PGE synthase and synthesis of PGE(2)in endometrial adenocarcinoma: a possible autocrine/paracrine regulation of neoplastic cell function via EP2/EP4 receptors. Br J Cancer. **85**, 1023–1031 (2001)
233. L Yu, WK Wu, ZJ Li, HT Li, YC Wu, CH Cho, Prostaglandin E(2) promotes cell proliferation via protein kinase C/extracellular signal regulated kinase pathway-dependent induction of c-Myc expression in human esophageal squamous cell carcinoma cells. Int J Cancer. **125**, 2540–2546 (2009). doi:10.1002/ijc.24607

234. M Camacho, X Leon, MT Fernandez-Figueras, M Quer, L Vila, Prostaglandin E(2) pathway in head and neck squamous cell carcinoma. Head Neck. **30**, 1175–1181 (2008). doi:10.1002/hed.20850
235. TT Jung, NT Berlinger, SK Juhn, Prostaglandins in squamous cell carcinoma of the head and neck: a preliminary study. Laryngoscope. **95**, 307–312 (1985)
236. EG Cohen, T Almahmeed, B Du, D Golijanin, JO Boyle, RA Soslow, K Subbaramaiah, AJ Dannenberg, Microsomal prostaglandin E synthase-1 is overexpressed in head and neck squamous cell carcinoma. Clin Cancer Res. **9**, 3425–3430 (2003)
237. R Kawata, S Hyo, T Maeda, Y Urade, H Takenaka, Simultaneous expression of cyclooxygenase-2 and microsomal prostaglandin E synthase in squamous cell carcinoma of the larynx. Acta Otolaryngol. **126**, 627–632 (2006). doi:10.1080/00016480500452541
238. CJ Brown, S Lain, CS Verma, AR Fersht, DP Lane, Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer. **9**, 862–873 (2009). doi:10.1038/nrc2763
239. MR Junttila, GI Evan, p53–a Jack of all trades but master of none. Nat Rev Cancer. **9**, 821–829 (2009)
240. J Kucharczak, MJ Simmons, Y Fan, C Gelinas, To be, or not to be: NF-kappaB is the answer–role of Rel/NF-kappaB in the regulation of apoptosis. Oncogene. **22**, 8961–8982 (2003). doi:10.1038/sj.onc.1207230
241. M Karin, FR Greten, NF-kappaB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol. **5**, 749–759 (2005). doi:10.1038/nri1703
242. GA Webster, ND Perkins, Transcriptional cross talk between NF-kappaB and p53. Mol Cell Biol. **19**, 3485–3495 (1999)
243. V Tergaonkar, ND Perkins, p53 and NF-kappaB crosstalk: IKKalpha tips the balance. Mol Cell. **26**, 158–159 (2007). doi:10.1016/j.molcel.2007.04.006
244. WC Huang, TK Ju, MC Hung, CC Chen, Phosphorylation of CBP by IKKalpha promotes cell growth by switching the binding preference of CBP from p53 to NF-kappaB. Mol Cell. **26**, 75–87 (2007). doi:10.1016/j.molcel.2007.02.019
245. ON Ozes, LD Mayo, JA Gustin, SR Pfeffer, LM Pfeffer, DB Donner, NF-kappaB activation by tumour necrosis factor requires the Akt serine-threonine kinase. Nature. **401**, 82–85 (1999). doi:10.1038/43466
246. A Khwaja, Akt is more than just a Bad kinase. Nature. **401**, 33–34 (1999). doi:10.1038/43354
247. M Delhase, N Li, M Karin, Kinase regulation in inflammatory response. Nature. **406**, 367–368 (2000). doi:10.1038/35019154
248. I Vivanco, CL Sawyers, The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer. **2**, 489–501 (2002). doi:10.1038/nrc839
249. J Friedman, L Nottingham, P Duggal, FG Pernas, B Yan, XP Yang, Z Chen, C Van Waes, Deficient TP53 expression, function, and cisplatin sensitivity are restored by quinacrine in head and neck cancer. Clin Cancer Res. **13**, 6568–6578 (2007). doi:10.1158/1078-0432.CCR-07-1591
250. KV Gurova, JE Hill, C Guo, A Prokvolit, LG Burdelya, E Samoylova, AV Khodyakova, R Ganapathi, M Ganapathi, ND Tararova, D Bosykh, D Lvovskiy, TR Webb, GR Stark, AV Gudkov, Small molecules that reactivate p53 in renal cell carcinoma reveal a NF-kappaB-dependent mechanism of p53 suppression in tumors. Proc Natl Acad Sci USA. **102**, 17448–17453 (2005). doi:10.1073/pnas.0508888102
251. W Wang, WC Ho, DT Dicker, C MacKinnon, JD Winkler, R Marmorstein, WS El-Deiry, Acridine derivatives activate p53 and induce tumor cell death through Bax. Cancer Biol Ther. **4**, 893–898 (2005). doi:10.4161/cbt.4.8.2134
252. K Gurova, New hopes from old drugs: revisiting DNA-binding small molecules as anticancer agents. Future Oncol. **5**, 1685–1704 (2009). doi:10.2217/fon.09.127
253. AV Gorbachev, AV Gasparian, KV Gurova, AV Gudkov, RL Fairchild, Quinacrine inhibits the epidermal dendritic cell migration initiating T cell-mediated skin inflammation. Eur J Immunol. **37**, 2257–2267 (2007). doi:10.1002/eji.200636708
254. T Collins, MA Read, AS Neish, MZ Whitley, D Thanos, T Maniatis, Transcriptional regulation of endothelial cell adhesion molecules: NF-kappa B and cytokine-inducible enhancers. FASEB J. **9**, 899–909 (1995)
255. MA Read, MZ Whitley, AJ Williams, T Collins, NF-kappa B and I kappa B alpha: an inducible regulatory system in endothelial activation. J Exp Med. **179**, 503–512 (1994). doi:10.1084/jem.179.2.503
256. M Wagner, CL Klein, TG van Kooten, CJ Kirkpatrick, Mechanisms of cell activation by heavy metal ions. J Biomed Mater Res. **42**, 443–452 (1998). doi:10.1002/(SICI)1097-4636(19981205)42:33.0.CO;2-H
257. W Konig, W Schonfeld, M Raulf, M Koller, J Knoller, J Scheffer, J Brom, The neutrophil and leukotrienes–role in health and disease. Eicosanoids. **3**, 1–22 (1990)
258. KM Stuhlmeier, JJ Kao, FH Bach, Arachidonic acid influences proinflammatory gene induction by stabilizing the inhibitor-kappaBalpha/nuclear factor-kappaB (NF-kappaB) complex, thus suppressing the nuclear translocation of NF-kappaB. J Biol Chem. **272**, 24679–24683 (1997). doi:10.1074/jbc.272.39.24679
259. L Thommesen, W Sjursen, K Gasvik, W Hanssen, OL Brekke, L Skattebol, AK Holmeide, T Espevik, B Johansen, A Laegreid, Selective inhibitors of cytosolic or secretory phospholipase A2 block TNF-induced activation of transcription factor nuclear factor-kappa B and expression of ICAM-1. J Immunol. **161**, 3421–3430 (1998)
260. A Palmetshofer, SC Robson, V Nehls, Lysophosphatidic acid activates nuclear factor kappa B and induces proinflammatory gene expression in endothelial cells. Thromb Haemost. **82**, 1532–1537 (1999)
261. A Pupe, H Degreef, M Garmyn, Induction of tumor necrosis factor-alpha by UVB: a role for reactive oxygen intermediates and eicosanoids. Photochem Photobiol. **78**, 68–74 (2003). doi:10.1562/0031-8655(2003)0782.0.CO;2
262. A Pupe, R Moison, P De Haes, GB van Henegouwen, L Rhodes, H Degreef, M Garmyn, Eicosapentaenoic acid, a n-3 polyunsaturated fatty acid differentially modulates TNF-alpha, IL-1alpha, IL-6 and PGE2 expression in UVB-irradiated human keratinocytes. J Invest Dermatol. **118**, 692–698 (2002). doi:10.1046/j.1523-1747.2002.01615.x
263. A Heller, T Koch, J Schmeck, K van Ackern, Lipid mediators in inflammatory disorders. Drugs. **55**, 487–496 (1998). doi:10.2165/00003495-199855040-00001
264. X Chen, A Gresham, A Morrison, AP Pentland, Oxidative stress mediates synthesis of cytosolic phospholipase A2 after UVB injury. Biochim Biophys Acta. **1299**, 23–33 (1996)
265. I Kurose, H Saito, S Miura, H Ebinuma, H Higuchi, N Watanabe, S Zeki, T Nakamura, M Takaishi, H Ishii, CD18/ICAM-1-dependent oxidative NF-kappaB activation leading to nitric oxide production in rat Kupffer cells cocultured with syngeneic hepatoma cells. J Clin Invest. **99**, 867–878 (1997). doi:10.1172/JCI119251
266. C Holscher, Quinacrine acts like an acetylcholine receptor antagonist rather than like a phospholipase A2 inhibitor in a passive avoidance task in the chick. Neurobiol Learn Mem. **63**, 206–208 (1995). doi:10.1006/nlme.1995.1022
267. KM Stuhlmeier, Effects of quinacrine on endothelial cell morphology and transcription factor-DNA interactions. Biochim Biophys Acta. **1524**, 57–65 (2001)
268. S Fabbri, C Prontera, M Broggini, M D'Incalci, Differential inhibition of the DNA binding of transcription factors NF kappa B and OTF-1 by nitrogen mustard and quinacrine mustard: transcriptional implications. Carcinogenesis. **14**, 1963–1967 (1993). doi:10.1093/carcin/14.9.1963
269. SI Na, MY Lee, JS Heo, HJ Han, Hydrogen peroxide increases [3H]-2-deoxyglucose uptake via MAPKs, cPLA2, and NF-kappaB signaling pathways in mouse embryonic stem cells. Cell Physiol Biochem. **20**, 1007–1018 (2007). doi:10.1159/000110541
270. C Guo, AV Gasparian, Z Zhuang, DA Bosykh, AA Komar, AV Gudkov, KV Gurova, 9-Aminoacridine-based anticancer drugs target the PI3K/AKT/mTOR, NF-kappaB and p53 pathways. Oncogene. **28**, 1151–1161 (2009). doi:10.1038/onc.2008.460
271. LD Mayo, JE Dixon, DL Durden, NK Tonks, DB Donner, PTEN protects p53 from Mdm2 and sensitizes cancer cells to chemotherapy. J Biol Chem. **277**, 5484–5489 (2002). doi:10.1074/jbc.M108302200
272. SJ Jeong, CA Pise-Masison, MF Radonovich, HU Park, JN Brady, Activated AKT regulates NF-kappaB activation, p53 inhibition and cell survival in HTLV-1-transformed cells. Oncogene. **24**, 6719–6728 (2005). doi:10.1038/sj.onc.1208825
273. N Sizemore, N Lerner, N Dombrowski, H Sakurai, GR Stark, Distinct roles of the Ikappa B kinase alpha and beta subunits in liberating nuclear factor kappa B (NF-kappa B) from Ikappa B and in phosphorylating the p65 subunit of NF-kappa B. J Biol Chem. **277**, 3863–3869 (2002). doi:10.1074/jbc.M110572200
274. KJ Jung, A Dasgupta, K Huang, SJ Jeong, C Pise-Masison, KV Gurova, JN Brady, Small-molecule inhibitor which reactivates p53 in human T-cell leukemia virus type 1-transformed cells. J Virol. **82**, 8537–8547 (2008). doi:10.1128/JVI.00690-08

275. S Hassan, RE Carraway, Involvement of arachidonic acid metabolism and EGF receptor in neurotensin-induced prostate cancer PC3 cell growth. Regul Pept. **133**, 105–114 (2006). doi:10.1016/j.regpep.2005.09.031
276. H Heimpel, W Heit, Drug-induced aplastic anaemia: clinical aspects. Clin Haematol. **9**, 641–662 (1980)
277. F Colotta, P Allavena, A Sica, C Garlanda, A Mantovani, Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. **30**, 1073–1081 (2009). doi:10.1093/carcin/bgp127
278. CM Ulrich, J Bigler, JD Potter, Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. Nat Rev Cancer. **6**, 130–140 (2006). doi:10.1038/nrc1801
279. A Dey, V Tergaonkar, DP Lane, Double-edged swords as cancer therapeutics: simultaneously targeting p53 and NF-kappaB pathways. Nat Rev Drug Discov. **7**, 1031–1040 (2008). doi:10.1038/nrd2759

doi:10.1186/1478-811X-9-13
Cite this article as: Ehsanian *et al.*: Beyond DNA binding - a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. *Cell Communication and Signaling* 2011 **9**:13.

Regulatory Toxicology and Pharmacology 56 (2010) 166–173

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats"

Ernest E. McConnell [a,*], Jack Lippes [b], Roger G. Growe [c], Patricia Fail [d], Michael I. Luster [e], Errol Zeiger [f]

[a] ToxPath Inc., 3028 Ethan Lane, Raleigh, NC 27613, USA
[b] University of Buffalo, 31 Hampton Hill Dr., Buffalo, NY 14221, USA
[c] International Services Assistance Fund, P.O. Box 13067, Research Triangle Park, NC 27709, USA
[d] Patricia Fail Associates, P.O. Box 464, Chanute, KS 66720, USA
[e] M.I. Luster Associates, LLC, Morgantown, WV 26508, USA
[f] Errol Zeiger Consulting, Chapel Hill, NC 27514, USA

ARTICLE INFO

Article history:
Received 2 July 2009
Available online 4 January 2010

Keywords:
Quinacrine
Female reproductive tract
Uterus
Neoplasms
Maximum tolerated dose

ABSTRACT

This companion article offers an alternative interpretation for the quinacrine-induced uterine tumors observed in a 2-year bioassay in rats (CaBio, Cancel et al., 2010), and provides additional data from two new experiments that support a different interpretation and analysis. Our major premise is that the design of the Cancel et al. bioassay was flawed, particularly regarding dose selection that allowed for misinterpretation of carcinogenic activity. We feel the totality of the information provided herein dictates that the doses (70/70, 70/250 and 70/350 mg/kg quinacrine) causing uterine tumors in their study clearly exceeded the maximum tolerated dose (MTD) typically administered in chronic cancer studies. Our new data support this conclusion and serve to explain the development of lesions, especially the uterine tumors, they have reported. We argue that the rat uterus is not a valid surrogate for the human fallopian tube. Further, we maintain that quinacrine is not genotoxic *in vivo*, as suggested in their paper. In summary, we believe that quinacrine is not carcinogenic in rats at doses that do not exceed the MTD.

1. Introduction

The purpose of this paper is to offer an alternative interpretation of "A Lifetime Cancer Bioassay of Quinacrine Administered into the Uterine Horns of Female Rats" (Cancel et al., 2010) and provide new data to buttress this opinion. Cancel et al. (2010) report that two doses of quinacrine in methylcellulose (MC), introduced into the uterine horn of rats approximately 21 days apart, resulted in the development of uterine tumors after 2 years at doses of 70/70 and 70/250–350 mg/kg quinacrine, but not at 10/10 mg/kg. We believe that the exposures causing the uterine tumors in their research exceeded the maximum tolerated dose. Our opinion is supported by additional studies and commentaries presented herein.

One of the most important issues in the design of a 2-year rodent bioassay for determining the carcinogenic potential of a chemical is the selection of the doses to be used in the study. A fundamental tenet in this process is to use a dose that meets, but does not excessively exceed, what is accepted, understood and referred to as the maximum tolerated dose (MTD). This is so critical because, when exceeded, the MTD can result in marked tissue and cellular destruction that lead to neoplastic cell growth, therefore confounding the interpretation of the carcinogenic potential of the xenobiotic in the test species and humans.

2. Background

In January of 2007, the 2-year rat carcinogenicity study of quinacrine conducted by Family Health International (FHI), as reported by Cancel et al. (2010), came to our attention. The reported tumors were unusual and rare, including primitive types of both epithelial (mixed Mullerian tumor, carcinosarcoma, squamous cell carcinoma and yolk sac carcinoma) and mesenchymal (granular cell tumor, hemangioma and hemangiosarcoma) origin. These are unexpected and rare observations in a standard 2-year cancer bioassay (CaBio) of a chemical. Another unusual feature is that only a single example of each of these rare tumors was found in the study. In a typical CaBio, an increased incidence of tumors that normally occur from a uterine carcinogen include endometrial adenomas and carcinomas, endometrial stromal polyps and sarcomas, leiomyomas and leiomyosarcomas and schwannomas (Leininger and Jokinen, 1990). In our opinion, the occurrence of the unusual tumors observed in Cancel et al. (2010) would likely result from se-

* Corresponding author. Fax: +1 919 848 1576.
E-mail addresses: toxpathmcc@bellsouth.net (E.E. McConnell), jlip@buffalo.edu (J. Lippes), roger_growe@earthlink.net (R.G. Growe), patriciafail@cox.net (P. Fail), miklus22@comcast.net (M.I. Luster), zeiger@nc.rr.com (E. Zeiger).

0273-2300/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2009.12.007

vere cell damage to the endometrium and myometrium in which only a few stem cells survived.

In order to reconstruct what may have happened in the rat uterus as a result of exposure to quinacrine, we asked and received permission from FHI to examine the histopathologic slides from a prechronic multidose study (Cancel et al., 2010) involving the same 2-dose procedure employed in the 2-year study and used to help establish doses for the CaBio.

Briefly, FHI's range-finding study #2 (Cancel et al., 2010) used quinacrine doses of 0.7/0.7, 7/7, 14/14, 35/35 and 70/70 mg/kg. The rats were exposed twice (21 days apart) with quinacrine in an MC slurry via transcervical instillation, and were sacrificed 21 days after the second exposure with no interim sacrifices. For example, the 70/70 mg/kg dose represents a dose of 35 mg/kg into each uterine horn and a second dose of 35 mg/kg into each uterine horn 21 days later. Examination of the histopathologic slides from this study by one of us (EEM) confirmed the severe pathology reported by Cancel et al. (2010) at doses of 14/14 mg/kg quinacrine and above, and the absence of lesions at 7/7 mg/kg or 0.7/0.7 mg/kg quinacrine. Moreover, in addition to uterine dilation reported by them, there was chronic purulent inflammation in several animals and complete occlusion of one horn in one rat exposed to 14/14 mg/kg quinacrine. It is probable that other uterine horns were also obstructed because of the high incidence of dilation, but the tissue sampling approach used in the study (described by Fail et al., 2000) would have precluded finding most of the occlusions because they selected three consistent cross-sections (proximal, middle and near the cervix) with no attempt at opening the remaining uterus in search of lesions.

With the above information in mind, two studies were conducted under the auspices of the International Services Assistance Fund (ISAF). The first was designed in an attempt to explain the dilation of the uterine horns. The second, a multidose study, was initiated to better define the early lesions and establish whether the dose levels met or exceeded the definition of MTD and, thus, might not be relevant to the human experience.

3. ISAF study of the effect of ligating a single uterine horn in the rat

To understand the marked uterine dilation noted in the FHI prechronic study, a hypothesis was developed: Could occlusion of a uterine horn, in and of itself, result in dilation and observed pathology as a result of mechanical pressure from the obstruction? To test this hypothesis, one of us (JL) conducted a study at the University of Buffalo, Buffalo, NY. A brief discussion of this research follows.

3.1. Study protocol

The following study was conducted in accordance with the Animal Welfare Act and was approved by the Institutional Animal Care Use Committee. Ten female Sprague Dawley rats, at 10 weeks of age and each weighing about 250 g, were selected for this investigation. Before surgery, the rats were housed in multi-cage units and were fed Harlan 2018 rat diet. Prior to surgery, incision(s) site(s) were shaved, scrubbed with antiseptic soap, wiped with alcohol, and followed by antiseptic paint.

Bupremorphine was injected for analgesia subcutaneously before anesthesia and then post-operatively as oral tablets on the next day at 0.05 mg/kg, and as needed thereafter. Rats were anesthetized with isofluorine, 4% for induction and 2% for maintenance. At 10-min intervals, corneal reflexes, positive toe pinch and the color of mucous membranes were assessed to be sure that the animals were pain free. A midline incision was made to expose the reproductive organs. The left uterine horn was ligated at both the cervical end and the utero-oviductal junction. Great care was taken to place needles with 4–0 Vicryl close to the serosa, avoiding any diminution of the blood supply to the rat uterine horn, as described previously by Lippes et al. (1972). The abdominal incision was closed in anatomical layers using interrupted sutures of 4–0 Vicryl. The skin was closed with a subcuticular running stitch of 4–0 Vicryl. Time elapsed for this surgery was approximately 1 h.

Following surgery, rats were housed individually in open-top polycarbonate caging with aspen bedding. After 21 days, animals were euthanized in a carbon dioxide chamber. Death was assured by cutting the chest open. The uteri were photographed *in situ*, removed, and placed unopened in 10% neutral buffered formalin. A single (5 μm) cross-section from the mid-portion of each uterine horn was made and stained with hematoxylin and eosin. The sections were examined microscopically by one of us (EEM) to determine the extent of damage, if any, from the ligation. The unligated horn served as the control.

3.2. Results

One rat died early in the study (day 7). The ligated horns of all of the surviving rats showed marked dilation (Fig. 1). Most of the uterine glands were not present due to pressure atrophy. Interestingly, the bursa of the ovary was also dilated (Fig. 2). No uterine lesions, especially purulent inflammatory material as seen in the Cancel et al. (2010), were observed in these rats.

3.3. Interpretation

This research demonstrates that ligation (occlusion) alone can result in uterine horn dilation of the severity that was also observed in the CaBio's dose range-finding study #2 and in Fail et al. (2000). And, that such dilation can occur within 21 days of the ligation. But we emphasize there was no evidence of uterine inflammation or cell damage other than atrophy in any of the animals whose uterine horns were ligated.

We believe the explanation for this relates to the anatomy of the rat reproductive tract. Unlike the fimbria of the human fallopian tube which is open to the ovary, and indirectly to the abdominal cavity, the rat ovary is completely encased in a bursa that is an extension of the fallopian tube. Therefore, increased pressure from occlusion would not be released into the abdominal cavity as

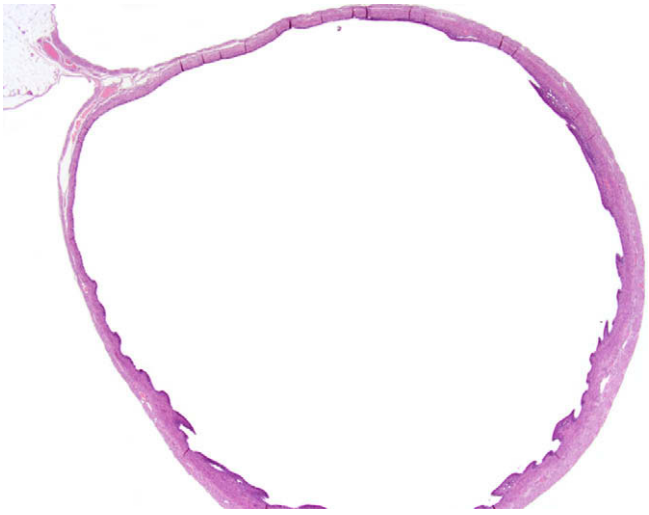


Fig. 1. Marked dilation of a ligated uterine horn. H&E stain, Original magnification 20×.

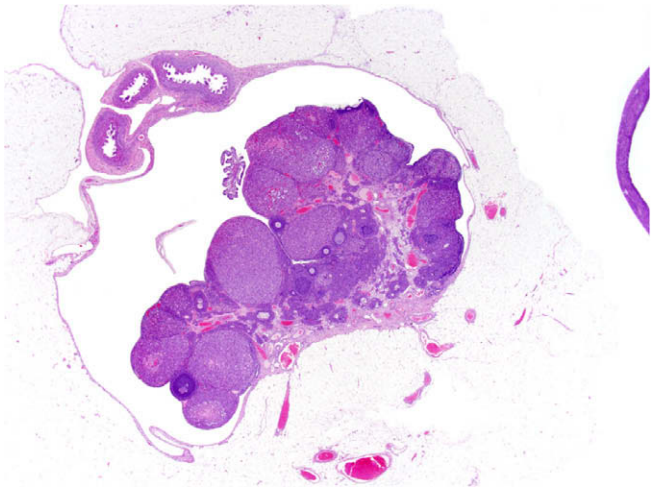


Fig. 2. Dilated ovarian bursa. Original magnification 20×.

would occur in women. The complete encapsulation of the ovary is clearly demonstrated by the dilated bursa in Fig. 2.

It is doubtful if dilation alone can result in tumor formation in a 2-year carcinogenesis bioassay. However, it is known that chronic inflammation can result in tumors in various organs in animals and humans (Kundu and Surh, 2008; Matés et al., 2008). The inflammation seen in the FHI prechronic dose range-finding study #2 (2010) likely resulted from a direct response to quinacrine-induced necrosis, while in this ligation study there was no evidence for necrosis, but rather pressure atrophy.

4. ISAF four-day study of quinacrine in rats

The purpose of this study was to define the early sequential changes in: (1) uterine histopathology; (2) plasma quinacrine concentrations; and (3) presence of residual quinacrine in intrauterine lumen fluids following quinacrine exposure with doses from 10 to 250 mg/kg in female rats. Until this investigation, there were no histologic studies pertaining to the uterus immediately following treatment with quinacrine. The plasma quinacrine concentrations and residual quinacrine findings will be presented in a subsequent publication because the data are not available at this time.

4.1. Materials and methods

Virgin female Sprague–Dawley rats (>66 days of age) were individually housed in stainless-steel wire-bottomed cages with *ad libitum* access to Certified Rodent Diet® #5002 meal (PMI Nutrition International, Inc., St. Louis, MO) and chlorinated deionized water. Groups of 9 or 10 rats were randomly assigned to exposure groups of either 10, 20, 70, or 250 mg/kg quinacrine suspended in 1% MC (4000 centipoise, Spectrum Chemical, New Brunswick, NJ, USA), 1% MC alone, or 0.9% saline alone. Although not employed in dosing humans, methylcellulose was used to mimic the conditions in the Cancel et al. (2010) study. The quinacrine slurry was administered transcervically, half into each uterine horn at a volume of 0.2 mL/horn, during diestrus.

Dosages in the 4-day study were selected on the basis of data from the prechronic and chronic studies reported in this issue by Cancel et al. The highest dose we used was 250 mg/kg quinacrine, chosen because it was the same as the one in the CaBio that caused mortality. The next lowest dose (70 mg/kg quinacrine) was selected because it caused tumors in the CaBio without mortality. The lowest dose (10 mg/kg quinacrine) was chosen because it was the one in the CaBio that did not cause uterine tumors. The 20 mg/kg quinacrine dose was included to better establish a clear dose response curve. Five additional rats were added at 250 mg/kg, because of unexpected mortality of four rats within 1 h after treatment.

Three rats per treatment group were sacrificed at 6-h, 24-h and 96-h post-exposure by carbon dioxide asphyxiation. Necropsies were performed to determine the early changes that occur after quinacrine exposure and time-course events. The uteri were photographed and weighed. The uterine horns were opened longitudinally. Approximately half of the right uterine horn was saved for possible future evaluation. The left horn and one-half of the right horn were pinned (mucosal side up) flat on an index card and fixed in 10% neutral buffered formalin for histologic evaluation. The formalin fixed tissues were submitted to Experimental Pathology Laboratories, Research Triangle Park, NC, where a single 4–5 μm longitudinal histopathologic section of the entire length of the uterine horns was prepared and stained with hematoxylin and eosin (H&E). The sections were examined by one of us (EEM) in a semi-blind manner, i.e. without knowledge of the dosage group, to determine the extent of damage, if any. Lesions were recorded using a severity scale of 0–4 (0 = normal, 1 = minimal, 2 = mild, 3 = moderate and 4 = severe pathology). The lesions were in turn reviewed by another veterinary pathologist (JS – see acknowledgment).

4.2. Results

Four animals in the high dose group died within an hour after exposure to 250 mg/kg quinacrine. No clinical signs were observed in the remaining animals in this group or any in the other dose groups. Histopathologic examination of the H&E stained slides showed various dose- and time-related pathological changes in the endometrium and at times in the myometrium. These changes consisted primarily of necrosis, inflammation and hemorrhage, both in the epithelium and in some cases in subjacent lamina propria stroma (Table 1). Stromal edema was striking in some animals and was correlated with the degree of necrosis. Of note was the fact that in some animals the lesions were of equal severity throughout the length of the horn, while in others it was more focal. While no lesions were observed in any animals in the saline control, minimal changes in the epithelium and glandular portion of the endometrium were observed in a few animals exposed to methylcellulose alone.

4.2.1. Uterine pathology in the 250 mg/kg quinacrine dose group

The uteri of rats that died after exposure to 250 mg/kg quinacrine showed mild to severe necrosis of the endometrium. The uterine lesions in the rats that survived at this dose were more severe than in those that died. At 6-h there was no viable epithelium, but there was superficial inflammation (primarily neutrophils and lymphocytes) and moderate hemorrhage. Diffuse necrosis and severe stromal edema of the lamina propria were observed to the level of the myometrium, i.e. no viable tissue was seen in the endometrium. *Note:* for the purpose of this study we used the term "ulceration" when no viable tissue was found to the level of the myometrium, and recorded whether the ulcers were focal or diffuse. Focal ulcers were macroscopically $\leqslant$ 2 mm diameter, while diffuse ulcers often were a centimeter or more in length and multifocal. Complete epithelial necrosis was still present at 24-h, but accompanied by more intense inflammation. By 96-h, there was significant, but not total, repair in the epithelium while inflammation was less apparent, and there was no evidence of hemorrhage. The glandular portion also showed some degree of repair. Diffuse ulceration was found in 3/3 rats at 6-h, 1/4 at 24-h and 1/3 at 96-h.

Table 1
Histologic findings from female rats exposed to quinacrine: average injury severity per dose group by time exposure, three animals per exposure group/dose.

Dose	h	Epithelium			Endometrium				
		Necrosis	Inflam.	Hem.	Necrosis	Inflam.	Hem.	Edema	Ulcer
Control	6	0	0	0	0	0	0	0	0
	24	0	0	0	0	0	0	0	0
	96	0	0	0	0	0	0	0	0
MC	6	.3	0	1	0	0	0	.3	0
	24	0	0	0	.7	0	0	0	0
	96	.7	0	.7	.7	0	0	.7	0
10 mg	6	3.3	2	2.7	1.7	.7	.7	3	0
	24	3	2.3	.7	1.7	1.7	0	2.7	2 – F
	96	.7	2	0	0	1	0	1.3	0
20 mg	6	2	0	1	1.7	0	1.3	2.7	2 – F, 1 – D
	24	2.3	2.7	.7	.3	1.3	.7	1.7	1 – F
	96	.7	1.3	.3	0	1.3	0	2	0
70 mg	6	3	2.3	1.3	2	2	2	2.3	3 – D
	24	3	3	.7	1	1.7	.7	2.3	1 – F
	96	.3	2.3	.7	.7	1.7	0	.7	0
250 mg	FD	2.3	0	2.3	3	0	3.3	2.3	1 – F, 2 – D
	6	4	.7	2.7	3.3	2	2	3.7	3 – D
	24	3.8	2.3	2	2	1.5	2	2.5	1 – D
	96	1.3	1	.7	2	1	1	1.7	1 – D

F = focal, D = diffuse, FD = found dead.

4.2.2. Uterine pathology in the 70 mg/kg quinacrine dose group

Mild to severe necrosis was observed in the epithelium in rats exposed to 70 mg/kg quinacrine group at 6-h. A minimal to mild amount of inflammation and hemorrhage were also present. Mild necrosis and edema in the lamina propria were observed to the level of the myometrium (Figs. 3 and 4). All three rats had diffuse ulcer development (Fig. 4). At 24-h, the epithelial necrosis was still complete in 2/3 rats, but the necrosis in the subjacent tissues appeared to be slightly less severe. One rat had a focal ulcer. At 96-h, there was evidence of significant epithelial and endometrial repair although inflammation was still apparent in both tissues.

4.2.3. Uterine pathology in the 20 mg/kg quinacrine dose group

At 6-h, mild necrosis of the epithelium and subjacent tissues was observed and was accompanied by a moderate amount of inflammation, edema and some evidence of hemorrhage. Again, necrosis was present to the level of the myometrium and ulcers were noted in all three rats, but only one was diffuse (Fig. 5). At 24-h, the severity of the necrosis of the epithelium was similar to that at 6-h but had decreased in the lamina propria, although the severity of inflammation had increased in both tissues. One rat is this group had a focal ulcer. At 96-h, there was no evidence of necrosis in the lamina propria and only a minimal amount in the epithelium. In some animals, it was nearly normal (Fig. 6).

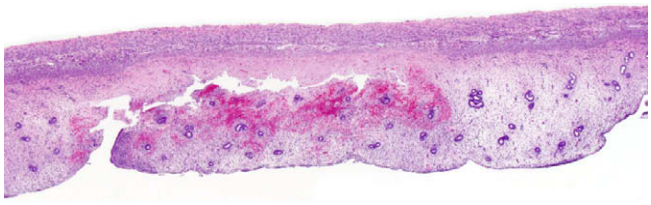


Fig. 4. Full thickness necrosis and edema of the endometrium and incipient ulcer at 6 h. 70 mg/kg. Original magnification 32×.

4.2.4. Uterine pathology in the 10 mg/kg quinacrine dose group

At 6-h, there was mild to severe necrosis of the epithelium, a mild to moderate amount of inflammation and a mild to moderate amount of hemorrhage. There was mild necrosis in the lamina propria, primarily limited to the endometrial glands. A moderate

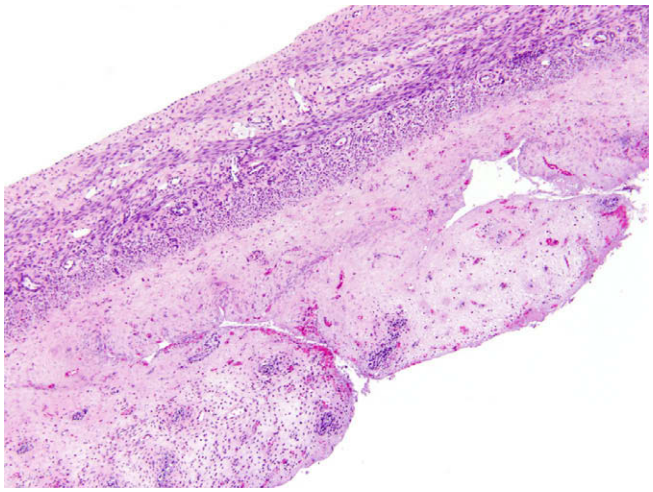


Fig. 3. Full thickness necrosis and edema of the endometrium at 6 h. 70 mg/kg. Original magnification 80×.

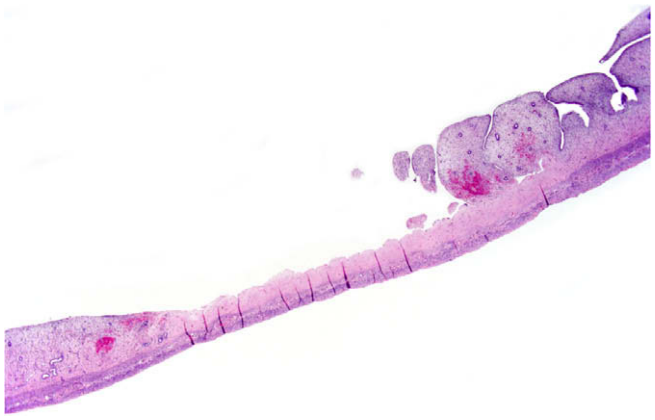


Fig. 5. Ulcer and full thickness necrosis of the endometrium attended by a moderate amount of inflammation, edema and some evidence of hemorrhage at 6 h. 20 mg/kg. Original magnification 20×.

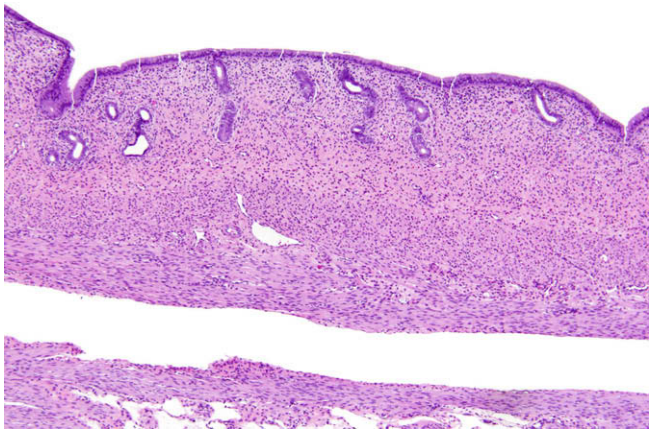


Fig. 6. Almost complete regeneration. 96 h. Original magnification 40×.

amount of stromal edema was also observed. The lesions at 24-h were similar to those found at 6-h (Fig. 7), although 2 of the 3 rats had focal ulcers. At 96-h, almost total repair to the epithelium was observed, although the severity of inflammation in the epithelium was still moderate.

4.2.5. Interpretation

The results of this study show dose- and time-related lesions in the endometrium of rats exposed to quinacrine and a negative association with inflammation (i.e., as the dose decreased the degree of inflammation increased). The major difference in dose response was the incidence and severity of ulceration. While ulceration was found in 2/9 rats at 10 mg/kg and 4/9 at 20 mg/kg, only one rat (20 mg/kg) had diffuse involvement. Again, 4/9 rats at 70 mg/kg showed ulceration, but in 3/4 the ulcers were diffuse. Five of 10 rats at 250 mg/kg showed ulceration and all were diffuse. The presence of ulceration is particularly important because it probably explains the mode of action for uterine occlusions as discussed below. In addition, it is generally believed that the mechanism of action responsible for quinacrine sterilization in humans is initiated via an acute (self-limiting) inflammatory response followed by remodeling and development of a fibrotic scar limited to the uterotubal junction (Lu et al., 2003).

5. Discussion

The quinacrine pellet method of birth control, termed quinacrine sterilization (QS), was developed by Zipper in Chile in 1977 (Zipper et al., 1980) and has to this date been used by more than 100,000 women in many countries (Kessel, 1997). The method requires two transcervical insertions into the uterus (2 doses of 252 mg/dose) of 7 pellets of quinacrine, one month apart, by means of a device similar to an IUD inserter. With a serious complication rate of only 1/50th that of surgical tubal ligation (Lippes, 2002), QS is much safer. Zipper et al. (1980) method placed the pellets in a straight line down the middle of the uterus, beginning at the fundus. The insertion technique described by Hieu et al. (1993), placed all of the pellets at the fundus, improving the efficacy rate to 98% at 4 years (Bilgrami and Shah, 2003). Furthermore, QS is more acceptable to women than surgical techniques (Hieu et al., 2003; Randic, 2000), can be delivered by trained non-physician clinicians as an outpatient service (Hieu et al., 1993), and is inexpensive, estimated to cost $0.53/dose when mass produced (Presource Technologies, Inc., Monmouth Junction, NJ).

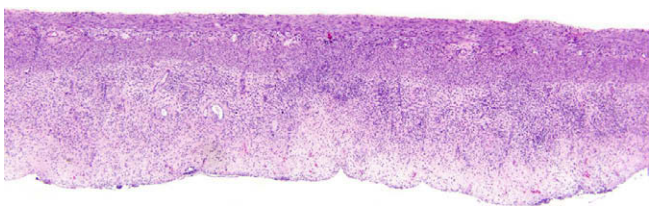


Fig. 7. Complete necrosis of the endometrial epithelium attended by mild to moderate inflammation and a minimal amount of hemorrhage, and a mild amount of necrosis in the lamina propria. 24 h. 10 mg/kg. Original magnification 40×.

Short-term complications and side effects following intrauterine quinacrine insertion have been studied in numerous countries (Agoestina and Kusuma, 1992; Ferreira et al., 2003; Sarin, 1999; Soroodi-Moghaddam, 2003). All such outcomes have been minor except for rare cases of successfully managed allergic reaction. Hospitalization due to a side effect or complication is exceedingly rare. These sequellae are mostly limited to non-infective fever, headache, lower abdominal pain, dysuria, leucorrhea, and back pain. Pain usually lasts for only a few days and is treated with ibuprofen or a similar drug. Notably, chronic pelvic pain is not reported. Menstrual patterns remain the same following insertion, indicating a normally functioning uterus. Permanent damage is limited to the uterotubal junction of the fallopian tube and results in a mature scar filling the intramural portion of the tube (Lu et al., 2003). El-Kady et al. (1991) have described the progression of the development of the scar in the tube from day 7 to day 25. Others (Bhatt et al., 1980; Laufe et al., 1996; Merchant et al., 1986; 1995; Sarin et al., 1998) have undertaken similar prehysterectomy studies and have identified these salient features.

Family Health International has undertaken extensive long-term follow-up studies in Vietnam and Chile, and has recently published three papers on these experiences. In its paper, "Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam" (Sokal et al., 2008), a study of 2735 women who had quinacrine insertions between 1989 and 1993 compared to 1623 who received the IUD, the cumulative years of follow-up for the quinacrine and IUD cohorts were 28,697 and 17,382 person-years respectively. Losses to follow-up were 6% and 7%, respectively. FHI found that the risk of cancer, hysterectomy, pelvic/gynecologic surgery and death were similar in the two groups. A second FHI study, "Quinacrine Sterilization and Gynecologic Cancers: a case-control study in northern Vietnam," (Sokal et al., in press) was conducted for a 7-year period in 12 provinces in northern Vietnam, where a relatively large number of women had received intrauterine quinacrine. Cases of incident cervical, ovarian and uterine cancer were identified at provincial or referral hospitals in Hanoi. The prevalence of quinacrine exposure was 1.2% among cases and 1.1% among controls. FHI concluded, "We found no evidence of a relationship between quinacrine sterilization and gynecologic cancer." In its third study (Sokal et al., 2010) of women in Chile, where QS had its inception, FHI evaluated a quinacrine cohort from 1977 to 2007 and found their total follow-up time to be 23,894 person-years. FHI discovered that gynecologic cancers are within the range of expected numbers, suggesting that quinacrine does not increase their risk. ISAF currently has completed data collection on larger follow-up studies in Vietnam and China.

In collaboration with the FDA, ISAF mounted a Phase I study which was begun in 2001. Following its successful completion in 2003 (Lippes et al., 2003), ISAF requested permission to conduct a Phase III clinical trial in the United States. An Investigational New Drug (IND) application was approved by the FDA for this purpose in 2006, but was placed on clinical hold in early 2007, when Cancel et al. (2010) reported tumors produced at 70/70 mg/kg quinacrine and above in the CaBio. Therefore, the results of the CaBio are of critical importance and should be interpreted appropriately. In our opinion, the findings in their investigation, along with

their prechronic research, provide data supportive of the conclusion that: the doses causing tumors in their research clearly exceeded the MTD, and were secondary to the tissue destruction caused by the quinacrine doses used and the method of administration. Our rationale follows.

The severe endometrial destruction (diffuse ulceration) was likely responsible for the scarring and subsequent occlusion of the horn observed in the FHI prechronic and 2-year studies. While there was clear evidence of healing and regeneration of both the epithelium and glandular portions of the uterus in most animals, it was not uniform throughout the length of the uterus. Diffuse ulceration with subsequent scarring and chronic inflammation clearly exceed the definition of maximum tolerated dose, as discussed below. Just as importantly, the lesions observed at 10 mg/kg would qualify as a dose that met the definition of the MTD because the necrotic lesions, particularly in the epithelium, were of a moderate severity, accompanied by a significant amount of inflammation in subjacent tissues, but were repairable. If the purpose of this study was to determine the doses for a 2-year rat carcinogenicity bioassay for submission to a regulatory authority, the results clearly suggest that the highest dose level would be 10 mg/kg quinacrine because it did not show diffuse ulceration and therefore would not cause tubal occlusion.

While Cancel et al. (2010) offer their rationale for selection of the doses in their CaBio, their choices exceeded the contemporary definition of MTD, as documented by the United States Food and Drug Administration (United States Food and Drug Administration, 2008, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129112.pdf), the International Conference on Harmonisation, (International Conference on Harmonisation, 2008, http://www.emea.europa.eu/pdfs/human/ich/038395en.pdf), the National Toxicology Program (Bucher et al., 1996; Bucher, 2002; McConnell, 1989) and the Environmental Protection Agency (United States Environmental Protection Agency, 1998, http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-4200.pdf) for high dose selection. The reasons Cancel and co-authors give for their dose selection are:

> "(1) the need to produce local tissue necrosis and fibrosis in the uterus, similar to that produced in women; (2) the need to test dose levels that provided exposures that were equivalent to and greater than those occurring routinely in clinical, non-surgical sterilization programs in women; and (3) the tolerance of the rat to any local or systemic toxicity produced by the quinacrine instillation"

We agree that these criteria are to some degree in concert with the spirit of MTD, but by definition the doses they selected exceeded their criteria. For example, the lesions produced at levels of 20 mg/kg in our study, at 14/14 mg/kg in the FHI prechronic study and at 70/70 mg/kg in the CaBio produced lesions far in excess of what are found in women (see below). Also, local toxicity that could not be repaired, e.g. diffuse ulceration, fibrosis (scarring) and chronic inflammation, would exceed what would be considered "tolerance." Finally, we feel that the dose metric of comparing the animal dose to the human dose on a mg/kg basis is not appropriate for these studies. While a mg/kg comparison is suited to a systemic exposure, this would not be appropriate for our current studies, which are essentially topical applications to the uterine epithelium.

In terms of dose selection, FDA's 2008 guidance, developed in collaboration with the International Conference on Harmonisation (ICH), states, "In the United States, dose selection based on the MTD has traditionally been considered the only appropriate practice" (USFDA & International Conference on Harmonisation, 2008). In fact, it affirms that, "There is no scientific consensus on the use of toxicity endpoints other than the MTD." Sections of this guidance germane to this study include the need to use as the highest dose one that is minimally toxic and is tolerated without chronic dysfunction or pathological changes that would interfere with the interpretation and, therefore, the validity of the study.

Next, the National Toxicology Program (NTP) is widely known for developing guidelines to be used in dose selection for CaBios. Regarding selection of the highest dose group in a CaBio, it makes clear that, "When toxicity limits the top dose selected for a chronic study, attempts are made to use a maximum tolerated dose, or, perhaps more accurately, a *minimally toxic dose* (our emphasis) or minimally toxic exposure to ensure that animals are sufficiently challenged during a chronic study to reveal the carcinogenic potential of the chemical" (Bucher et al., 1996).

Finally, we feel that the Environmental Protection Agency (EPA) guidelines (United States Environmental Protection Agency, 1998) on the dermal route of exposure also apply to dose selection in the case of quinacrine. This is because intrauterine instillation is actually a topical application of the chemical rather than a systemic exposure. The EPA guidelines clearly state that the highest dose used in a dermal study should be one that *does not cause "ulceration"* (our emphasis).

As detailed above, the dose selection criteria used in the Cancel et al. (2010) CaBio are notably different from the FDA/ICH/NTP and EPA Guidelines. The fact that the two high dose groups demonstrated greater than 30% mortality indicates that those doses clearly exceeded the MTD. This also raises the question of whether the 70/70 mg/kg quinacrine dose group also exceeded the MTD. We contend it did for the following reasons:

1. Their prechronic studies showed severe endometrial pathology including occlusive fibrosis at doses of 14 mg/kg quinacrine and higher.
2. The pathology observed in their prechronic investigations (endometrial necrosis, cystic degeneration, ulceration, and inflammation) persisted throughout the 2-year study.
3. The results of our 4-day study reveal pathology at 20 mg/kg quinacrine and above that exceeds the accepted definition of MTD, based on severe endometrial necrosis and diffuse ulceration.

With the above points in mind, we contend that a dose between 7 mg/kg (the one not causing permanent damage in the prechronic study) and 10 mg/kg quinacrine (the dose that caused endometrial necrosis but no diffuse ulceration in our 4-day study), represents the highest scientifically supported dose that can be used in the CaBio for quinacrine given via intrauterine exposure.

Destruction of the uterus (diffuse ulceration), as seen in the rat in these studies, is not found in women using this method of birth control. In the human, quinacrine is administered in the uterus resulting in a well-defined fibrotic scar limited to the uterotubal junction and intramural segment of the fallopian tube, effectively producing a fibrotic scar in the fallopian tubes of > 90% of women after a single dose (Lu et al., 2003). The consistency of this response is well documented in ultrasounds of 128 Brazilian women while undergoing their quinacrine procedures (Ferreira et al., 2003). Most importantly, there is no endometrial ulceration or long-lasting pathology in the uterus.

Furthermore, Laufe et al. (1996) reported on the histopathologic examination of the uteri of women, previously scheduled for a hysterectomy, who then agreed to undergo transcervical intrauterine instillation of quinacrine before their surgery so that possible uterine pathology could be determined. Histopathologic sections of these uteri did not show pathology as a result of quinacrine of a nature different from what would be expected in a normal-cycling

woman. In addition, in a study of 100 women, Agoestina and Kusuma (1992) report that during the month following insertion, women experienced only minor transitory complaints, and rarely, considerable bleeding or pain. In our opinion, if women experienced the extensive damage to the uterus as was seen in rats at 70 mg/kg quinacrine and above, they would be reporting significant bleeding within hours of the insertion, with significant pain continuing, possibly for their lifetime.

Cancel et al. (2010) chose to evaluate quinacrine in the uterine horn of rats at dose levels that produced fibrosis in the fallopian tube in women (Laufe et al., 1996; Merchant et al., 1995). Yet Merchant says, "The sections through the regenerated endometrium, cervix, and myometrium of the uterus in all cases of Groups I [straight quinacrine pellet inserter] and II [curved quinacrine pellet inserter] did not reveal any abnormality, thereby indicating that the chemical has no lasting effect on these structures [in women]." Additionally, Laufe reported no pathology in the endometrium in women from one-month trials. In their research, the permanent damage was considered to be confined to the fallopian tube. Drs. Fail and Zipper, with six studies between them, have the most experience conducting and evaluating the use of quinacrine in the rat uterus. They judge that the requirements of a carcinogenesis study would make the rat uterus an inadequate surrogate model for the human fallopian tube (personal communications).

We agree that if one wishes to examine the carcinogenicity of quinacrine, as used in sterilization, investigators would need to administer quinacrine into the rat uterus and look for neoplasms in the reproductive tract. But, the intent of such a study would be to assess the potential carcinogenicity in the uterus, not the fallopian tube, and most importantly, such a study would not administer dose levels that destroy the endometrium and cause permanent scarring. This would be akin to using an ulcerogenic dose in skin paint or stomach gavage studies which would not be condoned for use in animal studies for both scientific and ethical reasons.

We consider it improper to use the rat uterus as a human fallopian tube surrogate for anatomical reasons. The rat uterus is a complex organ with a thick endometrium consisting of an epithelial lining, numerous subjacent glands and a thick lamina propria. As a proportion, the endometrium is approximately twice as thick as the myometrium. In contrast, the fallopian tube has a very simple structure. It is lined by a single layer of columnar ciliated cells with a scattering of secretory and clear cells and a negligible amount of lamina propria (Leininger and Jokinen, 1990).

In general, the reaction to a given chemical is tissue-specific and depends on a myriad of local tissue and organ-specific chemical/cell interactions. While years of experience support the use of various rat organs as surrogates for the same organs in humans, there is little scientific support for using one organ to predict what would happen in one that is anatomically dissimilar (Quayle, 2002; Pioli et al., 2004; Itoh et al., 2006).

We conclude that the series of events that led to the induction of the tumors in the CaBio are as follows:

(1) Acute severe necrosis with ulceration of the endometrium was followed by scarring and occlusion at dose levels where total uterine length repair was not possible.
(2) Dilation of the uterine horn occurred proximal to the occlusion due to pressure atrophy in this "closed system." As our experiment has shown, dilation, by itself, cannot account for necrosis and inflammation.
(3) Excessive cell necrosis and chronic inflammation at the tissue site allowed for an environment that promoted the formation of reactive oxygen and nitrogen species. The generation of free radicals is known to produce DNA damage and enhanced cell proliferation, which is most likely responsible for the tumor response observed in the CaBio.
(4) The wide range of tumor types found, with different types in different animals receiving the same dose, none of them statistically significant, is not the expected response to a specific chemical insult as would be expected from a genotoxic carcinogen. Instead, such a reaction is strong evidence of the non-specific nature of tumor induction, as would be expected from a response to tissue necrosis and subsequent cell proliferation, coupled with chronic inflammation.

With regard to the Cancel et al. (2010) conclusion – that quinacrine was carcinogenic in the rat CaBio via a genotoxic mechanism because the tumors were seen after only two doses – we offer the following opinion:

They fail to note that the Cancel et al. 2006 neonatal mouse study concluded that the only histopathology of concern consisted of slight increases in benign stromal polyps at the intermediate and high doses, not significantly different from the control. They also omit the fact that the high dose was lethal to 25% of the high-dose animals following the second administration. There is a consensus that the neonatal mouse assay is effective for distinguishing between genotoxic and non-genotoxic carcinogens, and is negative for the latter (Flammang et al., 1997; McClain et al., 2001). In summarizing a collaborative study coordinated by the International Life Sciences Institute (ILSI), it was concluded that "Negative data in [the neonatal assay] are also mechanistically meaningful, indicating that the drug is not likely to be a trans-species carcinogen; that the drug is unlikely to have *in vivo* genotoxic activity; and the drug is unlikely to be a direct-acting carcinogen. In addition, negative data will contribute to weight of evidence that a tumor response observed in the rat is more likely to involve an epigenetic mode of action" (McClain et al., 2001).

The negative carcinogenicity results in the neonatal mouse assay, and the finding that tumors were only seen in rats with massive uterine tissue destruction in the surviving animals, do not suggest a genotoxic mode of action for the uterine tumors.

We contend that massive cell necrosis in the endometrium, along with chronic inflammation resulting in free radical generation, are the most plausible causes for tumor formation in Cancel et al. (2010). There was clear evidence of initial massive uterine necrosis followed by sustained inflammation in both the prechronic and chronic studies under discussion. Chronic inflammation and free radical generation is a common mechanism for tumor initiation and progression, believed to be responsible for approximately 25% of all tumors in humans (Kundu and Surh, 2008). When tumors arise from this process, they are characterized by being organ-specific, as were seen with quinacrine, rather than having multiple organ involvement. The mechanisms for inflammatory-induced tumors, although complicated, are fairly well understood as due to multiple inflammatory mediators produced by infiltrating inflammatory cells. Two of the more important mediators are reactive oxygen and reactive nitrogen species. These are also produced during cell necrosis and cause DNA damage (strand breaks, cross-linking and genomic instability). The other group of important mediators are cytokines, also products of inflammatory cells, and are responsible for enhanced cell proliferation of initiated cells, altered apoptosis, tumor neovascularization and protein modification (e.g., histone modification and hypermethylation).

6. Conclusions

In conclusion, the study by Cancel et al. (2010) clearly shows that there was no evidence of carcinogenic activity of quinacrine at 10 mg/kg, the highest dose that would have been used in their CaBio if they had been guided by the basic tenets for maximum tol-

erated dose. Further, we think there is strong evidence that the dose (70 mg/kg quinacrine) that produced tumors in their study significantly exceeded the MTD. Therefore, the findings at this dose level should be censored from evaluation of the carcinogenic activity of quinacrine in the rat uterus.

Conflict of Interest statement

The authors declare that this work has not been published previously nor is it under consideration for publication elsewhere. The article is approved by all authors. Dr. McConnell is an unpaid science advisor to ISAF and therefore has no conflict of interest. Dr. Lippes has been the principal investigator on the Phase I and Phase III studies. Roger Growe, Drs. Fail, Luster and Zeiger are paid consultants to ISAF.

Funding source

This work was supported with funds through a grant from the Fred H. Bixby Foundation.

Acknowledgments

The authors thank Family Health International for allowing us to review the histopathologic slides from their prechronic study; Dr. John Curtis Seely (Experimental Pathology Laboratories, Inc.) for his advice on the histopathology; Drs. Leslie Curtin and Tiffany Whitcomb (State University of New York at Buffalo, Department of Comparative Medicine-Lab Animal Facilities) for their animal care and surgery; Drs. Parthena Martin and Elise Lewis (Charles River Laboratories) for their skill and guidance in the design and conduct of the study; Margaret Miller Growe (ISAF) for her editorial assistance and coordination of the authors and collaborators in preparation of this manuscript; Irene Rosenfeld for her editing expertise.

References

Agoestina, T., Kusuma, I., 1992. Clinical evaluation of quinacrine pellets for chemical female sterilization. Adv. Contracept. 8, 141–151.

Bhatt, R.V., Aparicio, A., Laufe, L.E., Parmley, T.H., King, T.M., 1980. Quinacrine-induced pathologic changes in the fallopian tube. Fertil. Steril. 33, 666–667.

Bilgrami, M., Shah, L., 2003. Marie Stopes Society, Pakistan: 1000 cases of quinacrine sterilization (QS). Int. J. Gynecol. Obstet. 83 (2), S125–S127.

Bucher, J.R., Portter, C.J., Goodman, J.I., Faustman E.M., Lucier, G.W., 1996. Workshop Overview. National Toxicology Program Studies: principles of dose selection and applications to mechanistic based risk assessment, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.

Bucher, J.R., 2002. The national toxicology program rodent bioassay: designs, interpretations, and scientific contributions. Ann. N.Y. Acad. Sci. 982, 198–207.

Cancel, A.M., Smith, T., Rehkemper, U., Dillberger, J.E., Sokal, D., McClain, R.M., 2006. A one-year neonatal mouse carcinogenesis study of quinacrine dihydrochloride. Int. J. Toxicol. 25, 109–118.

Cancel, A.M., Dillberger, J.E., Kelly, C.M., Bolte, H.F., Creasy, D.M., Sokal, D.C., 2010. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 156–165.

El-Kady, A.A., Mansy, M.M., Nagib, H.S., Kessel, E., 1991. Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. Adv. Contracept. 7, 1–9.

Fail, P.A., Martin, P., Sokal, D., 2000. Comparative effects of quinacrine and erythromycin in adult female rats: a nonsurgical sterilization study. Fertil. Steril. 73 (2), 387–394.

Ferreira, C.R., Magalhães, D.R., Ferreira, D.C., Hanan, M.Z., Camargos, A.F., 2003. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women. Int. J. Gynecol. Obstet. 83 (Suppl 2), S59–66.

Flammang, T.J., Von Tungeln, L.S., Kadlubar, F.F., Fu, P.P., 1997. Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Regul. Toxicol. Pharmacol. 26, 230–240.

Hieu, D.T., Luong, T.T., Anh, P.T., Ngoc, D.H., Duong, L.Q., 2003. The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15, 190 cases. Int. J. Gynecol. Obstet. 83 (Suppl 2), S77–85.

Hieu, D.T., Tan, T.T., Tan, D.N., Nguyet, P.T., Than, P., Vinh, D.Q., 1993. 31, 781 cases of nonsurgical female sterilization with quinacrine pellets in Vietnam. Lancet 342, 213–217.

International Conference on Harmonisation, 2008. In: European Medicines Agency, Note for Guidance on dose selection for carcinogenicity studies of pharmaceuticals, ICH Expert Working Group, Topic S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals. 7 Westferry Circus, Canary Wharf, London, E14 4HB, United Kingdom.

Itoh, H., Nasu, K., Nishida, M., Matsumoto, H., Yuge, A., Narahara, H., 2006. Human oviductal stromal fibroblasts, but not oviductal epithelial cells, express toll-like receptor 4: the site-specific mucosal immunity of the human fallopian tube against bacterial infection. Am. J. Reprod. Immunol. 56, 91–101.

Kessel, E., 1997. 100, 000 quinacrine sterilizations. Adv. Contracept. 12, 69–76.

Kundu, J.K., Surh, Y.-J., 2008. Inflammation: gearing the journey to cancer. Mutat. Res. 659, 15–30.

Laufe, L.E., Sokal, D.C., Cole, L.P., Shoupe, D., Schenken, R.S., 1996. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception 54, 181–186.

Leininger, J.R., Jokinen, M.P., 1990. Oviduct, Uterus and Vagina, in Pathology of the Fischer Rat: Reference and Atlas. Academic Press, NY. pp. 443–458.

Lippes, J., Enders, R.G., Pragay, D.A., Bartholomew, W.R., 1972. The collection and analysis of human fallopian tubal fluid. Contraception 5, 85–103.

Lippes, J., 2002. Editorial. Quinacrine sterilization: the imperative need for American clinical trials. Fertil. Steril. 77 (6), 1106–1109.

Lippes, J., Brar, M., Gerbracht, K., Neff, P., Kokkinakis, S., 2003. An FDA phase I clinical trial of quinacrine sterilization (QS). Int. J. Gynecol. Obstet. 83 (Suppl 2), S45–S49.

Lu, W., Zhu, J., Zhong, C., Zhao, Y., 2003. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China. Int. J. Gynecol. Obstet. 83 (Suppl 2), S51–8.

Matés, J.M., Segura, J.A., Alonso, F.J., Márquez, J., 2008. Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. Arch. Toxicol. 82, 273–299.

McClain, R.M., Keller, D., Casciano, D., Fu, P., MacDonald, J., Popp, J., Sagartz, J., 2001. Neonatal mouse model: review of methods and results. Toxicol. Pathol. 29 (Suppl.), 128–137.

McConnell, E.E., 1989. The maximum tolerated dose: the debate. J. Am. Coll. Toxicol. 6, 1115–1120.

Merchant, R.N., Doctor, V.M., Thaku, S.S., Sinha, M., Jhaveri, C.L., Kessel, E., Mumford, S.D., 1986. Clinico-pathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets. Adv. Contracept. 2, 79–90.

Merchant, R.H., Prabhu, S.R., Kessel, E., 1995. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. Int. J. Fertil. 40, 47–54.

Pioli, P.A., Amiel, E., Schaefer, T.M., Connolly, J.E., Wira, C.R., Guyre, P.M., 2004. Differential expression of toll-like receptors 2 and 4 in tissues of the human female reproductive tract. Infect. Immun. 72, 5799–5806.

Quayle, A.J., 2002. The innate and early immune response to pathogen challenge in the female genital tract and the pivotal role of epithelial cells. J. Reprod. Immunol. 57, 61–79.

Randic, L., 2000. Results of Phase II QS trials in Croatia. Presentation to Planned Parenthood Federation of America's National Medical Committee's Ad Hoc Committee on Quinacrine Sterilization, July 18, 1999. In: Quinacrine Newsletter 2000, International Services Assistance Fund, Research Triangle Park, NC.

Sarin, A.R., 1999. Quinacrine sterilization: experience among women at high risk for surgery. Adv. Contracept. 15 (3), 175–178.

Sarin, A.R., Mohindroo, A., Chandra, P., Gill, S.S., 1998. Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion. Fertil. Steril. 70 (Suppl. 1), S164 (abstr. P-121) <http://www.quinacrine.com/archive/sari98.pdf>.

Sokal, D.C., Hieu, D.T., Loan, N.D., Hubacher, D., Nanda, K., Weiner, D.H., Vach, T.H., 2008. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. Contraception 78, 66–72.

Sokal, D.C., Trujillo, V., Guzmán, S.C., Guzman-Serani, R., Wheeless, A., Hubacher, D., 2010. Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort. Contraception. 81, 75–78.

Sokal, D.C., Vach, T.H., Nanda, K., McCann, M.F., Weiner, D.H., Drobnes, C., Rochanawutanon, M., Duc, N.B., Loan, N.D., in press. Quinacrine sterilization and gynecologic cancers: a case-control study in northern Vietnam. Epidemiology.

Soroodi-Moghaddam, S., 2003. Quinacrine sterilization (QS) in Iran and the use of HSG as a measure of success. Int. J. Gynecol. Obstet. 83 (Suppl. 2), S93–S96.

United States Environmental Protection Agency. Health Effects Test Guidelines: OPPTS 870.4200 Carcinogenicity. Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-98-211, August 1998.

United States Food and Drug Administration and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008. Guidance for Industry: S1C(R2) Dose Selection for Carcinogenicity Studies. Revision 1, September 2008. U.S. Department of Health and Human Services Center for Drug Evaluation and Research, pp. 2–5.

Zipper, J., Cole, L.P., Goldsmith, A., Wheeler, R., Rivera, M., 1980. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int. J. Gynecol. Obstet. 18, 275–279.

Quinacrine Sterilization and Gynecologic Cancers

A Case–Control Study in Northern Vietnam

David C. Sokal,[a] *Trinh Huu Vach,*[b] *Kavita Nanda,*[a] *Margaret F. McCann,*[a] *Debra H. Weiner,*[a] *Claude Drobnes,*[a] *Mana Rochanawutanon,*[c] *Nguyen Ba Duc,*[d] *and Nguyen Dinh Loan*[e]

Background: Over 100,000 women worldwide have been sterilized by insertion of quinacrine into the uterus to induce tubal scarring. Concern has been expressed about possible carcinogenicity, and specifically the risk of uterine cancer.

Methods: From 2001 through 2006, we conducted a population-based, case–control study of gynecologic cancers in 12 provinces in northern Vietnam, where relatively large numbers of women had received quinacrine. Cases of incident cervical, ovarian, and uterine cancer were identified at provincial hospitals or at referral hospitals in Hanoi. For each case, 3 age- and residence-matched controls were randomly selected from the population registries of the case's home community.

Results: The prevalence of quinacrine exposure was 1.2% among cases and 1.1% among controls. For cervical cancer, analysis of 606 cases (9 exposed) and their 1774 matched controls (18 exposed) produced an odds ratio of 1.44 (95% confidence interval = 0.59–3.48) (adjusted for several covariates including human papillomavirus risk score). For ovarian cancer, based on 262 cases (3 exposed) and 755 controls (8 exposed) and adjusted for age and number of years of ovulation, the odds ratio was 1.26 (0.21–5.45). For uterine cancer, none of the cases—including 23 cases of leiomyosarcoma—was exposed to quinacrine. The 95% confidence interval, based on 161 cases (none exposed) and 470 controls (7 exposed) and adjusted only for age, was 0–1.85.

Conclusion: We found no evidence of a relationship between quinacrine sterilization and gynecologic cancer.

(*Epidemiology* 2010;21: 164–171)

Female sterilization is a popular family planning choice in many countries,[1] but the necessity of surgery limits its availability. A simple, low-cost nonsurgical sterilization procedure has the potential to make sterilization more widely available.

One option for nonsurgical sterilization involves the insertion of quinacrine pellets into the uterus, using a modified intrauterine device (IUD) inserter. The quinacrine pellets dissolve and lead to sclerosis and subsequent occlusion of the fallopian tubes. Each insertion delivers 7 36-mg pellets of quinacrine dihydrochloride dihydrate, for a total dose of 252 mg per insertion.[2] The most common dosage regimen is 2 insertions, 1 month apart.

Concerns about the potential carcinogenicity of quinacrine arose because quinacrine is mutagenic and because of a case report of a relatively rare uterine tumor (leiomyosarcoma) in a woman in Chile who had received quinacrine.[3,4] A follow-up study of a cancer cluster among women who had had quinacrine sterilization in Chile identified 5 cases of cancer: 2 cases of gallbladder cancer, 1 case of colon cancer, a brain cancer, and the initial case of leiomyosarcoma. The gallbladder cancers were judged to be part of a wider trend in Chile, where gallbladder cancer is unusually common (for unknown reasons).[5] The brain and colon cancers did not have a plausible connection with quinacrine, but some concern remained about the single provocative case of uterine leiomyosarcoma.[3] However, with further follow-up through 2007, no additional uterine corpus cancers have been identified, and the risk ratio for uterine cancers has decreased to 0.51 (95% confidence interval [CI] = 0.05–2.86) with 1 case observed compared with 2 expected.[6]

To respond to concerns about possible human carcinogenicity related to the intrauterine administration of quinacrine, Family Health International and the Ministry of Health of Vietnam conducted a 5-year case–control study of gynecologic cancers. This study was carried out in northern Vietnam among women living in the provinces in which quinacrine sterilization procedures had been most common.[7]

Quinacrine sterilization had been offered by the Vietnamese government as a pilot program in 2 provinces starting in 1989. By October 1992, 31,781 women in 24 provinces had received quinacrine sterilization.[7] The program was stopped in December 1993 amid controversy about potential health risks and the lack of adequate study of and regulatory approval for the intrauterine use of quinacrine.[8] It is estimated

Submitted 34 March 2009; accepted 7 July 2009.

From the [a]Family Health International, Durham, NC; [b]Research Center for Rural Population and Health, Hanoi, Vietnam; [c]Mahidol University, Bangkok, Thailand; [d]K Hospital, Hanoi, Vietnam; and [e]Ministry of Health of Vietnam, Hanoi, Vietnam.

Supported partially by Family Health International.

Correspondence: David C. Sokal, Family Health International, 2224 East NC Hwy 54, Durham, NC 27713. E-mail: Dsokal@fhi.org.

ISSN: 1044-3983/10/2102-0164
DOI: 10.1097/EDE.0b013e3181cb41c8

that since 1979, over 100,000 women in 13 countries have been sterilized using quinacrine,[9] with the greatest number being in Vietnam. Other studies in Vietnamese women treated with quinacrine have provided valuable data on non-cancer end points and contraceptive effectiveness,[10–15] but none was designed to evaluate cancer end points.

The primary objectives of this study were to assess whether quinacrine sterilization is associated with an altered risk of cervical cancer, ovarian cancer,[16] or nontrophoblastic uterine corpus cancer.

METHODS

We conducted a population-based case–control study of gynecologic cancers, with 3 controls, matched on age and residence, selected randomly for each case. Our sample size calculations were based on projections for the number of cancer cases we could identify in a 5-year study and an estimated quinacrine exposure among controls of 1.7%.

Study staff interviewed all study participants using the same questionnaire, which included questions about risk factors for gynecologic cancers and about quinacrine exposure.

Our goal was to identify all incident cases of gynecologic cancer over a period of 5 years among residents of 11 (later 12) study provinces (Ha Nam, Nam Dinh, Hai Duong, Hung Yen, Ninh Binh, Thai Binh, Ha Tay, Bac Ninh, Bac Giang, Vinh Phuc, and Phu Tho, and later Nghe An). We chose the provinces based on where the quinacrine sterilization program of 1989–1993 had been most active.[7]

Following a pilot study in 1999, we designed the protocol. The Ministry of Health of Vietnam reviewed and approved the study, and it was implemented by the Research Center for Rural Population and Health, Thai Binh Medical College, in collaboration with Family Health International. The institutional review board of Family Health International also approved the study protocol and the informed-consent procedures before study initiation, and reviewed the study annually.

We implemented the study in 2 phases. In April 2001, we began the study in 3 provincial hospitals and the 2 main referral hospitals in Hanoi: the National Cancer Institute (the K Hospital) and the Institute for the Protection of Mother and Newborn (the C Hospital). In September 2001, we expanded the study to the planned total of 17 hospitals in 11 provinces.

In November 2002, we assessed our study design assumptions regarding recruitment and quinacrine exposure among controls. Despite some evidence that the final study statistical power might be less than expected, we decided to continue the study and to add 10 hospitals in Hanoi to reduce the chance of missing eligible cases. Also, one inactive provincial hospital was replaced by a hospital in a 12th province. We completed case enrollment in May 2006 and finished most control interviews by August 2006.

Cases

We recruited cases at 15 provincial hospitals in the 12 study provinces and at 12 hospitals in Hanoi. Inclusion criteria were diagnosis of a new primary invasive cancer of the cervix, ovary, or uterus within 6 months before start of the study, or enrollment within 12 months after the diagnosis if the diagnosis occurred after the start of the study; born in 1947–1966 inclusive; residing in one of the study provinces; and mentally competent and willing to participate.

Case Identification

To identify suspected cancer cases, a study coordinator/interviewer worked with doctors at each participating hospital. Whenever a clinician saw a woman with a suspected gynecologic cancer, the clinician referred the woman to the study coordinator for informed consent and study enrollment procedures. All case participants had disease status confirmed by physical examination, ultrasound if needed, and cytology or histology when possible. All available histologic, cytologic, or other specimens were sent to the K Hospital pathology department for pathologic review and classification. These results were recorded on study data collection forms and also sent to the treating physicians.

Case Confirmation

A panel of 3 specialists (the Diagnosis Review Committee) met weekly to review all clinical and pathologic data from recently enrolled suspected cancer cases. Cases confirmed as cancer were classified according to the International Classification for Diseases-Oncology (ICD-O) coding system. If no specimen was available, the Diagnosis Review Committee determined whether the woman had cancer on the basis of available clinical, radiologic, and laboratory data. An outside consulting pathologist (M.R.) independently reviewed all available pathologic specimens.

An FHI study clinician (usually K.N.) reviewed the Diagnosis Review Committee diagnosis, the independent pathologist's conclusions, and the available clinical data and requested that the committee and the consulting pathologist conduct a joint review of inconsistencies. None of the pathologists or reviewers had information on the quinacrine exposure status of suspected cases.

Controls

For each index case, the interviewers randomly selected 3 control participants from the same hamlet and 5-year birth cohort (1947–1951, 1952–1956, 1957–1961, or 1962–1966), using population registers. Controls had to provide informed consent and be able to answer the questionnaire. We excluded controls from analysis if they had had a hysterectomy, and—if matched to ovarian cancer cases—if they had had an ovary removed.

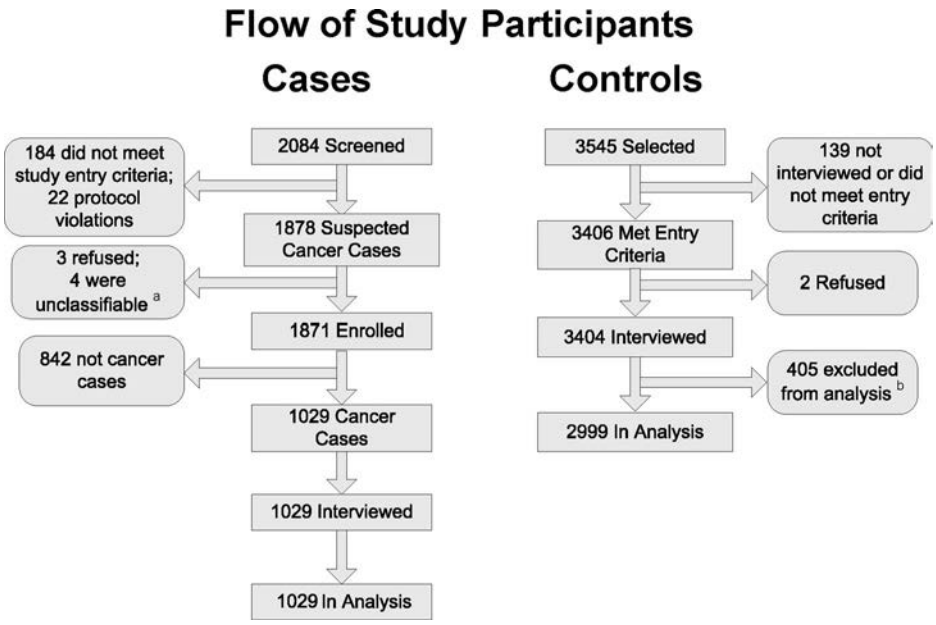


FIGURE. Flow of study participants. Footnote "a" indicates unable to classify due to lost pathology specimens; "b," controls were interviewed as soon as possible after suspected cases were identified. Most of these controls were excluded because they were matched to suspected cases that were later determined not to have cancer.

Interview

Data collection forms in Vietnamese were used to collect information on sociodemographic characteristics, tobacco use, medical history, parity, family planning, and other reproductive-related behaviors, including most established cancer risk factors of interest.[17] We did not assess the presence of human papillomavirus (HPV); we instead developed an HPV risk score based on reported HPV risk factors. We also calculated an ovulation index, ie, an estimate of the number of years of ovulation. The index is computed as the current age or age at menopause minus age of menarche. Time was subtracted for pregnancies, breastfeeding (up to 6 months per baby), and use of hormonal contraception.

Quality Assurance/Avoidance of Bias

Clinicians, pathologists, and analysts were blinded to quinacrine exposure data until the analysis plan was approved and data handling and analysis decisions were made. We conducted training sessions at study initiation and periodic refresher sessions, and a clinical monitor from Family Heath International conducted periodic site visits. The accuracy of data entry was verified on a sample of records.

To evaluate the reliability of questionnaire data, we reinterviewed all women who reported having used quinacrine, as well as a 5% sample of women (both cases and controls) who did not report quinacrine exposure. Among 303 women, we found 100% test/retest reliability on quinacrine exposure.

Statistical Methods

We used conditional logistic regression to estimate the association between quinacrine exposure and gynecologic cancer, stratifying on matched case–control sets. Because of the small number of discordant sets contributing to the analysis, exact methods were used for ovarian and uterine cancers (SAS [SAS Institute, Cary, NC] or LogXact 7.0 [Cytel Software Corporation, Cambridge, MA]). Exact conditional logistic regression was used to analyze ovarian cancer data and Monte Carlo estimation (100K iterations) of the exact estimate was used for the uterine cancer data. Simple regression models included only age (to control for any residual confounding within age cohort) and quinacrine exposure. Risk factors for the cancer site in question were regarded as potential confounders if adding the variable to the simple model changed the estimate of the quinacrine/cancer association by more than 10%. To adjust for the risk of cervical cancer due to potential exposure to HPV, we developed a risk score for HPV that assigned one point for each of the following: first sex at age 19 years or younger; more than one lifetime sexual partner; ever had STI or other genital infection; has had sex but never used condom; and has had sex but was never married. We defined the risk score and made other decisions on the modeling strategy and variable definitions before women's quinacrine exposure status was revealed.

Where possible, given data or computational limitations, we ran multivariable regression models that controlled for possible confounders. We computed odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS

Study Participants

We screened 2084 suspected cancer cases for enrollment into the study (Figure). Of these, many were benign fibroids or cases of cervical intraepithelial neoplasia. We enrolled 1029 invasive cancer cases who were confirmed by

the diagnostic review process. We identified 606 (59%) cervical cancers, 262 (25%) ovarian cancers, and 161 (16%) uterine corpus cancers, and histologic confirmation was available for most cases (99%, 87%, and 98%, respectively). The remaining cervical and uterine cases were confirmed based on cytology; 9% of ovarian cases were confirmed cytologically and 4% clinically only. Twenty three of the 161 cases of uterine cancers were leiomyosarcomas.

In study provinces participating for the full 5 years, the number of confirmed cases per province ranged from 45 to 142. The number of cases per 100,000 total population, based on the estimated 2003 female population of Vietnam by province, ranged from 10 to 14.

We randomly selected 3545 matched controls for interview (Figure). Two refused, 139 did not meet entry criteria, and 405 were excluded from the analysis, either because they had been matched to a suspected case who turned out not to have cancer or was otherwise ineligible (n = 307), or because they had had an ovariectomy or hysterectomy (n = 98). The final ratio of controls to cases was 2.9, close to the planned ratio of 3.0. No controls later became cases. One case was later chosen and interviewed as a control; she was excluded from the control group.

Participant Characteristics

Most participants worked as farmers and did not have secondary school education; almost all had been married (Table 1). Demographic characteristics of cases and controls were similar.

Quinacrine Sterilization Procedures

Few women reported exposure to quinacrine: 1.2% of cases (12 women) and 1.1% of controls (33 women). Among the 12 cases reporting quinacrine exposure, 9 women had cervical cancer, 3 had ovarian cancer, and none had uterine cancer (Table 2). Most women reported either 1 or 2 insertions of quinacrine (Table 2).

Association of Quinacrine Use With Gynecologic Cancers

Cervical Cancer

Nine of 606 cervical cancer cases (1.5%) and 18 of their 1774 matched controls (1.0%) were exposed to quinacrine (Table 3) (OR [controlling only for age] = 1.40 [95% CI = 0.61–3.22]). The variables that met our criterion as possible confounders were HPV risk score, douching, number of years husband/partner was in the south during the war with the United States, and ever-use of oral contraceptives. The final model, controlling for these confounders as well as age, produced a similar OR of 1.44 (0.59–3.48) (Table 3).

Ovarian Cancer

Three of 262 ovarian cancer cases (1.1%) and 8 of 755 matched controls (1.1%) were exposed to quinacrine, giving 11 discordant sets (Table 3) (OR [controlling for age] = 1.04 [0.18–4.36]). Because of data sparseness and computational limitations for exact testing, we could control for only one additional potential confounder; we chose ovulation index (number of years of ovulation) as the most clinically important risk factor. When we controlled for age and ovulation index, the OR was 1.26 (0.21–5.45).

Uterine Cancer

None of the 161 uterine cancer cases (0%), including the 23 women with leiomyosarcomas, was exposed to quinacrine, while 7 of their 470 controls (1.5%) were exposed, giving 7 discordant sets (Table 3). Because no cases were exposed, we used LogXact's Monte Carlo estimation procedure to approximate unbiased estimates and confidence intervals, adjusting only for age. The resulting 95% confidence interval was 0–1.85.

Other Quinacrine Exposure Tabulations

To explore possible biases, we examined quinacrine exposure data for the 834 suspected cases whose final diagnosis was not cancer (excluding 8 women with a non-study cancer or a benign condition at entry). Twenty women (2.4%) reported quinacrine exposure—twice the percent among confirmed cases. Exposure was most commonly reported among suspected cases of cervical cancer.

In considering 5-year birth cohorts combining cases and controls, quinacrine exposure was lowest for the youngest cohort, born in 1962–1966 (0.77%) and highest in the 1952–1956 cohort (1.47%). Exposure was 1.10% in the 1947–1951 cohort and 0.93% in the 1957–1961 cohort.

DISCUSSION

This study provides no evidence that the quinacrine previously used for female sterilization in Vietnam is associated with an increased risk of gynecologic cancer, although the confidence limits of our estimates are wide.

Strengths

Because the proportion of cases per 100,000 population was similar among the study provinces, we believe that case identification was reasonably complete. To maximize sensitivity, we asked screening clinicians to refer all patients with suspected gynecologic cancer. Thus many women were enrolled who turned out to have benign tumors or cervical intraepithelial neoplasia. Thus, true cases were unlikely to have been missed. We used a thorough and blinded pathology review process to confirm that cases were diagnosed correctly. We selected controls randomly from the village registers—a sampling frame that allowed population-based sampling. Virtually all identified study participants (both cases and controls) agreed to be in the study, minimizing nonresponse bias.

TABLE 1. Participant Characteristics by Case–Control Status

	Cervical Cancer		Ovarian Cancer		Uterine Cancer	
	Cases (n = 606)	Controls (n = 1774)	Cases (n = 262)	Controls (n = 755)	Cases (n = 161)	Controls (n = 470)
Age (years); median	48	48	48	48	52	52
Highest level of education less than secondary school; %	79.2	78.7	80.1	83.4	78.9	78.0
Has health insurance; %	28.9	28.0	34.0	24.4	39.8	32.3
Farmer; %	62.2	67.0	67.9	72.7	61.5	66.2
Cooking fuel used currently; %						
Hay or wood	55.8	57.2	59.9	62.2	57.2	60.6
Charcoal	25.7	26.8	25.2	24.1	24.2	23.2
Other nonmodern	0.3	0.7	0.4	0.4	0.6	0.6
Any use of modern method (gas or electric)	18.2	15.3	14.5	13.2	18.0	15.5
Ever married/lived with a man	99.2	96.5	88.9	96.2	88.7	95.9
Ever smoked 100 + cigarettes; %						
Woman	0.8	0.7	0.4	0.1	0.0	0.9
Husband/partner	68.3	56.1	54.2	60.5	49.7	51.5
Ever smoked water pipe 100 + times; %						
Woman	0.7	0.6	0.0	0.3	0.6	0.6
Husband	51.2	48.5	46.6	51.7	43.5	45.7
Ever chewed tobacco 100 + times; %	4.3	4.9	4.6	5.8	5.6	5.5
Spent time in the south during the war with the United States[a]						
Woman; %	2.5	2.3	0.4	2.1	3.7	4.9
Duration (years); median	3.0	3.0	7.0	3.0	3.5	4.0
Husband/partner; %	31.4	33.5	34.0	38.1	37.3	41.6
Duration (years); median	5.0	4.0	5.0	5.0	6.0	5.0
Body-mass index (kg/m^2)[b]; %						
<18.5	15.9	23.3	17.8	23.4	22.7	23.3
18.5–22.9	63.6	63.1	61.2	63.7	55.8	62.2
23.0–24.9	11.5	9.8	14.0	8.3	13.0	9.1
25.0+	9.0	3.8	7.0	4.6	8.4	5.3
Median	20.8	20.0	20.3	20.0	20.8	20.1
Age at first menses (years); median	16	16	16	16	16	16
Postmenopausal; %	28.6	35.8	38.5	33.8	53.1	55.5
Ever taken pills for menopause; %	0.0	0.3	0.0	0.8	1.2	1.5
Ever had sexual intercourse; %	100.0	96.7	99.3	96.3	88.8	96.0
2+ lifetime partners; %	10.0	3.7	5.6	4.5	6.3	3.1
Age at first sex (years); median	21	21	22	22	22	22
Ever been pregnant; %	98.3	95.5	87.0	94.8	83.2	95.1
No. deliveries[c]; %						
1–2	28.4	28.8	37.6	25.1	31.5	22.5
3–4	53.8	50.9	43.8	52.7	54.6	56.0
5+	17.8	20.3	18.6	22.3	13.8	21.6
Age at first pregnancy (years); median	22	23	24	23	24	23
Ever breastfed; %	97.0	94.4	84.4	93.5	78.3	93.8
No. infants breastfed; %						
1–2	31.6	31.6	39.8	27.3	34.1	24.3
3+	68.4	68.4	60.2	72.7	65.9	75.7
Ever used family planning method; %						
IUD	67.5	68.9	52.7	71.4	52.2	68.5
Oral contraceptives	8.7	6.4	5.0	5.8	4.3	5.5
Hormonal injection	0.8	0.8	0.0	0.5	0.6	0.6
Condom	16.7	12.5	13.0	11.1	10.6	10.9
Surgical sterilization	6.4	5.7	3.8	3.6	2.5	4.9
Quinacrine sterilization	1.5	1.0	1.1	1.1	0.0	1.5
Other[d]	31.2	31.2	24.0	24.5	23.0	23.4

(*Continued*)

TABLE 1. (*Continued*)

	Cervical Cancer		Ovarian Cancer		Uterine Cancer	
	Cases (n = 606)	**Controls (n = 1774)**	**Cases (n = 262)**	**Controls (n = 755)**	**Cases (n = 161)**	**Controls (n = 470)**
Ever douched; %	14.4	8.0	7.3	8.3	9.3	8.9
Ever had genital infection[e]; %	19.1	10.1	12.2	11.3	10.0	9.2
Socioeconomic status[f]; %						
0	1.2	0.6	0.8	1.3	2.5	2.1
1–2	50.9	55.9	56.4	61.5	55.3	54.4
3–4	30.7	26.9	27.2	24.6	19.9	26.3
5–6	17.2	16.5	15.7	12.6	22.3	17.2
HPV risk (possible range: 0–5)[g]; %						
0	9.8	11.0	19.3	10.6	17.8	11.7
1	49.0	58.7	46.7	58.8	55.4	60.5
2	31.8	26.5	29.3	25.4	23.6	24.6
3+	9.5	3.9	4.6	5.2	3.2	3.2
Ovulation index (years)[h]; median	25.6	25.3	26.4	25.0	29.4	26.5

[a]This is of interest because being in the south of Vietnam during the war with the United States could have led to dioxin exposure.
[b]Weight (kg)/height (m^2). Uses current weight unless weight of 1 year ago is higher; if so, weight of 1 year ago is used.
[c]Live births plus stillbirths.
[d]Includes withdrawal and rhythm method.
[e]Includes sexually transmitted infection (STI) or other genital infection.
[f]Points for woman's occupational status (1 point for not being a farmer), educational attainment (0–3 points; no. points increasing with education), modern cooking fuel (1 point for gas or electricity), and health insurance (1 point if has insurance).
[g]One point for each of the following: first sex at age 19 years or younger; more than 1 lifetime sexual partner, ever had STI or other genital infection; has had sex but never used condom; has had sex but was never married.
[h]Estimated no. years with menses. Current age or age at menopause, minus age at menarche, and then minus: duration of pregnancies, breast-feeding (up to 6 months per infant), and hormonal contraceptive.

TABLE 2. Details of Quinacrine Sterilization Procedures (Among Women Who Reported Having Received Quinacrine)

	Cervical Cancer		Ovarian Cancer		Uterine Cancer	
	Cases (n = 9)	**Controls (n = 18)**	**Cases (n = 3)**	**Controls (n = 8)**	**Cases (n = 0)**	**Controls (n = 7)**
No. insertions						
1	5	8	2	5		3
2	4	8	1	3		3
3–4	0	2	0	0		1
Time since quinacrine sterilization (years)						
Median (range)[a]	12.5 (9–14)	12.5 (10–17)	15 (15)	13 (9–15)		12 (9–13)

[a]Excludes women who said they did not know or who gave an impossible value: for cervical cancer, 3 cases and 2 controls; for ovarian cancer, 2 cases and 1 control; and for uterine cancer, 0 cases and 2 controls.

Limitations

A major limitation of the study is the small number and proportion of women who were exposed to quinacrine, limiting the precision of our results. The proportion of quinacrine-exposed women among the controls (1.1%) was less than the proportion we had expected when we planned the study (1.7%). Given the low proportion, the study had power to detect only large odds ratios, and so our results do not exclude the possibility of potentially important increases in risk. Even so, northern Vietnam has the largest number of women sterilized with quinacrine, providing one of the best opportunities to address this issue.

Another limitation of our study is that we did not know the HPV status of controls. While HPV is a necessary cause of cervical cancer,[17] there is uncertainty as to the value of a single cervical HPV DNA test as a measure of past exposure.[18] We expected that HPV prevalence among the controls would be low.[19] We think it is unlikely that receipt of quinacrine is associated with HPV infection, making it unlikely that unmeasured HPV is confounding our results. Our

TABLE 3. Tally of Exposure Status of Case–Control Sets and Association of Quinacrine Sterilization With Cervical, Ovarian, and Uterine Cancer

Exposure Status of Cases	No. Controls Exposed				Age-Adjusted OR (95% CI)	Multivariable-Adjusted OR (95% CI)
	3	2	1	0		
Cervical cancer (n = 606[a])						
Exposed	0	0	1	8	1.40 (0.61–3.22)	1.44 (0.59–3.48)
Not exposed	0	1	15	581		
Ovarian cancer (n = 262[a])						
Exposed	0	0	0	3	1.04 (0.18–4.36)	1.26 (0.21–5.45)
Not exposed	0	0	8	251		
Uterine cancer (n = 161[a])						
Exposed	0	0	0	0	0 (0–1.85)	—
Not exposed	0	0	7	154		

[a]No. matched case–control sets.

HPV risk score was associated with cervical cancer (OR = 1.43 [95% CI = 1.25–1.64]), supporting its validity as a means of controlling for possible confounding.

If quinacrine exposure increases cancer risk, its latency is unknown. The case of leiomyosarcoma in Chile was diagnosed 7 years after quinacrine sterilization,[3] which would be a relatively short latency period for human carcinogenesis. Our study recruited women who were approximately 8–17 years postexposure to quinacrine, which could also be considered a relatively short follow-up period.

We analyzed uterine corpus cancers as a single group, combining endometrial cancers and uterine sarcomas. This was not a major limitation, however, as no women with either type of uterine cancer reported having used quinacrine.

Interpretation and Generalizability

The uterine cavity receives most of the quinacrine that is inserted, resulting in endometrial necrosis. Since the identification of the Chilean case of uterine leiomyosarcoma (a relatively rare cancer), no further uterine corpus cancers have been observed in the Chile cohort.[6]

Our case–control study found results for cervical and ovarian cancers similar to those in the Chilean cohort study, but with wider confidence intervals. For cervical cancer, the risk ratio in the Chile data was 0.83 (95% CI = 0.39–1.52), with 10 cases observed compared with 12.1 expected; and for ovarian cancer, the risk ratio was 0.32 (0.03–1.81), with 1 case observed compared with 3.1 expected.[6]

Simultaneous with the conduct of this study, Family Heath International was working on preclinical studies of quinacrine required by the US Food and Drug Administration, including rodent carcinogenicity studies in mice and rats. The mouse study results were not suggestive of an increased risk of cancer,[20] but the rat study found an increased risk of a variety of genital tract tumors.[21] The quinacrine dosages in rats were higher than those given to women for tubal closure, so it is difficult to evaluate the relevance of the rat data to human risk.[22,23]

In conclusion, our results suggest that the case of uterine leiomyosarcoma observed in Chile was a chance occurrence and that the risk of uterine cancer—within the confidence limits given above—was not increased. While the possibility of an increased risk of cervical or ovarian cancer seems less plausible, the confidence limits in our results are wide. This case–control study provides no evidence to suggest that the doses of quinacrine used in Vietnam are associated with an increased risk of gynecologic cancers.

ACKNOWLEDGMENTS

The study could not have been conducted without the generous help of the Provincial Hospital Directors and their staff and other local officials, as well as the K Hospital, the C Hospital and other hospitals in Hanoi. In addition, the following people provided essential assistance to the study: the Diagnosis Review Committee of the K Hospital in Hanoi, Ngo Thu Thoa, Dinh The My, Tran Van Hop, and Dinh Xuan Tuu (deceased); and Robert Hanenberg, study manager for the initiation and first half of the study. Other FHI staff who assisted with the study were Lalitha Venkatasubramanian, Catherine Hart, Jaim-Jou Lai, Kate Honeycutt, Sarah Beddingfield, Haddie Kiernan, and Shacondra Brown.

REFERENCES

1. Population Reference Bureau. Contraceptive use among married women 15–49, female sterilization (%). Data comparisons by geography: select variable. Available at: http://www.prb.org/Datafinder/Topic/Rankings.aspx?sort=r&order=a&variable=87. Accessed November 20, 2008.
2. Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. *Int J Gynaecol Obstet*. 1995;51(suppl 1):S57–S69.
3. Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. *Fertil Steril*. 1995;64:325–334.
4. Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk

among women sterilized with transcervical quinacrine in Chile: an update through 1996. *Fertil Steril*. 2000;74:169–171.
5. Andia ME, Hsing AW, Andreotti G, Ferreccio C. Geographic variation of gallbladder cancer mortality and risk factors in Chile: a population-based ecologic study. *Int J Cancer*. 2008;123:1411–1416.
6. Sokal DC, Trujillo V, Guzmán SC, Guzman-Serani R, Wheeless A, Hubacher D. Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort. *Contraception*. 2010;81:75–78. Epub.
7. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet*. 1993;342:213–217.
8. Death of a study: WHO, what, and why. *Lancet*. 1994;343:987–988.
9. Kessel E. 100,000 quinacrine sterilizations. *Adv Contracept*. 1996;12:69–76.
10. Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. *Fertil Steril*. 2000;74:1084–1091.
11. Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. *Fertil Steril*. 2000;74:1092–1101.
12. Sokal DC, Hieu DT, Loan ND, et al. Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam. *Contraception*. 2008;78:66–72.
13. Sokal DC, Hieu DT, Loan ND, et al. Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam. *Contraception*. 2008;78:61–65.
14. Hieu DT, Luong TT. The rate of ectopic pregnancy for 24,589 quinacrine sterilization (QS) users compared to users of other methods and no method in 4 provinces in Vietnam, 1994–1996. *Int J Gynaecol Obstet*. 2003;83(suppl 2):S35–S43.
15. Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong LQ. The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases. *Int J Gynaecol Obstet*. 2003;83(suppl 2):S77–S85.
16. Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. *Am J Epidemiol*. 2007;166:894–901.
17. Schottenfeld D, Fraumeni JF. Cancer Epidemiology and Prevention. 3rd ed. New York: Oxford University Press; 2006.
18. Banura C, Franceschi S, van Doorn LJ, et al. Prevalence, incidence and clearance of human papillomavirus infection among young primiparous pregnant women in Kampala, Uganda. *Int J Cancer*. 2008;123:2180–2187.
19. Pham TH, Nguyen TH, Herrero R, et al. Human papillomavirus infection among women in South and North Vietnam. *Int J Cancer*. 2003;104:213–220.
20. Cancel AM, Smith T, Rehkemper U, Dillberger JE, Sokal D, McClain RM. A one-year neonatal mouse carcinogenesis study of quinacrine dihydrochloride. *Int J Toxicol*. 2006;25:109–118.
21. Cancel AM, Dillberger JE, Kelly CM, Bolte HF, Creasy DM, Sokal DC. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. *Regul Toxicol Pharmacol*. 2009 Jul [Epub ahead of print].
22. Sokal D, Haneke K, Robinson E, Katz K, Dorflinger L. FHI's Decision to halt development of quinacrine: why and how. *Contraception*. 2007;76:173–174.
23. McConnell EE, Lippes J, Growe RG, Fail P, Luster MI, Zeiger E. An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats." *Regul Toxicol Pharmacol*. 2010 Jan 4 [Epub ahead of print].

ELSEVIER

Contraception 81 (2010) 75 – 78

Contraception

Original research article

Cancer risk after sterilization with transcervical quinacrine: updated findings from a Chilean cohort☆

David C. Sokal[a,*], Valentin Trujillo[b], Sergio C. Guzmán[c], Rene Guzman-Serani[c], Angie Wheeless[a], David Hubacher[a]

[a]*Family Health International, Durham, NC 27709, USA*
[b]*San Jose Hospital, 8380000 Santiago, Chile*
[c]*Escuela de Medicina, Universidad Austral de Chile, 5090000 Valdivia, Chile*

Received 3 June 2009; revised 14 July 2009; accepted 14 July 2009

Abstract

Background: Dating back to the 1970s, thousands of women worldwide have voluntarily been sterilized with transcervical insertion of quinacrine pellets. The safety and efficacy of the technology are still being assessed today; in particular, better estimates on the incidence of human cancers are now feasible.
Methods: We conducted a cohort study of 1492 women in Santiago and Valdivia, Chile, who received transcervical quinacrine pellets for contraceptive sterilization between l977 and l989. We periodically interviewed women with the last interviews in 2006–2007 and reviewed their medical records. We calculated age and site-specific incidence of invasive cancers and compared the observed cases to the number of expected cases based on data from the Cali, Colombia, cancer registry, gathered by the International Agency for Research on Cancer.
Results: During 23,894 person-years of follow-up, 41 invasive cancers were identified, including 16 new cases that had occurred since the previous analysis. Ten cases of cervical cancer were observed, compared with 12.1 expected. Since the initial study's confirmation of a single case of leiomyosarcoma, no other uterine cancers have been diagnosed. We would expect 2.0 uterine cancers during this number of observed women-years. One case of ovarian cancer was diagnosed, compared with 3.1 expected.
Conclusion: Rates of cancer among women exposed to intrauterine quinacrine are similar to population-based rates.

Keywords: Quinacrine non-surgical sterilization; Safety; Cancer; Cohort study

1. Introduction

Quinacrine was first used for non-surgical female sterilization by Zipper in Chile, and various formulations and doses have been tested [1]. The most commonly used regimen is seven 36-mg pellets of quinacrine hydrochloride introduced into the endometrial cavity by a modified intrauterine device inserter at two separate insertions one month apart (504 mg total) [2]. Although over 100,000 women around the world have received intrauterine quinacrine as a method of permanent contraception [3], this agent has not been specifically approved for non-surgical female sterilization by any regulatory authority. If long-term safety issues could be addressed, quinacrine could potentially provide a safe, low-cost method for permanent contraception in low-resource settings. During World War II, quinacrine was widely used as an oral anti-malarial agent.

One concern about the use of quinacrine for sterilization has been its long-term safety, including the potential risk of cancer, since quinacrine is mutagenic [4]. Because of a confirmed case of uterine leiomyosarcoma in 1986 in a Chilean woman who had received quinacrine [5], we conducted a retrospective cohort study of quinacrine users to evaluate the risk of cancer [5] and then continued following the cohort prospectively [6]. In this report, we

☆ **Funding:** This study was supported in part by Family Health International (FHI), with funds from an anonymous donor.

* Corresponding author. Family Health International, PO Box 13950, Research Triangle Park, NC 27709, USA. Tel.: +1 919 544 7040x11232; fax: +1 919 544 7261.
E-mail address: dsokal@fhi.org (D.C. Sokal).

0010-7824/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2009.07.006

present further follow-up of the cohort of Chilean women updating the cohort analysis with data gathered from 1997 through 2007. The primary objective of this analysis is to use the additional years of follow-up to expand the previous estimates of observed cases versus expected cancer cases.

2. Materials and methods

In 1990, we used clinic records from sites in Santiago and Valdivia to identify 1492 Chilean women who underwent voluntary transcervical quinacrine sterilization between 1977 and 1989. In 1991–1992, we attempted to contact and interview as many of these women as possible, and we repeated the process in four additional interview rounds over a 16-year period: in 1994–1996, 1999–2001, 2003–2005 and 2006–2007. Findings through the 1996 interviews have been published [5–7]. The current report updates the findings based on subsequent rounds of interviews.

In each round of data collection, we attempted to contact and interview all women in the cohort, reviewed hospital records for all cancer cases and requested slides of the gynecological cancers for review by an independent pathologist in the US. All research efforts were approved by Family Health International's institutional review board.

To determine whether women exposed to quinacrine experienced a typical incidence of cancer, we compared the incidence of gynecologic cancers from our cohort to that expected in an age-standardized general female population. We used the published rates of age- and period-specific gynecologic cancers reported in the cancer registry of Cali, Colombia [8,9], for comparative purposes, and estimated the expected numbers of cancers given our cohort's age structure, year the cancer was detected and person-years of follow-up. The Cali cancer registry contains rates for different periods of time; the latest periods that we incorporated into this analysis were 1992–1996 and 1998–2002, from Volumes VIII and IX, respectively, of the data maintained by the International Agency for Research on Cancer (IARC) [8,9].

We focused on female cancers: breast, cervix, ovary and uterus. However, we also included a category labeled "all cancers combined except skin." To estimate the expected number of cancer cases, we used the rates from the Cali registry and multiplied those by the number of person-years of observation for women in the 5-year age groups. We calculated person-years of observation by summing the number of years between the sterilization procedure and the last interview, if no cancer diagnosis was made. For women with a cancer diagnosis, person-year accumulation ceased at the time of diagnosis. To provide additional information on the cancer cases, we used dates to calculate age at diagnosis and years between quinacrine insertion and cancer.

Because of the latency between exposure and cancer diagnoses, we did additional calculations by reducing person-time in the denominator (by 5 years for each participant) and by ignoring any cancer cases that occurred in the first 5 years. Because (a) high dose exposures to mutagenic agents have been associated with relatively short latency periods for various cancers, e.g., leukemia [10] and soft-tissue sarcomas [11], and (b) the local exposure of uterine tissue is at high, cytotoxic concentrations, we present the data including all the follow-up time as the primary results.

We estimated expected numbers of cases for each period of time that corresponded to the published rates from the Cali registry (1977–1981, 1982–1986, 1987–1991, 1992–1996 and 1998–2002) and summed the estimates. For person-years after 2002, we used the latest available rates, i.e., 1998–2002. Then, we calculated ratios with 95% confidence limits of the observed number of cases to the expected number of cases.

3. Results

Since the last report [6], we increased the overall number of women contacted and interviewed at least once. At the Santiago site, follow-up data were available for 1147 of the 1341 women (86.0%), and at the Valdivia site, 144 of 151 women (95.4%) provided follow-up data. However, loss to follow-up has increased over time, and in the last round of interviews, 2006–2007, we were unable to contact 25 women (16.6%) in Valdivia and 811 women (60.5%) in Santiago. The total follow-up time for the cohort was 23,894 person-years. The median age (and age quartiles) of the cohort was 51 (46–57) years. The median length of follow-up (and quartiles) of the cohort was 18.5 (14.3–22.9) years.

Since the last report, we found 16 additional cases of cancer, including seven cases of breast cancer and two cases of cervical cancer. Including the previously identified cases, the present analysis was based on 41 total cancer cases: 13 breast, 10 cervix, 1 ovary, 1 uterine and 16 other cases at various sites (Table 1). An independent pathologist reviewed one additional case of cervical cancer, but slides were not available for independent review of the second case of cervical cancer.

Table 1
Observed and expected cancer diagnoses for breast, cervical, uterine and ovarian cancers, quinacrine cohort 1977–2007

Site	Observed	Expected[a]	Ratio[b]	95% confidence interval for ratio
All	41	59.7	0.69	0.49–0.93
Breast	13	17.0	0.76	0.41–1.31
Cervix	10	12.1	0.83	0.39–1.52
Ovary	1	3.1	0.32	0.03–1.81
Uterus	1	2.0	0.51	0.05–2.86

[a] Expected numbers were calculated from age- and gender-specific incidence rates from the Cali, Columbia, cancer registry. Volumes V through IX were used for person-years contributed for the different time periods. See Material and methods for more details.

[b] Observed number of cases: expected number of cases.

Table 2
Information on breast and cervical cancer cases

Type of cancer	Cases	Median time (range) between sterilization and diagnosis, in years	Median age at diagnosis (range), in years
Breast	13	16.1 (2.1–28.5)	51 (40, 59)
Cervix	10	9.0 (1.8–21.6)	43.5 (35–50)

For all cancers combined, the number of observed cases in the quinacrine cohort was significantly lower than the number of expected cases from a general population (Table 1). For individual cancers, the number of observed cases in the quinacrine cohort was lower than the expected number; however, the estimated ratios and confidence limits showed that these differences were not statistically significant.

For the 13 cases of breast cancer, the median age at diagnosis was 51 years and the median number of years between quinacrine exposure and diagnosis was 16 years (Table 2). For the 10 cases of cervical cancer, the median age at diagnosis was 43 years, and median number of years since quinacrine exposure was 9.

Excluding data from the first 5 years of follow-up, the number of person-years decreased to 17,022 person-years, and nine cancers were eliminated, including three breast cancers, two cervical cancers and the sole ovarian cancer. In terms of the observed-expected ratios and 95% confidence limits, the estimates are similar to those reported in Table 1: 0.62 (0.42–0.87) for all cancers, 0.67 (0.31–1.23) for breast cancer, 0.83 (0.35–1.64) for cervical cancer, 0 (0.0–1.09) for ovarian cancer, and 0.56 (0.06–3.13) for uterine cancer.

4. Discussion

This analysis of the risk of cancer in a cohort of Chilean women who received quinacrine between 1977 and 1989, with follow-up through 2007, does not provide evidence of an overall increased risk of cancer or an increased risk of reproductive tract cancers. No additional cases of uterine leiomyosarcoma have been diagnosed, and other gynecologic cancers are within the range of expected numbers, suggesting that quinacrine does not increase the risk of developing gynecologic cancers.

The strengths of this study include the long period of follow-up, excellent medical records and independent pathologist review of gynecologic cancer cases. Limitations include high loss to follow-up at one site over the 20–30 years since quinacrine insertion. While a high percentage of women have been interviewed at least once, loss to follow-up has increased in recent years, especially in Santiago. Loss to follow-up was higher in Santiago compared to Valdivia, probably because Santiago is a large urban area with high mobility, while Valdivia is a relatively small rural area with a less mobile population. It is important to note that loss to follow-up can affect both numerator (undercounting of cancer cases) and denominator (undercounting of person-years of follow-up for both cases and non-cases); the combined impact of loss to follow-up is unknown. The loss to follow-up rate in our study, however, is similar to that of the Center for Disease Control cohort study on sterilization, where researchers were only able to interview 57.7% of women after 14 years of follow-up [12]. Another limitation is the relatively small number of women in this cohort, which makes it difficult to rule out an increased risk of a rare event, such as uterine sarcoma.

Another possible limitation was the use of the cancer registry rates from Cali, Colombia, because there was no well-established cancer registry in Chile when this study began. As we mentioned in our first report, the Cali registry was chosen initially because it had mid-level cancer rates among the Latin American registries. However, since our last analysis, an IARC cancer registry was established in Valdivia, Chile, and IARC has reported their data for the period 1998–2002. Using the Valdivia rates, we repeated our approach and calculated expected numbers of cancers. Limiting our analysis to the 1998–2007 period, we found that the expected number of breast cancers was lower using Valdivia rates compared to Cali (6.9 versus 10.0), but expected numbers for gynecologic cancers were similar. For the three gynecologic cancers, expected numbers, based on Valdivia and Cali rates, respectively, were: for cervical cancer, 4.3 and 5.3; for ovarian cancer, 1.9 and 1.8 and for uterine cancer, 1.2 and 1.3.

However, for the analysis reported in Table 1, we made an a priori decision not to use the Valdivia rates for the full period because they could be unstable due to the small number of cases on which the rates are based. For example, the rates from the Valdivia registry for the cancers of interest during 1998–2002 are based on a total of 351 cases of cervical, uterine and ovarian cancers [13], while the rates from the Cali registry are based on 2028 cancers for the same sites during the same time period [8].

A case-control study of gynecologic cancers in Northern Vietnam looked at a larger population of women in an area where quinacrine had been used and did not find evidence for an increased risk of gynecologic cancer due to quinacrine exposure [14]. That study included over 20 cases of leiomyosarcoma all of which occurred in women without exposure to quinacrine, suggesting that the single case that occurred in Chile in a quinacrine user was a chance occurrence. The lack of any cases of endometrial carcinoma in both this cohort and among quinacrine-exposed women in the Vietnam study is intriguing, but the confidence limits are too wide to draw any conclusions about a possible protective effect [15]. With respect to the potential protective effect of tubal occlusion on ovarian cancer [16], this study found fewer than expected ovarian cancers, but the Vietnam case-control study did not find a reduced risk of ovarian cancer [14].

In conclusion, after incorporating 10 additional years of follow-up data into this cohort study, we found no evidence of an increased risk of gynecologic cancers in this Chilean cohort.

Acknowledgments

FHI is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, STDs and AIDS. Views expressed in this report are those of the authors and do not necessarily reflect those of FHI. The authors thank Melissa Hays for assistance with data analysis; Vera Halpern, M.D., for assistance with medical coding; Vivian Bragg and Belinda Irsula for study monitoring and Dr. Jaime Zipper for his mentoring and guidance.

References

[1] Zipper J, Trujillo V. 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases. Int J Gynaecol Obstet 2003;83(Suppl 2): S23–9.
[2] Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. Int J Gynaecol Obstet 1995;51(Suppl 1):S57–69.
[3] Kessel E. 100,000 quinacrine sterilizations. Adv Contracept 1996;12: 69–76.
[4] Clarke JJ, Sokal DC, Cancel AM, et al. Re-evaluation of the mutagenic potential of quinacrine dihydrochloride dihydrate. Mutat Res 2001; 494:41–53.
[5] Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril 1995;64:325–34.
[6] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril 2000;74:169–71.
[7] Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 2000;61:379–84.
[8] Bravo LE, Carrascal E, Collazos T, et al. Cancer incidence in Cali Colombia 1998-2002. In: Curado MP, Edwards B, Shin HR, et al, editors. Cancer incidence in five continents. IARC Scientific Publications No. 160Lyon: IARC; 2007. http://www-dep.iarc.fr/. On-line database accessed on January 23, 2008.
[9] Parkin DM, Whelan SL, Ferlay J, Storm H. Cancer incidence in five continents, vol. I to VIII. IARC CancerBase No. 7. Lyon: IARC; 2005. http://www-dep.iarc.fr/. On-line database accessed on January 23, 2008.
[10] Smith PG, Doll R. Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays. Br Med J (Clin Res Ed) 1982;284:449–60.
[11] Pendlebury SC, Bilous M, Langlands AO. Sarcomas following radiation therapy for breast cancer: a report of three cases and a review of the literature. Int J Radiat Oncol Biol Phys 1995;31:405–10.
[12] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol 1996;174: 1161–8 [discussion 1168-70].
[13] Bertrán ME, Mora KE, Jofré AM. Cancer incidence in Valdivia, Chile, 1998-2002. In: Curado MP, Edwards B, Shin HR, et al, editors. Cancer incidence in five continents. IARC Scientific Publications No. 160Lyon: IARC; 2007. http://www-dep.iarc.fr/. Accessed on January 23, 2008.
[14] Sokal DC, Vach TH, Nanda K, et al. Quinacrine sterilization and gynecologic cancers: a case-control study in Northern Vietnam. Epidemiology [in press].
[15] Dabancens A, Pruyas M, Zipper J, Rivera M, Velasco V. Intrauterine quinacrine and risk of endometrial cancer. Ginecol Reprod 1998;6: 21–6.
[16] Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. Am J Epidemiol 2007;166: 894–901.

Quinacrine sterilization for human immunodeficiency virus–positive women

Déborah Randazzo Barbosa de Magalhães, Ph.D.,[a] *Cláudia Ramos de Carvalho Ferreira, M.D., Ph.D.,*[a] *Estefânia Barbosa Magalhães, M.D.,*[a] *Aroldo Fernando Camargos, Ph.D.,*[a] *Jack Lippes, M.D.,*[b] *and Diana Carvalho Ferreira, M.D.*[a]

[a] School of Medicine, Department of Obstetrics and Gynecology, Federal University of Minas Gerais, Belo Horizonte, Brazil; and [b] School of Medicine, State University of New York at Buffalo, Buffalo, New York

Objective: To evaluate the safety of nonsurgical quinacrine sterilization for HIV-positive (HIV+) women.
Design: An open trial of quinacrine sterilization was carried out in women infected with HIV and women who were HIV negative (HIV−). Comparison of the results with the two groups provided an assessment of the safety and effectiveness of quinacrine sterilization for HIV+ women.
Setting: University Medical School outpatient services.
Patient(s): A total of 258 women who desired sterilization were offered quinacrine sterilization as a means of limiting family size. Sixty-four were HIV+, and 194 were HIV−. Women who were HIV+ had CD4 counts >200 and were otherwise healthy.
Intervention(s): A modified Copper T intrauterine device inserter was used to place 252 mg of quinacrine, divided into seven pellets (36 mg each) into the uterine cavity. Three insertions of this formulation were performed, 1 month apart. Viral load and CD8 and CD4 lymphocytes were measured both before and after quinacrine sterilization and at follow-up visits. Pregnancies and adverse events were recorded carefully. A decrement life table was made to statistically analyze results.
Result(s) and Main Outcome Measure(s): No serious adverse event occurred in any patient in this study. Adverse effects related to quinacrine sterilization were abdominal cramping, vulvar itching, nausea, and vaginal bleeding. Vaginal bleeding was the only short-term side effect noted to occur more frequently in HIV-infected women after quinacrine sterilization. Among HIV+ women, 35.9% had complaints of increased bleeding, whereas only 8.2% of those who were HIV− had such complaints, which probably were insertion related. Viral load and the CD4+ and CD8+ lymphocyte measures displayed no statistically significant difference after quinacrine sterilization.
Conclusion(s): Quinacrine sterilization is a safe method for the sterilization of HIV-infected women and has no short-term effect on the pathology of the disease. (Fertil Steril® 2009;92:108–15. ©2009 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, QS, HIV, CD4+, CD8+, lymphocytes, viral load, ART

An increase in the world population of HIV-positive (HIV+) women in the reproductive age (between 15–49 years of age) to 18 million was reported in 2006 (1). Life expectancy for such women has improved because of the advances in antiretroviral therapy. Women infected with HIV are exposed to the same chance of becoming pregnant as those who are HIV negative (HIV−). Obviously, there is a need to educate all women and men about contraception (2). In spite of the increasing epidemic of AIDS, there is no consensus about the best method to control reproduction for HIV-infected women (2).

Received March 21, 2008; revised August 7, 2008; accepted August 11, 2008; published online October 29, 2008.
D.R.B.d.M. has nothing to disclose. C.R.d.C.F. has nothing to disclose. E.B.M. has nothing to disclose. A.F.C. has nothing to disclose. J.L. has nothing to disclose. D.C.F. has nothing to disclose.
Reprint requests: Jack Lippes, M.D., SUNY at Buffalo, 31 Hampton Hill Drive, Buffalo, NY 14221 (FAX: 716-633-5664; E-mail: jlip@buffalo.edu).

Quinacrine nonsurgical sterilization was introduced by Zipper et al. (1970) (3). Subsequent research sought the best dose, the optimum number of quinacrine applications, and possible adjuvants to enhance efficacy (4–8). Today, quinacrine when used for sterilization is given in the form of slow-releasing pellets to avoid rapid absorption of the drug (9). Since the 1970s, experiments have been conducted to evaluate the efficacy and safety of quinacrine sterilization in >175,000 women of unknown serologic findings (10–14). Extensive literature has been published on the simultaneous use of aminoacridines and antiretroviral drugs in HIV-infected women in malaria-endemic areas, during pregnancy and breastfeeding periods, without any evidence of negative drug antagonisms (15–21).

This investigation addresses pursuant questions: Does quinacrine affect HIV pathophysiology? Conversely, does HIV alter the pharmacology of quinacrine, especially its effect in

0015-0282/09/$36.00
doi:10.1016/j.fertnstert.2008.08.066

scarring the oviduct? Furthermore, will antiviral drug therapy enhance or inhibit quinacrine sterilization? Are adverse events of quinacrine sterilization different in HIV+ women, both those given and those not given antiretroviral therapy?

MATERIALS AND METHODS

This open clinical trial was carried out from February 2005 to August 2006 at the Family Planning Clinic, School of Medicine of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. The research design, protocol, and informed consent were approved by the UFMG Ethics and Research Committee (the Brazilian equivalent of a US institutional review board). The women who volunteered to participate in this research freely signed the informed consent. Quinacrine pellets (Sipharm, Sisseln, Switzerland), already sterilized and packed in modified Copper T intrauterine device inserters, were used in this trial. Each inserter held seven 36-mg quinacrine pellets, a total of 252 mg for each of the three monthly insertions. Two hundred fifty-eight women were involved, of whom 194 were HIV− and 64 were HIV+. The HIV+ women were further divided into two subgroups: 42 patients who received antiretroviral therapy and 22 who did not. All subjects were sexually active. Each requested definitive contraception or sterilization. Their demographic characteristics are shown in Table 1. The women were advised to use an alternative contraceptive method after their first quinacrine insertion and for as long as 12 weeks afterwards, allowing time for subsequent inflammation and cicatrization of the lumens of the fallopian tubes. Women infected with HIV were included only if CD4 lymphocyte counts were >200 cells/mm^3 and without opportunistic infection. As required by the School of Medicine of the UFMG, women younger than 25 years or mothers with fewer than two living children were excluded. However, exceptions were made when there was a formal recommendation for sterilization from other clinics. Further exclusion criteria were pregnancy, being <60 days post partum, uterine bleeding, alcoholism, use of primaquine, being a carrier of psoriasis or porphyria, glucose-6-phosphate dehydrogenase deficiency, pelvic tumors, and pelvic inflammatory disease.

Seven quinacrine pellets, 36 mg each for a total of 252 mg, were inserted transcervically, high into the uterine cavity during the follicular phase of the menstrual cycle under aseptic conditions as described by Hieu et al. (22). After the procedure, the participants rested in a supine position for 1 hour. Quinacrine insertions were performed three times about 4 weeks apart. Six women received a fourth insertion because of bleeding that occurred immediately after or during quinacrine sterilization. Three of these women were HIV−, and three were HIV+. Another woman had an arcuate uterus found by ultrasound examination and had two simultaneous quinacrine insertions of 252 mg inserted into each uterine cornu for a total dose of 504 mg (Fig. 1).

Follow-up visits were scheduled for 1, 3, 6, and 12 months after the last quinacrine sterilization insertion. Short-term adverse effects (AEs) were considered those events that occurred during the procedure or 1 hour after insertion or that were obtained by history during the follow-up 1-month visit. Transvaginal ultrasonography searched for echogenic spots (scars) in the oviducts during the second visit after quinacrine sterilization.

The biologic monitoring by viral load and CD4+ and CD8+ lymphocyte counting was done before quinacrine sterilization and 4 to 6 months after the last quinacrine sterilization procedure. Blood for these tests was always drawn in the morning, with use of the MultiSET program at laboratories supervised by the Sistema de Controle de Laboratórios (Laboratory Test Control System), Belo Horizonte, Brazil. The viral load was determined with use of the branched DNA HIV-1–RNA method (version 3.0 VERSANT; Bayer S.A., São Paulo, Brazil), with detection sensitivity of 50 copies per milliliter (1.69 log) and maximum detection limit of 500,000 copies per milliliter (5.699 log). The T-CD4+ and -CD8+ lymphocytes were quantified by flow cytometry. Differences between two consecutive results of viral load >0.5 log or >70% of the absolute value of the number of copies per milliliter were considered significant (real differences). With CD4+ and CD8+ counting, variations >25% of the absolute value were considered significant (real differences). The sampling calculation was based on the type I α error of 5% and type II β error of 90%. Statistical calculations were done by Minitab (version 14.0; Minitab, State College, PA) and SPSS programs (version 12.0; SPSS, Inc., Chicago, IL). The χ^2 test was used to detect meaningful differences in qualitative variables inside the same group (homogeneity test, users or nonusers antiretroviral therapy). The Student's *t*-test was used to compare the groups according to quantitative variable means. The comparison of AEs was defined for significance by using the *z* test. Statistical evaluation for the presence of oviductal scars between groups that were HIV+ and HIV−, as well as the subgroups of HIV+, that is, those receiving antiretroviral therapy and those not receiving antiretroviral therapy, was calculated with the *z* test for proportions. The 95% confidence interval (CI) was applied, and the acceptably significant level for the hypothesis was $P<.05$.

RESULTS

The frequency of short-term AEs is presented in Table 2. Adverse events were abdominal cramping, nausea, yellow discharge, vulvar itching, and uterine bleeding. All women reported yellow vaginal discharge lasting from 3 to 20 days. In women who had four quinacrine insertions, AEs were similar to those in women who had three insertions. These AEs were managed easily as follows. Patients complaining of cramps were prescribed acetaminophen, which was taken only when needed. The yellow discharge was prevented or diminished by patients who douched with water for 1 or 2 days after quinacrine sterilization. Patients who douched also avoided vulvar itching. Uterine bleeding was the only AE with a higher frequency rate (23 [35.9%] vs. 16 [8.2%], $P<.001$) in HIV-infected women (Table 2).

TABLE 1

Demographic data of the women who chose to be sterilized by means of quinacrine sterilization.

	Negative HIV							Positive HIV							
Variables	No.	%	Average	Median	SD	Min	Max	No.	%	Average	Median	SD	Min	Max	*P*
Age (y)	194	—	34.6	34	5.15	20	46	64	—	32.3	33	4.93	21	43	.001[a]
Years of education	185	—	6.55	8.0	2.48	0	15	64	—	6.75	7.5	2.03	1	11	.554[a]
Hysterometry (cm)	194	—	7.94	8.0	0.67	6.5	10.5	64	—	8.11	8	0.74	6.5	10	.079[a]
White race	44	32.1	—	—	—	—	—	12	18.8	—	—	—	—	—	.034[b]
Black race	55	38.7	—	—	—	—	—	30	46.9	—	—	—	—	—	.275[b]
Other race	40	29.2	—	—	—	—	—	22	34.4	—	—	—	—	—	.466[b]
Married	167	86.1	—	—	—	—	—	35	54.7	—	—	—	—	—	<.001[b]
Single	26	13.4	—	—	—	—	—	23	35.9	—	—	—	—	—	<.001[b]
Widow	1	0.5	—	—	—	—	—	6	9.4	—	—	—	—	—	<.001[b]
Pregnancy															
0–3	130	67.0	—	—	—	—	—	44	68.8	—	—	—	—	—	<.001[b]
4–7	59	30.4	—	—	—	—	—	19	29.6	—	—	—	—	—	<.001[b]
8–10	5	2.6	—	—	—	—	—	1	1.6	—	—	—	—	—	<.001[b]
Antiretroviral therapy users	—	—	—	—	—	—	—	42	65.6	—	—	—	—	—	<.001[c]
Antiretroviral therapy nonusers	—	—	—	—	—	—	—	22	34.4	—	—	—	—	—	—
Antiretroviral therapy after quinacrine sterilization	—	—	—	—	—	—	—	2	9.1	—	—	—	—	—	—

Note: Min = minimum; Max = maximum.

[a] *P* value, *t*-test.

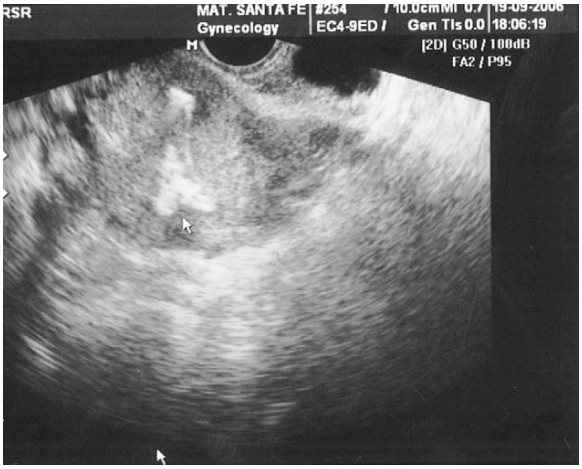
[b] *P* value, *z* test.

[c] *P* value, χ^2 test.

de Magalhães. Quinacrine sterilization for HIV-positive women. Fertil Steril 2009.

FIGURE 1

Arcuate uterus found by ultrasound examination; two simultaneous quinacrine insertions of 252 mg were placed into each uterine cornu for a total dose of 504 mg.



de Magalhães. Quinacrine sterilization for HIV-positive women. Fertil Steril 2009.

Increased bleeding was minimal, and the flow was less than menses and lasted up to 72 hours. There was no difference between those receiving and those not receiving antiretroviral therapy in regard to bleeding (16 [38.1%] vs. 5 [25.0%], P=.285). Generally, bleeding lasted a maximum of 72 hours. Abdominal cramping was the only short-term AE significantly more frequent among those who received antiretroviral therapy (13 [31.0%] vs. 1 [5.0%], P=.025) (Table 2). Five outlier results of the viral load were excluded from the calculations. The variations of viral load were <0.5 log or <70% of the absolute value of the number of copies per milliliter (42 [71.2%], P=.001). The CD4+ variations <25% of the observed value were significantly greater than real variation (41 [64.1%] vs. 23 [36.0%], P=.024) (Table 3). The variations of CD8+ counts were not significant (39 [61.9%] vs. 24 [38.1%], P=.059) (Table 3).

No significant difference occurred in the percentage of altered examinations and nonaltered examinations of viral load and CD8+ in both tails (viral load: antiretroviral therapy 11 [27.5%] vs. non-antiretroviral therapy 4 [23.5%], P=1.000, z test); (CD8+: antiretroviral therapy 13 [31.7%] vs. non-antiretroviral therapy 10 [50%], P=.170, z test). CD4+ counts altered were significantly greater in patients given antiretroviral therapy than in those who were not given antiretroviral therapy (18 [52.9%] vs. 3 [15.0%], P=.004, z test).

There was no significant difference in the occurrence of sonographically visualized oviductal scars between HIV+ and HIV− patients (52 [81.3%] vs. 138 [71.1%], P=.881, z test). Furthermore, in the HIV+ subgroup, there was no significant difference in fallopian tube scarring between antiretroviral therapy users and nonusers (32 [76.2%] vs. 20 [90.9%], P=.193, z test]. No sudden illnesses followed any quinacrine sterilization procedures.

Pelvic inflammatory disease was not reported after quinacrine sterilization in any HIV+ women, although it was reported in one HIV− woman who received treatment and made a complete recovery. In this series of quinacrine sterilization cases, no ectopic pregnancy occurred. The incidence of less common AEs such as nausea, vomiting, dizziness, headache, vulvar herpes, and fever varied from 0.5% to 3.0% of all cases and was not different between HIV− and HIV+ women (Table 2). The transvaginal ultrasonography enabled us to guide the necessary two quinacrine insertions, one each, into the two horns of the arcuate uterus (Fig. 1).

No pregnancy has occurred in the HIV-infected group. Two women from the HIV− group became pregnant. One pregnancy occurred at the third month after quinacrine sterilization. The patient did not use the prescribed alternative contraceptive method. The other pregnancy occurred 8 months after the last insertion of quinacrine. The pregnancies did not have any complications. The babies were born at term, in normal deliveries. They were in good health, and they were examined by expert specialists who did not detect any malformations. The average number of months of follow-up for HIV− women was 10.79 and for HIV+ women was 10.14. Pearl's index for the 258 women in this quinacrine sterilization study was 0.8753 per 100 woman-years including the 2,742 observed cycles. The cumulated survival in the lifetime table was 0.9875 (SE 0.0089), 95% CI (0.970–1.000). The women continue to be followed. The HIV+ women are being followed up every 6 months, and the HIV− group is being tested yearly. The loss to follow-up was minimal, and there was no differential loss in the two groups.

DISCUSSION

Among HIV+ women, the motivation to prevent pregnancy is high. Women infected with HIV do not want to transmit the HIV to their infant. Even if treatment with antiretroviral therapy prevents a horizontal transmission, they do not wish to leave another child motherless. They have great difficulty finding a surgeon willing to perform elective surgery in anyone who is HIV+ because surgeons are fearful that an inadvertent needle stick may make them a victim of this disease. Therefore, quinacrine sterilization can be a great benefit for HIV+ women. It is a simple, safe, and inexpensive outpatient office procedure. Quinacrine sterilization is 10% of the cost of surgical sterilization and has 2% of the complication rate of surgical sterilization (23). In Vietnam, women given the choice of quinacrine sterilization or surgical sterilization chose quinacrine sterilization over surgery by 11 to 1. Short-term AEs with quinacrine sterilization are mild, easily managed, and readily tolerated and frequently cease spontaneously as reported here and elsewhere (13, 14, 23–30). Quinacrine sterilization is not an ongoing treatment that must be interrupted because of a sudden change of the

TABLE 2

Distribution of AEs by HIV status of women who chose to be sterilized by means of quinacrine sterilization.

	Negative HIV		Positive HIV			Positive HIV				
						Antiretroviral therapy users		Antiretroviral therapy nonusers		
AEs	Freq	%	Freq	%	P[a]	Freq	%	Freq	%	P[b,c]
No symptoms	104	53.6	23	35.9	.011	10	50.0	13	31.0	.151
Headache	2	1.0	0	0.0	1.000	0	0.0	0	0.0	1.000
Cramps	39	20.1	14	21.9	.764	1	5.0	13	31.0	.025
Diarrhea	0	0.0	1	1.6	.248	0	0.0	1	2.4	1.000
PID	1	0.5	0	0.0	1.000	0	0.0	0	0.0	1.000
Weakness	2	1.0	0	0.0	1.000	0	0.0	0	0.0	1.000
Ectopic pregnancy	0	0.0	0	0.0	1.000	0	0.0	0	0.0	1.000
Vulvar herpes	0	0.0	1	1.6	.248	1	5.0	0	0.0	.323
Nausea	4	2.1	0	0.0	.575	0	0.0	0	0.0	1.000
Uterine perforation	0	0.0	0	0.0	1.000	0	0.0	0	0.0	1.000
Vulvar itching	36	18.6	9	14.1	.384	4	20.0	5	11.9	.453
Bleeding	16	8.2	23	35.9	$<.001$	5	25.0	16	38.1	.285
Sensation of fever	5	2.6	2	3.1	1.000	0	0.0	2	4.8	1.000
Dizziness	5	2.6	0	0.0	.337	0	0.0	1	2.4	1.000
Vomiting	0	0.0	1	1.6	.248	0	0.0	0	0.0	1.000
Base[d]	194	—	64	—	—	20	—	42	—	—

Note: Freq = frequency; PID = pelvic inflammatory disease.

[a] Negative compared with positive HIV.

[b] Antiretroviral therapy users compared with nonusers.

[c] $P<.05$, significantly different.

[d] The percentage does not necessarily total 100%.

de Magalhães. Quinacrine sterilization for HIV-positive women. Fertil Steril 2009.

disease. Uterine bleeding was the only side effect with a significant increase in HIV-infected women ($P<.001$). The AE of uterine bleeding occurring in women with negative HIV serologic findings was similar to values already reported (Table 2). No explanation is offered for the increased bleeding after quinacrine sterilization in HIV+ women. There was no difference in bleeding between antiretroviral therapy and non-antiretroviral therapy users.

Although immunocompromised women are more susceptible to vulvar itching, in these quinacrine sterilization cases vulvar itching probably was related to quinacrine being discharged by the uterus into the vagina. Except for bleeding, the incidence of AEs is similar to that reported in previous studies (13, 14, 23–37), that is, they were mild and tolerable and frequently ceased spontaneously. Some of the less common side effects may be masked or enhanced by the disease or the antiretroviral therapy. In this article, all AEs were considered as associated with quinacrine sterilization.

Pelvic inflammatory disease was not reported after quinacrine sterilization in HIV-infected women. Antiretroviral therapy users and nonusers presented similar AEs after quinacrine sterilization. In regard to safety, AEs and the absence of serious AEs corroborate similar findings in studies involving >175,000 women (unknown HIV serologic findings) who had quinacrine sterilization (10–14, 23–37]. The serial measures of the viral load and CD4+ and CD8+ lymphocytes are important tools to monitor HIV-infected subjects. The viral load is a predictor of the immunodeficiency progression within a determined period of time (38). The normal variations of viral load (<70%) were significantly more frequent than the expected changes (>70%) in the groups under analysis. Antiretroviral therapy users and nonusers presented similar variations of viral load, before and after quinacrine sterilization. Some studies have shown that with antiretroviral therapy, aminoacridines (quinacrine belongs to the family of aminoacridines) present anti-HIV activity in vitro and in vivo, with persistent reduction of the viral load for a period of 48, 96, and 144 weeks (18–20, 39, 40). The enhanced anti-HIV activity correlates with the aminoacridine concentration in the blood (41, 42) and with the length of time it has been in use (43). The fact that the viral load did not show any reduction during this investigation may be due to the low dose of quinacrine and to the short period of exposure of quinacrine as used for quinacrine sterilization. This is further evidence for the safety of quinacrine sterilization. The

TABLE 3

Distribution of HIV-infected women based on variation of the viral load and CD4+ and CD8+ lymphocytes of women who chose to be sterilized by means of quinacrine sterilization (before and after sterilization).

		Antiretroviral therapy users			Antiretroviral therapy nonusers			Total		
Variables		**Freq**	**%**	***P*[a,b]**	**Freq**	**%**	***P*[b]**	**Freq**	**%**	***P*[b]**
Viral load	Not sig.	29	72.5	.004	13	76.5	.029	42	71.2	.001
	Sig. >70%[c]	4	10.0	.366	1	5.9	.317	6	10.2	.225
	Sig. <−70%	7	17.5	—	3	17.6	—	11	18.6	—
CD4+	Not sig.	24	57.1	.355	17	85.0	.002	41	64.1	.024
	Sig. >25%	11	26.2	.346	2	10.0	.564	14	21.9	.297
	Sig. <−25%	7	16.7	—	1	5.0	—	9	14.1	—
CD8+	Not sig.	28	68.3	.019	10	50.0	1.000	39	61.9	.059
	Sig. >25%	5	12.2	.405	2	10.0	.058	7	11.1	.041
	Sig. <−25%	8	19.5	—	8	40.0	—	17	27.0	—

Note: Freq = frequency; Not sig. = not significant; Sig. = significant.
[a] *P* significantly different at <.05.
[b] After sterilization compared with before sterilization.
[c] Variation of the viral load >70% and variation of CD4+ and CD8+ >25%.

de Magalhães. Quinacrine sterilization for HIV-positive women. Fertil Steril 2009.

counting of CD4+ lymphocytes is fundamental to evaluate the disease status (38). The observed variation of CD4+ counting (<25%) was significantly more frequent than the CD4+ real variations (P=.024). In this study, no real variation of the CD4+ lymphocyte counting was observed in women after quinacrine sterilization. As quinacrine is in the aminoacridine family, the results obtained from this study corroborate the data presented in the literature. Published research shows the lack of significance in the variations of CD4+ lymphocyte counts with hydroxychloroquine (an aminoacridine) treatment at 8, 16, and 144 weeks of treatment, with no harm to the immune system of HIV-infected women (19, 42, 43). The CD8+ cytotoxic T-lymphocytes have important roles in the control of infections including lysing cells infected by viruses, protozoans, and some fungi. In this study, there was no significant variation in the CD8+ lymphocyte count after quinacrine sterilization (P=.059). There are no data in the literature concerning variations in CD8+ counting after the use of aminoacridines. On the basis of the results, quinacrine sterilization did not affect the viral load values or CD4+ or CD8+ lymphocyte counts and did not interfere with the evolution of the disease.

Transvaginal ultrasonography provided safety for inserting quinacrine sterilization into an arcuate uterus. The use of transvaginal ultrasonography in this one case provides additional evidence confirming the value of sonography with quinacrine sterilization as reported in a previous study by Ferreira (30). These findings show that although HIV-infected women present varied responses to inflammatory processes, they respond to the action of intrauterine quinacrine in a way similar to that of women who are HIV−.

To measure efficacy requires a longer follow-up than presented here. Therefore these women will continue to be monitored. So far, no pregnancy has occurred in the HIV-infected group. Two women from the HIV− group became pregnant. The average follow-up was 10.63 months. The average number of months of follow-up for HIV− women was 10.79 and for HIV+ women was 10.14. The Pearl index for the 258 women in this quinacrine sterilization study was 0.8753 per 100 woman-years, and the cumulated survival in the lifetime table was 0.9875 (SE 0.0089), CI 95% (0.970–1.000).

Worldwide, the Center for Research of Population and Security has documented 100,000 women who have received quinacrine sterilization with no mortality and no complications serious enough to require surgery (35). Only two patients were hospitalized, and those were for an allergic reaction. Both patients recovered within 24 hours.

In 2003, the International Federation of Gynecology and Obstetrics (FIGO) annual meeting of October 3, 2003, devoted a half-day session entirely to quinacrine sterilization. Furthermore, the organization's journal, the *International Journal of Obstetrics and Gynecology,* devoted a supplement of its October 2003 issue to quinacrine sterilization, with 25 articles covering >42,000 cases of quinacrine sterilization. These clinical trials revealed the safety and efficacy of this technology in many countries with diverse cultures including China, India, Chile, Indonesia, Iran, Vietnam, Pakistan, Egypt, and the United States.

Currently in our center in Brazil, 560 women have had this procedure. No serious AEs were reported that required hospitalization. These patients will continue to be monitored.

In conclusion, HIV-infected women who undergo quinacrine sterilization experience a typical side-effect profile similar to that of noninfected women. The incidence of AEs was similar for antiretroviral therapy users and nonusers except for uterine bleeding, which was the only side effect more frequent in HIV-infected women. These were mild and easily managed, and some AEs receded spontaneously. In evaluating the use of quinacrine sterilization in HIV-infected patients there was no significant variation of the viral load or CD4+ and CD8+ lymphocytes in HIV-infected women regardless of whether they received antiretroviral therapy. The presence of the scars at the uterine cornus was the same in the two groups and in antiretroviral therapy users or nonusers. Quinacrine sterilization is a safe method of sterilization for HIV-infected women.

Acknowledgments: The authors thank the Center for Research on Population and Security, Research Triangle Park, North Carolina, which supplied the quinacrine pellets and inserters; the Ultrasonography Department of the Santa Fé Hospital and Otto Cirne Maternity of the Hospital das Clínicas of the School of Medicine of UFMG for their help with sonography; and Ms. Margaret Miller Growe, Elton Kessel, M.D., and Stephen Mumford, M.D., Ph.D., for their helpful suggestions and editorial assistance.

REFERENCES

1. UNAIDS–Joint United Nations Programme on HIV/AIDS (Uniting the World Against AIDS). The 2006 report on global AIDS epidemic: executive summary. A UNAIDS 10th anniversary special edition [Internet] [cited 9 Sep 2006]. Available from: http://data.unaids.org/pub/globalreport/2006/2006_GR_Executivesummary_en.pdf.
2. Waters L, Barton S. Contraception and HIV: what do we know and what needs to be done? J Fam Plann Reprod Health Care 2006;32:110–4.
3. Zipper JA, Stachetti E, Mendel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. Fertil Steril 1970;21:581–9.
4. Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvant to quinacrine nonsurgical female sterilization. Adv Contracept 1995;11:303–8.
5. Randic L, Haller H, Sojat S. Non-surgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen. Fertil Steril 2001;75:830–1.
6. Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. Fertil Steril 2000;74:1084–91.
7. Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. Fertil Steril 2000;74:1092–100.
8. Thakur PS. Quinacrine sterilization in Tripura, India. Contraception 2001;64:277–9.
9. Wheeler RG. Delivery systems for applying quinacrine as a tubal closing agent. In: Zatuchni GI, Shelton JD, Godsmith A, Sciarra JJ, eds. Female transcervical sterilization. Philadelphia: Harper & Row, 1983:105–15.
10. Bhatt RV. Quinacrine nonsurgical female sterilization in Baroda, India: 23 years of follow-up of 84 women. Int J Gynecol Obstet 2003;83:S31–4.
11. Pal SK. Quinacrine sterilization of 1997 women in Daharpur, Midnapore, West Bengal, India: a comparison of 3 protocols. Int J Gynecol Obstet 2003;82:S97–100.
12. Roy A. A 22-years experience with quinacrine sterilization in a rural private clinic in Midnapore, India: a report on 5 protocols and 1838 cases. Int J Gynecol Obstet 2003;82:S87–93.
13. Sarin AR, Sarin RK. Quinacrine sterilization (QS) among high-risk women: a study of 134 cases. Int J Gynecol Obstet 2003;82:S73–6.
14. Suhadi A, Anwar M, Soejoenoes A. 10-years follow-up of women who elected quinacrine sterilization (QS) in Wonosobo, Central Java, Indonesia. Int J Gynecol Obstet 2003;82:S137–40.
15. Savarino A, Gennero L, Chen HC, Serrano D, Malavasi F, Boelaert JR, et al. Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity. AIDS 2001;15:2221–9.
16. Savarino A, Mothanje BL, Rastrelli E, Rutella S, Golotta C, Morra E, et al. Anti-HIV effects of chloroquine. Inhibition of viral particle glycosylation and synergism with protease inhibitors. J Acquir Immune Defic Syndr 2004;35:223–32.
17. Weber SM, Levitz SM. Chloroquine antagonizes the proinflammatory cytokine response to opportunistic fungi by alkalizing the fungal phagolysosome. J Infect Dis 2001;183:935–42.
18. Boelaert JR, Dom GM, Huitema ADR, Beijnen JH, Lange JMA. The boosting of didanosine by allopurinol permits a halving of the didanosine dosage. AIDS 2002;16:2221–3.
19. Patton NI, Aboulhab J. Hydroxychloroquine, hydroxyurea and didanosine as initial therapy for HIV-infected patients with low viral load: safety, efficacy and resistance profile after 144 weeks. HIV Med 2005;6:13–20.
20. Patton NI, Aboulhab J, Karin F. Hydroxychloroquine, hydroxycarbamide and didanosine as economic treatment for HIV-1. Lancet 2002;359:1667–8.
21. Boelaert JR, Appelberg R, Gomes MS, Blasi E, Mazolla R, Grosset J, et al. Experimental results on chloroquine and AIDS-related opportunistic infections. J Acquir Immune Defic Syndr 2001;26:300–1.
22. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. Lancet 1993;342:213–7.
23. Lippes J, Brar M, Gerbracht K, Neff P, Kokkinakis S. An FDA phase I clinical trial of quinacrine sterilization (QS). Int J Gynecol Obstet 2003;83:45–9.
24. Hieu DT. A retrospective study of quinacrine sterilization in Vietnam. Quinacrine Sterilization Dissemination Meeting; 1995 Feb. Hanoi, Vietnam: 1995.
25. Trujillo V, Zipper J, Dabancens A, Guzman S. Quinacrine non-surgical female sterilization: experience in Chile [Abstract]. Int J Gynecol Obstet 2000;70:73.
26. Bhatt R, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. Fertil Steril 1985;44:303–6.
27. Lu W, Zhu J, Zhong C, Zhao Y. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China. Int J Gynecol Obstet 2003;83:S51–8.
28. Soroodi-Moghaddan S. Quinacrine sterilization in Iran and the use of HSG as a measure of success. Int J Gynecol Obstet 2003;82:S93–6.
29. El Sahwi S, Kamel M, El Faham M, El Makhzangy I. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization: results in 180 women. Int J Gynecol Obstet 2003;83:S101–6.
30. Ferreira CRC. Esterilização feminina não-cirúrgica com quinacrina: avaliação da eficácia do método e estudo ecográfico do útero [thesis]. Belo Horizonte, Brazil: Faculdade de Medicina, Universidade Federal de Minas Gerais, 2003.
31. Chalbaud AG, Mora GP. Female sterilization with quinacrine using hysterosalpingography (HSG) as an endpoint after a single-insertion protocol in Caracas, Venezuela. Int J Gynecol Obstet 2003;83:S107–12.
32. Garabedian V. Quinacrine sterilization (QS) in Syria: a preliminary report on 297 cases. Int J Gynecol Obstet 2003;83:S133–5.
33. Alpizar F. Quinacrine sterilization (QS) in Costa Rica: 694 cases. Int J Gynecol Obstet 2003;83:S141–5.
34. Zipper J, Trujillo V. 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases. Int J Gynecol Obstet 2003;82:S23–30.
35. Kessel E. 100,000 quinacrine sterilizations. Adv Contracept 1996;12:69–76.
36. El Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. Fertil Steril 1993;59:301–4.

37. Zipper JA, Dabancens A, Guerrero A, Trujillo V. Quinacrine revised. Hum Reprod Update 1995;1:153–72.
38. Rachid M, Schechter M. In: Manual de HIV/AIDS. 8th ed. Rio de Janeiro: Revinter Ltda, 2005:3–40.
39. Sotelo J. Could an aminoacridine interfere with the cellular mechanisms involved in the process of human immunodeficiency virus infection? Med Hypotheses 1996;47:43–7.
40. Jiang MC, Lin JK, Chen SS. Inhibition of HIV-1 Tat-mediated transactivation by quinacrine and chloroquine. Biochem Biophys Res Commun 1996;226:1–7.
41. Tett SE, Day RO, Culter DJ. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis—a cross sectional study. J Rheumatol 1993;20:1874–9.
42. Sperber K, Louie M, Kraus T, Proner J, Sapira E, Lin S, et al. Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1. Clin Ther 1995;17:622–36.
43. Sperber K, Chiang G, Chen H, Ross W, Chusid E, Gonchar M, et al. Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with HIV-1. Clin Ther 1997;19: 913–23.

Non-surgical female sterilization with quinacrine-induced tubal occlusion: a clinical trial

Seifi L.1*
Ramezanzadeh F.1
Jafarabadi M.1
Shariat M.2
Masumi M.1

1- Reproductive Health Research Center
2- Maternal- Fetal- Neonatal Health Research Center
Tehran University of Medical Sciences

* Corresponding author: Vali-e-asr Hospital, Keshavarz Blvd , 14149, Tehran, IRAN
Tel: +98-21-66939320
email: drlseifi@yahoo com

Abstract

Background and Objective: Non-surgical tubal sterilization using the drug quinacrine has been conducted for over 35 years. Over this period, more than 150,000 women in 40 countries have undergone this procedure. Given the scarcity of studies where tubal occlusion has been sonographically confirmed, our research aims to investigate the tubal scars, the endometrial pattern post-quinacrine administration, and evaluate its efficacy, side effects, and patient acceptance. **Methodology:** This prospective, single-group clinical trial (without a control group) was conducted at the Vali-e-Asr Reproductive Health Research Center, affiliated with Tehran University of Medical Sciences, from May 2005 to August 2006. A total of 100 eligible women underwent tubal occlusion. Three months post-procedure, transvaginal sonography was performed to assess the tubal scars. As the study was observational and descriptive in nature, only descriptive statistical analyses were performed. **Findings:** All participants reported satisfaction, with no side effects observed. The pregnancy rate per woman-year was zero. As of this report, approximately three years post-initiation of the study, no pregnancies have been reported in this cohort. Transvaginal sonographic examination revealed normal endometrial thickness and visible tubal scars. **Conclusion:** Quinacrine sterilization is a valuable method. Given its safety, efficacy, patient acceptance, simplicity, and cost-effectiveness, it is advocated as an outpatient procedure for family planning centers.

Keywords: Non-surgical female sterilization, quinacrine, failure, contraception method, acceptance.

Introduction

The concept of employing a non-surgical method for tubal sterilization, considering the anatomical position of the uterus and the potential to access the fallopian tubes via the vagina, has been contemplated for years. An ideal method would not necessitate anesthesia, a surgical suite, nor would it leave an abdominal scar. Various sclerosing agents have been utilized for this purpose, including silver nitrate, tetracycline, and quinacrine(1). In 1977, Dr. Zipper, a gynecologist and developer of the IUD (Cu-T) in Chile, employed a quinacrine solution (Atebrin) for non-surgical tubal sterilization(2). Quinacrine is a compound initially sourced from the bark of the Cinchona tree and was employed for intracellular DNA staining. This medication has been in use for over seven decades in gram doses (a hundredfold the amount needed for tubal occlusion). It has been utilized orally or via injection for treating or preventing conditions such as malaria, giardia, and discoid lupus erythematosus(3). It holds FDA approval for these applications. Observing its efficacy in palliative care for untreatable pulmonary patients, where its injection causes the two pleural layers to adhere(4,5), Dr. Zipper was inspired to use quinacrine for tubal occlusion in women by a similar mechanism. After successful animal trials(6), the procedure was carried out on women slated for hysterectomy with their informed consent. Subsequent histopathological examination of the fallopian tubes confirmed the presence of sclerosis(7). It was then performed on women who desired tubal occlusion as a method of contraception. Initially, this drug was administered in solution form (8), but

currently, it is available as small cylindrical tablets. The tablet is absorbed more gradually than the solution, thereby exerting a more pronounced effect(9). During the three years of using the solution form, three cases of brain cortex stimulation were reported; however, with the current tablet form, this side effect has not been observed (9,10). This method has been effectively employed in more than 40 countries globally. In countries such as Egypt, Libya, Syria, Pakistan, India, Indonesia, Thailand, Vietnam, China, Venezuela, Chile, Costa Rica, Brazil, and the Philippines, more than 150,000 women have been subjected to tubal sterilization with zero reported mortality. With one treatment session, a 15% failure rate was reported (11); however, with two sessions spaced one month apart, the probability of failure is reduced to 1%. In prior studies concerning this procedure, tubal occlusion confirmation was done using hysterosalpingography in countries like Egypt and Venezuela. It was observed that this method could increase the likelihood of procedure failure because the pressure from the contrast material used during hysterosalpingography could weaken the developed plaque, as researched by S. El. Sahwi from Egypt (12). The only study reporting tubal occlusion confirmation via transvaginal sonography was in 2003 at the State University of New York, USA, and it included a limited number of participants. Experiences from different countries over the past three decades concerning this method have been documented and discussed in a 160-page supplementary journal on Obstetrics and Gynecology during the International Congress of Obstetrics and Gynecology (FIGO 2003) held in Santiago, and the findings are available (13,14). In light of our country's 3.3% population growth during 1983-1984 and the fact that those born during this peak growth are now reaching reproductive age, it appears essential to enhance the availability of population control methods that are low-risk, accessible, diverse, cost-effective, and straightforward. Consequently, we embarked on studying the implications and potential side effects of quinacrine sterilization (Quinacrine Sterilization - QS) in Iranian women, mainly focusing on the formation of tubal scars using sonography.

Methodology

In this forward-looking, single-group clinical trial, 100 legally married women who visited the Vali-e-Asr Reproductive Health Research Center between 2005-2006, were in the latter stages of their reproductive age, had at least two children over two years of age, and had chosen tubal sterilization with their spouses' agreement, were included. These participants were then followed up for a year after the confirmation of tubal scarring. Based on WHO guidelines, the typical estimation of error and failure rates for a family planning method is always grounded on its results when correctly applied to 100 samples over the course of a full year (known as the Pearl Index). In this research, 100 samples were intervened upon and followed for a 12-month period to determine the method's failure rate. Quinacrine sterilization (QS) was not recommended for women with advanced liver diseases (since quinacrine accumulates in the liver), those with psoriasis (as quinacrine might intensify psoriasis), individuals known to have a PD_6G enzyme deficiency, or those cognizant of having a bicornuate uterus or a complete septum. Individuals presenting with unexplained uterine bleeding, those suspected of uterine malignancy, or those with mental health concerns were also excluded from the study. Subsequently, the necessary information about the method was provided to the couples. After expressing their interest and signing the consent form, participants were interviewed by a gynecological specialist. Variables such as personal characteristics, obstetric history, medical and drug history, marital lifestyle, history of cancer in oneself or family, especially gynecological cancers, previous contraceptive methods, and the number of spontaneous or induced abortions, among others, were recorded. Additionally, a pelvic examination was conducted, and a Pap smear was taken from the applicant. The Quinacrine QS (Sepharm, Switzerland) was available as

seven 36mg bright yellow tablets packaged inside an inserter similar to the IUD, pre-packaged, sterilized, and ready for use. The QS procedure was performed on an outpatient basis during the final days of menstrual bleeding. This is because, in addition to the lower probability of pregnancy, the endometrial growth is not extensive, ensuring no interference with the drug being administered. The examination room was equipped with tools to handle anaphylactic shock. The QS procedure was done via the vagina, similar to IUD insertion. This procedure typically takes about a minute. After the main procedure, it's recommended for the individual to lie on their back for approximately half an hour before leaving the medical center. After undergoing the QS procedure, the women were informed that they should contact or visit the clinic if they experienced a fever exceeding 38°C, severe pelvic pain, or any other complications. Otherwise, they were advised not to be concerned about yellow vaginal discharge, which is related to the drug's expulsion, or brief uterine pain. If the pain was intolerable, they could use diclofenac rectal suppositories. Routine NSAIDs were not prescribed for these participants. They were also advised that their partners should use another contraceptive method, such as a condom or the withdrawal method, for the following three months. The second appointment was scheduled for the final days of bleeding in the subsequent menstrual cycle. At this stage, patients were inquired about any complications following the initial procedure. Factors such as post-QS bleeding, its severity, analgesic usage, the number and days of usage, headaches, fever, yellowing of the skin or conjunctiva, painful intercourse, painful urination, menstrual timing variations, changes in menstrual bleeding volume, dysmenorrhea, and potential medication intake for any reason during this cycle were documented in the follow-up questionnaire. The second round of the QS procedure was then performed. One month later, a vaginal sonography was carried out to confirm the tubal occlusion, and patients were again asked similar questions regarding the past month. After the visualization of the scarring in the tubes via sonography, patients were allowed to engage in unprotected intercourse. In five cases, due to reasons such as the patient's unavailability or instances where severe pelvic adhesions were present and a previous surgeon couldn't locate the tubes after an abdominal incision, hysterosalpingography was utilized to confirm tubal occlusion post-QS. Both phases of the QS were executed by a single gynecologist to ensure uniformity in the procedural technique, while all sonographies were performed by another gynecologist. At the conclusion of the third month, patient satisfaction was assessed. Data was collected and analyzed using SPSS software, version 11. This research was descriptive and observational in nature; therefore, only descriptive statistics were computed. In this study, the researcher did not aim to identify a significant difference between the surgical method and this method. Rather, the equivalence of the efficacy of both methods was deemed sufficient due to the latter's lower risk, cost-effectiveness, simplicity, and other factors. The chi-square ($\chi 2$) test was employed for the comparison of quantitative values. P-values less than 0.05 were considered statistically significant.

Findings

The study included 100 urban Iranian women. Demographic characteristics and medical histories are detailed in Table 1. After undergoing the procedure, ten individuals reported feeling feverish and chills despite having a normal temperature. One percent reported mild headaches, which were effectively managed with common analgesics. 7% of participants reported experiencing increased vaginal discharge that persisted for about a week. 2% of participants reported bleeding on the first day, while 91% experienced no complications (Table 2).

Table 1: Characteristics of the Study Participants

Characteristics	Frequency (%)	Mean± SD
Age	-	37/48±3/89
BMI	-	26/67±4/44
Number of Children	-	2/65±0/85
Drug Addiction	-	-
Cigarette Consumption	2 (%2)	-
Previous Miscarriage	10 (%10)	-
Allergy	6 (%6)	-
Cardiovascular disease	8 (%8)	-
Thyroid	14 (%14)	-
Depression	4 (%4)	-
Migraine	3 (%3)	-
Diabetes	3 (%3)	-
Thrombophilia	1 (%1)	-
Gastrointestinal disease	1 (%1)	-
Hepatitis B	1 (%1)	-
More than Two Diseases	3 (%3)	-
Other Diseases	6 (%6)	-
Previous Contraception		-
Combined Male and Female Methods	29 (%29)	-
Coitus interruptus	20 (%20)	-
Female-Only Methods	29 (%29)	-
IUD	15 (%15)	-
Combined Birth Control Pill	14 (%14)	-
Norplant	2 (%2)	-
Depo Progesterone Injection	1 (%1)	-
Non-regular Menstrual Bleeding	3 (%3)	-
The volume of menstrual bleeding		-
Low	21 (%21)	-
Medium	68 (%68)	-
Heavy	11 (%11)	-

In 85% of cases, no menstrual changes were observed. In the instances where changes did occur, they presented as reduced bleeding volume or duration or menstrual delays in 14% of participants. Notably, many within this 14% had previously reported heavy menstrual flow before tubal occlusion, and the observed changes increased their satisfaction. One instance of polymenorrhea was observed after the administration of quinacrine (Table 2). There were no reported cases of allergic reactions, neurogenic shock, or any other complications necessitating hospitalization. During the follow-up period, no cases of pelvic pain or ectopic pregnancies were reported. Even after three years of monitoring, no symptoms associated with the Post-Tubal Ligation Syndrome—such as functional ovarian cysts, pelvic pain, or polymenorrhea—were observed. 93 of the participants underwent transvaginal sonography three months after the initial procedure. All of them showed scarring at the beginning of the tubes, measuring between 10-15 millimeters. The endometrial growth was consistent with the menstrual cycle phase, and no cases of endometrial atrophy were observed. Tubal occlusion in five

Table 2: Frequency of Studied Outcomes in the Sample Post-Intervention

Outcomes	Number (Percentage)
Vaginal bleeding	2 (%2)
Abnormal vaginal discharge	7 (%7)
No complications	91 (%91)
Changes in Menstrual Status	
Delayed menstruation	3 (%3)
Decreased volume of menstrual bleeding	5 (%5)
Reduced duration of menstrual bleeding	6 (%6)
Frequent menstruation	1 (%1)
No change	85 (%85)

individuals was confirmed through hysterosalpingography. Two participants declined the offer of sonography or salpingography. The last two individuals, now approximately two years post-tubal occlusion, have not become pregnant without utilizing any other contraceptive measures. All participants were queried about their satisfaction, and 100% expressed contentment.

Table 3: Review of Texts

	Summary	Method of Confirming the Procedure's Outcome
J. Zipper, 1978-2003, Chile	95.4% effectiveness without ectopic pregnancy, without congenital anomalies, and without increased cancer risk after 25 years.	Clinical follow-up
R.V.Bhatt, 1979-2003, India	96.3% efficacy without late complications.	Clinical follow-up
C. R. C. Ferreira, 1999-2003, Brazil	Endometrial assessment via vaginal sonography; the method's failure rate was 0.8%.	Sonographic examination
R. B. Whitny, 2000-2003, USA	High acceptance and without failure.	Clinical follow-up
J. Lippes, 2003, USA (FDA Phase1 clinical trial)	Safe and effective.	Sonographic examination
L. A. Alfonso, Philippines, 2000-2003	Safe and effective, without failure, and without ectopic pregnancy.	Clinical follow-up
A. Bashir, 1996-2001, Pakistan	In 11,000 cases studied, the failure rate was lower in breastfeeding women. Safe and effective - outcomes improved after training agents in the method.	Clinical follow-up
Ljiljana Randic, 1998-2000,Croatia (Phase2 clinical trial)	More acceptable than the surgical method, without ectopic pregnancy; the failure rate after five years was 6.35% in the Brofen group and 6.2% in the control group.	Clinical follow-up
W. Lu, 1995-98, China	Safe and effective - without death or life-threatening complications; more acceptable than the surgical method - the error rate in two hundred women was 1.2%.	Clinical follow-up
D T Hieu, 1994-1996, Vietnam	The ectopic pregnancy rate among 25,000 women using the Quinacrine method was 0.26% and with the surgical method was 0.42%.	Clinical follow-up
T. Agoestina, 1993-1995, Indonesia	A single-dose method was used. Without late complications. The pregnancy rate after ten years was 14.3%.	Clinical follow-up

Discussion

The results of this study indicated a zero failure rate, which is lower than the 1% rate reported in studies from other countries. The observed outcome might be attributed to the contraceptive methods employed in the first three months after the initial phase. In our study, the mandated contraceptive methods were strictly either condoms or natural methods. Other contraceptive methods, such as pills containing estrogen, could potentially increase the method's failure rate (14,15). In our study, only one practitioner conducted all the QS procedures, ensuring a uniform risk of procedural error across all cases. A study conducted by Bashir differentiated between two groups: one in which all procedures were performed by a single individual and another where multiple practitioners were involved. Bashir's study reported a higher failure rate in the group involving multiple practitioners (11). We observed menstrual changes in 15% of our participants. In contrast, centers like those in Vietnam, where depot medroxyprogesterone was administered concurrently with the initial tubal ligation, reported such changes in up to 50% of cases. This could likely be due to the influence of progesterone (16). No ectopic pregnancies have been observed among our study participants to date. Factors such as participants having an age above thirty and practicing monogamy could be responsible for the reduced incidence of ectopic pregnancies (E.P.) in our study. Educating the participants through discussions, providing written materials, and granting sufficient time for decision-making contributed to the high satisfaction rate among our study participants. Having at least two children older than two years and being married for over ten years are factors that have prevented any regrets among our study participants. The average duration since marriage in our study was 18 years. In our study, as with studies in the Philippines, Costa Rica, China, Egypt, and Libya, the method was widely accepted and without complications (13). In the current study, similar to research from New York University (Table 3), tubal occlusion was verified by observing tube scarring via sonography. To

determine sensitivity and specificity levels, the sonography results should be compared with a gold standard, such as hysterosalpingography. Given the recommendations in other articles, including the study by S. El. Sahwi from Egypt (12), we refrained from such an evaluation due to the potential increase in method failure risk. Even after a three-year follow-up, no symptoms typically associated with Post-Tubal Ligation Syndrome following surgical methods—such as functional ovarian cysts, pelvic pain, and polymenorrhea—were observed. The Post-Tubal Ligation Syndrome after surgical methods is speculated to possibly result from unavoidable damage to the mesosalpinx and consequently the ovarian vessels during surgery. However, as the method utilized in this study seals the tubes internally without damaging the ovarian vessels and mesosalpinx, none of these complications were observed. This particular feature can be deemed an advantage of our method over the surgical approach. Based on the collective findings, it appears that this method offers promising health and economic outcomes for the participants and, consequently, for the nation's family planning system.

References

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap LC. Williams obstetrics. 22nd ed. New York: McGraw-Hill: 2005.
2. Zipper J, Kessel E. Quinacrine sterilization: a retrospective. *Int J Gynaecol Obstet* 2003; 83 Suppl 2: 7-11.
3. Lippes J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2002; 77: 1106-9.
4. Gellhorn A, Zaidenweber J, Ullmann J, Hirschberg E. The use of atabrine (quinacrine) in the control of recurrent neoplastic effusions. A preliminary report. *Drugs Made Ger* 1961; 39: 165-76.
5. Rochlin DB, Smart CR, Wagner DE, Silva AR. The control of recurrent malignant effusion using Quinacrine hydrochloride. *Surg Gynecol Obstet* 1964; 118: 991-4.
6. Zipper JA, Prager R, Medel M. Biologic changes induced by unilateral intrauterine instillation of quinacrine in the rat and their reversal by either estradiol or progesterone. *Fertil Steril* 1973; 24:48-53.
7. Sarin AR, Mohindroo A, Chandra P, Gill SS. Histologic changes in fallopian tubes after lower dose of transcervical quinacrine insertion. *Fert Stril* 1998; 70 suppl 1: 164.
8. Zipper JA, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil Steril* 1970; 21: 581-9.
9. Guzman-serani R, Potts M, Wheeler RG. Non-surgical tubal occlusion. *Adv Contracept Deliv Syst* 1985; 1: 146-9.
10. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18: 275-9.
11. Bashir A, Bashir M, Afzal S. The effect of special training for quinacrine sterilization (QS) in Faisalabad, Pakistan: a report on an 1833-women subset of 11,000 cases. *Int J Gynaecol Obstet* 2003; 83 Suppl 2: 67-71.
12. el Sahwi S, Kamel M, el Faham M, el Makhzangy I. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization: results in 180 women. *Int J Gynaecol Obstet* 2003; 83 Suppl 2: 101-6.
13. Lu W, Zhu J, Zhong C, Zhao Y. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China. *Int J Gynaecol Obstet* 2003; 83 Suppl 2:51-8.
14. Malaviya B, Chandra H, Kar AB. Chemical occlusion of monkey oviducts with quinacrine: antagonism and reversal with estrogen. *Contraception* 1975; 12: 31-6.
15. Zipper J, Insunza S. Pharmacological agent that potentiate or inhibit the occlusive action of Quinacrine in the fallopian tube. Edited by Duncan GW. London: Academic press: 1972.
16. Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong LQ. The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases. *Int J Gynaecol Obstet* 2003; 83 Suppl 2: 77-85.

Non-surgical female sterilization with quinacrine-induced tubal occlusion: a clinical trial

Seifi L.1*
Ramezanzadeh F.1
Jafarabadi M.1
Shariat M.2
Masumi M.1

1- Reproductive Health Research Center
2- Maternal- Fetal- Neonatal Health Research Center
Tehran University of Medical Sciences

* Corresponding author: Vali-e-asr Hospital, Kesbavarz Blvd , 14149, Tehran, IRAN
Tel: +98-21-66939320
email: drlseifi@yahoo com

Abstract

Background: Over the last 35 years, quinacrine has been used to sterilize more than 150.000 women in 40 countries, first in the form of slurry and now in the form of cylindrical pellets. Some studies confirmed the tubal occlusion by hysterosalpyngography, but this method increases the chance of failure. Only a few studies on tubal occlusion have used transvaginal sonography for confirmation, and there were some doubts about the effect of quinacrine on the endometrium. We performed this study to evaluate the tubal scar and endometrial pattern by ultrasound and to determine the feasibility, acceptance, and side effects of quinacrine sterilization (QS) in Iranian women.

Methods: This prospective clinical trial was done at the Vali-e-Asr Reproductive Health Research Center of the Tehran University of Medical Sciences between April 2005 and July 2006. One hundred sexually active women ranging from 30 to 47 years of age, who had at least two children above two years old, requesting sterilization, were sterilized by this method. By the end of menstrual bleeding, seven pellets, each containing 36mg quinacrine, were inserted in the uterine fundal area via the cervical canal. The procedure was repeated one month later. Three cycles after the first step, transvaginal sonography was performed to visualize the tubal scar and determine the endometrial pattern. Patients were followed at one and three years after initiation of the procedure.

Results: All women were satisfied with the procedure. There were no side effects. No pregnancies had occurred, nor were there endometrial thickness abnormalities. Scar formation was visible in the tubes.

Conclusion: Quinacrine sterilization is a useful method for women and can be recommended to family planning services as an ambulatory procedure due to its efficacy, simplicity, acceptance and cost effectiveness.

Keywords: Nonsurgical female sterilization, quinacrine, contraception failure, method acceptability

ELSEVIER

Contraception 78 (2008) 61 – 65

Contraception

Original research article

Contraceptive effectiveness of two insertions of quinacrine: results from 10-year follow-up in Vietnam

David C. Sokal[a,*], Do Trong Hieu[b], Nguyen Dinh Loan[c], David Hubacher[a], Kavita Nanda[a], Debra H. Weiner[a], Trinh Huu Vach[d]

[a]*Family Health International, Research Triangle Park, NC 27709, USA*
[b]*Director (retired), Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi JA00146B, Vietnam*
[c]*Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi JA00146B, Vietnam*
[d]*Research Center for Rural Population and Health, Hanoi JB01387C, Vietnam*

Received 29 January 2007; revised 14 February 2008; accepted 19 February 2008

Abstract

Background: This study was conducted to evaluate the long-term effectiveness of two insertions of quinacrine pellets for nonsurgical sterilization among women in northern Vietnam.
Study Design: Observational cohort study of 1335 women who received two quinacrine insertions between 1989 and 1993.
Results: About 90% of the study population participated in the last round of interviews. Cumulative follow-up time for this cohort was 14,294 person-years. The 1-, 5- and 10-year cumulative pregnancy probabilities for quinacrine were 3.3% (95% CI, 2.4–4.3), 10.0% (95% CI, 8.4–11.6) and 12.1% (95% CI, 10.4–13.9), respectively. Pregnancy estimates with quinacrine in this cohort were higher than that reported from US-based research on surgical tubal sterilization and higher than results of quinacrine sterilization in Chile. Quinacrine effectiveness was better among older women.
Conclusion: The effectiveness of quinacrine in Vietnam was lower than other forms of sterilization. Factors such as inconsistent training and use of various insertion techniques may have contributed to the relatively high failure rate.

Keywords: Quinacrine; Tubal sterilization; Nonsurgical; Pregnancy; Effectiveness; Follow-up study

1. Introduction

Development of a safe, effective and technologically simple form of nonsurgical sterilization could provide women with another option to limit childbearing, particularly in areas where surgical procedures are not readily available. An US Food and Drug Administration-approved nonsurgical sterilization method is now available in the United States, but it is an expensive and complex procedure, requiring a skilled hysteroscopist [1].

Insertion of quinacrine pellets into the uterus to cause tubal occlusion has been studied since the 1970s [2–4]. The most widely accepted regimen involves inserting seven pellets, each with 36 mg of quinacrine dihydrochloride dihydrate, into the uterus using a modified intrauterine device (IUD) inserter. This delivers a total of 252 mg of quinacrine; the procedure is repeated 1 month later in order to achieve high rates of tubal occlusion.

Published pregnancy rates for two insertions of quinacrine vary considerably. For the first year of use, pregnancy rates vary from 0.3% [5], to 1.2% [6], to 2.6% [7]. After 5 years, researchers have reported pregnancy rates of 1.1% [5], 6.0% [8] and 6.4% [9]. Finally, after 10 years, the reported rates are 4.3% [10], 8.9 [9] and 11.7% [11].

The primary objective of this new report is to provide cumulative quinacrine effectiveness estimates out to 10 years for a cohort of Vietnamese women who received two insertions of quinacrine; our previous interim report provided only 5-year results [12]. This is our final report on the contraceptive effectiveness among this cohort, which remains one of the largest, long-term sources of information on quinacrine. As before, we report safety data in a companion article.

* Corresponding author. Tel.: +1 919 544 7040x232.
E-mail address: dsokal@fhi.org (D.C. Sokal).

0010-7824/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2008.02.010

2. Materials and methods

In 1994, we established an observational cohort of a sample of Vietnamese women who had received either one or two insertions of quinacrine between 1989 and 1993 when the Ministry of Health was providing quinacrine sterilizations. This report on contraceptive effectiveness concerns a subset of 1335 women who received two insertions. We conducted retrospective interviews in 1994 to collect detailed information on the sterilization procedures. Since establishing the cohort, we have attempted yearly interviews (1995–2002, inclusive) with each participant. Thus, the effort described in this report encompasses cumulative experiences that occurred during the 9 to 13 years after quinacrine pellet sterilization. Detailed information on the sampling frame, interview methods, use of weighted statistics, estimating participant age at time of quinacrine insertion, and so on, can be found in previous reports [12,13].

At each yearly interview, participants provided information on any pregnancies: estimated dates of conception and outcome, including abortions and menstrual regulations. Vietnam has the highest induced abortion rates of any country [14], and many procedures are done within a week or two of a missed period. This type of early termination is known as menstrual regulation and is usually done without a pregnancy test, especially in resource poor rural areas, because pregnancy tests may not be available. Thus, it is likely that some menstrual regulation procedures among participants in our cohort were done on women who were not pregnant.

To avoid overestimating quinacrine pregnancy rates by including nonpregnant women who had had menstrual regulation procedures, we used the same adjustments described in our previous publication [12]. Beginning in 1995–1996, we supplied pregnancy test kits to the area clinics, for use by study participants who presented for concerns about a possible pregnancy. Through analysis of the test results, we discovered that 58% of tests were negative; we assumed that this proportion would have undergone an unnecessary menstrual regulation procedure had pregnancy tests not been available. Therefore, we applied a correction factor to the subset of reported pregnancies that were not confirmed by a pregnancy test and were terminated with a menstrual regulation procedure within 7 weeks of the last menstrual period. Thus, the total number of pregnancies that met these criteria was reduced by 58% by counting each qualifying event as 0.42 of a pregnancy in the lifetable analysis. We applied this correction factor throughout the follow-up period.

We calculated annual cumulative pregnancy probabilities through 10 years using lifetable methods (monthly intervals), stratified by sampling stratification variables and weighted for sampling and nonresponse [12,13]. To be comparable in methodology to other research on sterilization failure [15], we did not censor women on age or menopause. Unlike our earlier analysis, the choice of age groups for this final analysis was data-driven. We divided women into three age groups, such that each age group included about one third of the women, an approach similar to that taken by researchers of the US Collaborative Review of Sterilization (CREST). Standard errors were computed by Greenwood's method [16], modified to handle weighted and stratified observations and pregnancy corrections. We used SAS system 9.1 (Cary, NC) and SUDAAN v8.0.1 (Research Triangle Institute, Research Triangle Park, NC).

We compared our estimates of quinacrine failure with published estimates of failure from tubal ligation, as reported by the CREST [15], and with estimates of quinacrine sterilization from Chile [9]. In the CREST effort, the investigators established a cohort of over 10,000 women who underwent tubal sterilization in the 1970s and 1980s. For comparisons, we used the subset of this cohort (n=2267) who had undergone laparoscopic bipolar electrocoagulation [15,17]. Bipolar electrocoagulation was the most common interval technique in the United States in the early 1990s when quinacrine was used in Vietnam [18]. It should be noted that improvements in bipolar technique during and since the CREST study have been identified that should reduce its pregnancy rate, assuming that they are adopted by all providers [17]. In the Chilean study, most women were sterilized at a single clinic in Santiago, and periodic follow-up visits have been ongoing since the late 1970s [9].

As explained in our previous report [12], we reviewed original logbooks of the quinacrine procedures and discovered that 23% of participants in our cohort received oral papaverine at the time of the procedure. Papaverine was used to reduce uterine cramping, and it is conceivable that this may have relaxed the fallopian tube ostia to permit more quinacrine into the fallopian tubes. In our previous article, an exploratory analysis showed that use of papaverine appeared to improve quinacrine's effectiveness. Thus, we will report quinacrine pregnancy probabilities for the subgroup of women who received papaverine.

3. Results

Participants in this cohort averaged 35 years of age at the time of the procedure and over 80% had at least four previous pregnancies (Table 1). Nearly 90% of the cohort was successfully contacted and interviewed during the last round (2002), and the average length of follow-up was 10 years. Over the follow-up period (14,294 cumulative person-years), 207 pregnancies were reported, including 88 menstrual regulations. After adjusting for unnecessary menstrual regulations, a total of 156 pregnancies contributed to the adjusted pregnancy probabilities reported below.

The cumulative first year probability of pregnancy after two insertions of quinacrine was approximately 3.3% (95% CI, 2.4–4.3) (Fig. 1). The cumulative probability increased over time with a probability of 12.1% (95% CI, 10.4–13.9)

Table 1
Baseline and follow-up information on participants who received two insertions of quinacrine (*N*=1335)

Age at insertion of quinacrine	
Mean (SD)	34.8 (7.7)
Median (min/max)	35 (25/48)
Number of pregnancies[a] *(% distribution)*	
2–3	16.5%
4–5	45.5%
6+	37.9%
Year of quinacrine insertion (% distribution)	
1989–1990	17.5%
1991	38.5%
1992	32.0%
1993	12.0%
Last year interviewed (% distribution)	
1994–1995	2.9%
1996–2001	5.9%
2002	91.2%
Length of follow-up (years)	
Mean (SD)	10.2 (3.6)
Median (min/max)	11 (<1/13)
Number of pregnancies for analysis[b]	156
Total number person-years of follow-up[c]	14,294

[a] At time of 1994 survey.
[b] Corrected for unnecessary menstrual regulations and rounded to nearest integer (see Materials and methods section).
[c] Includes any time after first pregnancy, if pregnancy occurred.

at 10 years, but most pregnancies occurred within the first three years. The 10-year pregnancy probability is approximately four times higher than after laparoscopic tubal sterilization (bipolar coagulation) as reported by CREST [15] but only about 36% higher than the rate of 8.9% reported in Chile [9].

Pregnancy probabilities varied by age at insertion (Fig. 2). Women who were under 33 years of age at the time of quinacrine insertion had pregnancy probabilities that were over three times higher than women who were at least 38 years of age. For the older age group, the 1-, 5- and 10-year cumulative probabilities of pregnancy were 1.2%, 5.1% and 5.9% (95% CI, 3.4–8.3), respectively. This age gradient is similar to the results seen in the CREST and Chilean studies. In the CREST study, women under 28 who had bipolar cautery had a 10-year pregnancy probability of 5.4%, while women 34 and above had a probability of 0.6%.

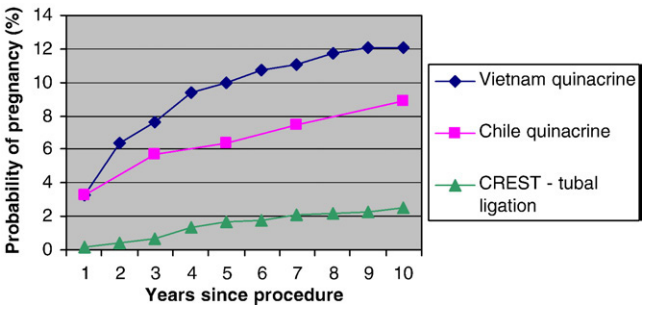


Fig. 1. Vietnamese quinacrine cumulative probability of pregnancy and estimates from Chile (quinacrine) and CREST (tubal ligation).

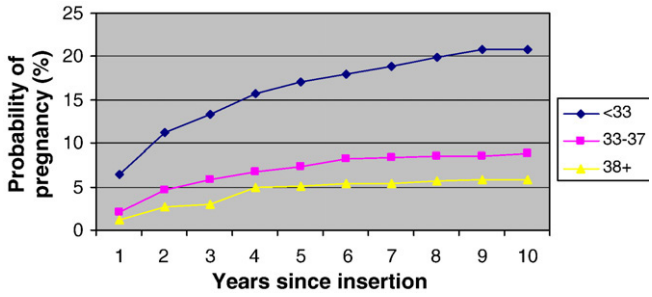


Fig. 2. Cumulative quinacrine pregnancy probabilities by age at insertion.

In the Chilean study, women less than 35 had a 10-year pregnancy probability of 10.7% compared to a probability of 3.1% for women 35 and above.

Women who received oral papaverine had pregnancy probabilities that were about half that of other women in the cohort (Fig. 3); the 1-, 5- and 10-year cumulative probabilities of pregnancy for the papaverine subgroup were 1.6%, 5.0% and 7.2% (95% CI, 4.0–10.5), respectively.

4. Discussion

The pregnancy probabilities we report in this analysis were calculated in a manner to be comparable with data from Chile and from the CREST study. As noted in our previous publication, we used other available information in a sensitivity analysis to make different adjustments in the analysis of pregnancy probabilities. For example, using information on unreported abortions, the first- and 10-year pregnancy probabilities are estimated at 4.5% and 15.9%, respectively; these probabilities are about a third higher than the 3.3% and 12.1% we reported in Fig. 1. If we were to ignore all extraneous information on unreported abortions and suppress adjustments for unnecessary menstrual regulations, the uncorrected pregnancy probabilities are 4.9% and 15.8% at 1 and 10 years, respectively. We reported various estimates based on different ways of computing pregnancy probabilities for up to 5 years in our previous publication [12].

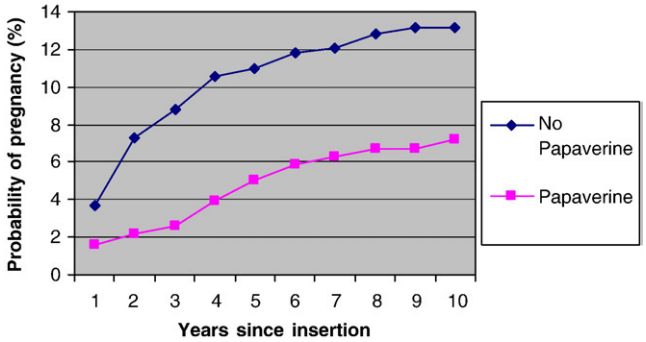


Fig. 3. Cumulative annual quinacrine pregnancy probabilities by papaverine use.

One of us (DTH) conducted an independent cross-sectional survey to estimate pregnancy probabilities after different sterilization methods in Vietnam [11], and found that 11.7% of women reported a pregnancy after two insertions of quinacrine. However, that result does not include any adjustment for unnecessary menstrual regulations. Based on a crude adjustment, a corresponding percentage for comparison with our result of 12.1% would be approximately 9.0%, which is similar to the 2-insertion, 10-year quinacrine pregnancy probability reported in Chile [9].

Although the results in Fig. 1 may underestimate the true pregnancy probability due to the occurrence of unreported abortions, the CREST results may also underestimate pregnancy probabilities for the same reason [15]. Using data from the US National Survey of Family Growth, researchers estimated that approximately 53% of abortions remain unreported during standard interviews [19]. Given that 27% of pregnancies in CREST resulted in induced abortion [15] and about a 50% underreporting of abortion in the US, CREST may have underestimated pregnancy probabilities by about 20%, but this would not substantially change the relative effectiveness of quinacrine vs. surgical sterilization. The lower pregnancy rates in older women are probably due to decreasing fecundity with age. A similar trend was observed in the CREST results [15].

On the other hand, some might argue, partly based on a critique of the quinacrine program in Vietnam by Hieu et al. [11], that we have overestimated pregnancy probabilities, despite our adjustment for unnecessary menstrual regulations. Many women who had postprocedure amenorrhea and who had not received adequate counseling may have assumed that the amenorrhea was due to a pregnancy. They would then have sought unneeded menstrual regulations. However, amenorrhea after quinacrine sterilization usually resolves after a few months, so it should only account for false reports of pregnancy during the first year after quinacrine procedures. Most of the pregnancies that we recorded occurred in later years. In addition, the observed difference in pregnancy probabilities by age group does not seem consistent with a major underestimate of unnecessary menstrual regulations.

In this article, we reported on women who underwent two separate quinacrine insertion procedures (N=1335); however, the complete Vietnamese cohort that we assembled includes an additional 1400 women who received only one insertion of quinacrine. Consistent with findings from our previous report, pregnancy probabilities are much higher after only one insertion (7.5% and 21.9% at 1 and 10 years, respectively); therefore, one insertion procedures are not recommended.

One reason for the wide variation in rates may be the use of different insertion techniques and different skill levels among physicians [20], with recent data [21] suggesting that use of the Hieu insertion technique might lead to lower pregnancy rates. As we reported previously [12], use of papaverine appeared to improve effectiveness. The findings of a recent animal study are suggestive that papaverine might have contributed to increasing quinacrine's effectiveness (K. Haneke, Family Health International, personal communication). However, papaverine may have been more commonly used by investigators who also used the Hieu insertion technique, developed by one of us (DTH).

The traditional technique developed by Dr. Zipper was based on the copper T (CuT) IUD insertion technique, and releases the pellets as the insertion tube is withdrawn; thus, the last few pellets are released nearer to the internal cervical os. The Hieu technique involves releasing all the quinacrine pellets at the fundus of the uterus. Data on the insertion technique itself were not recorded in the logbooks, but most of the women in this cohort are presumed to have had insertions done by the traditional CuT insertion technique, not the Hieu technique.

Some data suggest that the Hieu fundal release insertion technique may provide superior tubal sclerosing action compared to the CuT technique [21], while other data suggest that it may be important for women to remain supine after quinacrine insertion [6,21]. Unfortunately, there has been no randomized trial to evaluate the effectiveness of the Hieu technique compared with the traditional technique. If further clinical research were undertaken, it would be useful to consider randomized trials to evaluate the Hieu technique, the use of papaverine, the importance of remaining supine after quinacrine insertion, or other adjuncts to improve effectiveness.

Pregnancy probabilities with quinacrine in this cohort were higher than with surgical methods of sterilization, and slightly higher than among women in Chile who accepted quinacrine sterilization. The reason for the difference between pregnancy probabilities in Vietnam and Chile may be related to service delivery factors that were described by Hieu et al. [11]. Given the above issues, the efficacy rates reported here for the Vietnam program may not be generalizable, and higher efficacy rates might be possible in better controlled clinic environments.

FHI has recently decided not to pursue further research on quinacrine, partly because of the relatively high pregnancy rates after quinacrine compared to other contraceptive methods [22]. However, we remain convinced of the need for a safe, effective and low-cost method of nonsurgical sterilization.

Acknowledgments

This study was supported in part by Family Health International (FHI) with funds from an anonymous foundation. The views expressed in this article do not necessarily reflect those of the authors' institutions. FHI is an international not-for-profit organization that supports public health interventions and conducts research to improve health in developing countries. The authors wish to thank the study interviewers and staff of the Research Center for Rural Population and Health in Vietnam, and the District health

officials, and the Ministry of Health of Vietnam, without whose help this study could not have been completed. Thanks also to Robert Hanenberg who helped manage the study for FHI and to other FHI staff who worked on this study.

References

[1] Hastings-Tolsma M, Nodine P, Teal SB. Essure: hysteroscopic sterilization. J Midwifery Women's Health 2006;51:510–4.
[2] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 1980;18:275–9.
[3] Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception 1996;54:181–6.
[4] Lippes J, Brar M, Gerbracht K, Neff P, Kokkinakis S. An FDA phase I clinical trial of quinacrine sterilization (QS). Int J Gynaecol Obstet 2003;83(Suppl 2):S45–9.
[5] Bashir A, Bashir M, Afzal S. The effect of special training for quinacrine sterilization (QS) in Faisalabad, Pakistan: a report on an 1833-women subset of 11,000 cases. Int J Gynaecol Obstet 2003;83 (Suppl 2):S67–S71.
[6] Lu W, Zhu J, Zhong C, Zhao Y. A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China. Int J Gynaecol Obstet 2003;83(Suppl 2):S51–8.
[7] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. Lancet 1993;342:213–7.
[8] Randic L, Haller H, Sojat S. Nonsurgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen. Fertil Steril 2001;75:830–1.
[9] Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 2000;61:379–84.
[10] Suhadi A, Anwar M, Soejoenoes A. 10-year follow-up of women who elected quinacrine sterilization (QS) in Wonosobo, Central Java, Indonesia. Int J Gynaecol Obstet 2003;83(Suppl 2):S137–9.
[11] Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong LQ. The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases. Int J Gynaecol Obstet 2003;83 (Suppl 2):S77–S85.
[12] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. Fertil Steril 2000;74:1084–91.
[13] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. Fertil Steril 2000;74:1092–101.
[14] The Alan Guttmacher Institute. Sharing responsibility: women society and abortion worldwide. http://www.guttmacher.org/pubs/sharing.pdf, 1999 [Accessed October 20, 2007].
[15] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of SterilizationAm J Obstet Gynecol 1996;174: 1161–8 [discussion 1168–70].
[16] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980. p. 14–6.
[17] Peterson HB, Xia Z, Wilcox LS, Tylor LR, Trussell J. Pregnancy after tubal sterilization with bipolar electrocoagulation. U.S. Collaborative Review of Sterilization Working Group. Obstet Gynecol 1999;94: 163–7.
[18] Peterson HB, Hulka JF, Phillips JM, Surrey MW. Laparoscopic sterilization. American Association of Gynecologic Laparoscopists 1991 membership survey. J Reprod Med 1993;38:574–6.
[19] Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. Stud Fam Plann 2007;38:187–97.
[20] Sokal DC, Hanenberg R. Quinacrine family-planning method. Lancet 1994;343:1426–7.
[21] Ferreira CR, Magalhaes DR, Ferreira DC, Hanan MZ, Camargos AF. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women. Int J Gynaecol Obstet 2003;83(Suppl 2):S59–S66.
[22] Sokal D, Haneke K, Robinson E, Katz K, Dorflinger L. Reproductive Health 2007 Scientific Abstracts: FHI's decision to halt development of quinacrine: why and how (P48). Contraception 2007;76:173–4.

ELSEVIER

Contraception 78 (2008) 66–72

Contraception

Original research article

Safety of quinacrine contraceptive pellets: results from 10-year follow-up in Vietnam

David C. Sokal[a,*], Do Trong Hieu[b], Nguyen Dinh Loan[c], David Hubacher[a], Kavita Nanda[a], Debra H. Weiner[a], Trinh Huu Vach[d]

[a]*Family Health International, Research Triangle Park, NC, 27709, USA*
[b]*Director (retired), Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi JA00146B, Vietnam*
[c]*Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi JA00146B, Vietnam*
[d]*Research Center for Rural Population and Health, Hanoi JB01387C, Vietnam*

Received 29 January 2008; revised 14 February 2008; accepted 19 February 2008

Abstract

Background: This study was conducted to evaluate long-term safety of quinacrine pellets for nonsurgical sterilization among women in Vietnam.
Study Design: Observational cohort study of 2735 women who had quinacrine insertions between 1989 and 1993 compared to 1623 women who received an intrauterine device (IUD).
Results: Cumulative follow-up times for the quinacrine and IUD cohorts were 28,697 and 17,382 person-years, respectively, and losses to follow-up were 6% and 7%, respectively. Quinacrine users had a higher incidence of ectopic pregnancy compared to IUD users (risk ratio, 2.2; 95% confidence interval, 1.06–4.54); the risks of cancer, hysterectomy, pelvic/gynecologic surgery and death were similar in the two groups. Two quinacrine insertions appeared to lower the risk of ectopic pregnancy to that of surgical tubal occlusion.
Conclusions: Use of quinacrine in this cohort appeared to have minimal health risks. Other research, including preclinical studies, needs to be considered in an overall evaluation of whether the combination of safety and efficacy provide a basis for quinacrine's approval by appropriate regulatory agencies.

Keywords: Quinacrine; Tubal sterilization; Nonsurgical; Safety; Follow-up study

1. Introduction

Development of a safe, effective and technologically simple form of nonsurgical sterilization could provide women with another option to limit childbearing, particularly in areas where surgical procedures are not readily available. Insertion of pellets of quinacrine into the uterus to cause tubal occlusion was first reported as a method of nonsurgical sterilization in 1980 [1]. Since then, the method has undergone clinical testing in a number of different countries, including the United States, where three US Food and Drug Administration (FDA)-approved Phase I studies were conducted in the 1980s [2], and another Phase I study was completed in 2002 [3]. Although the basic approach has not changed much over the years, different quinacrine regimens have been used. The most widely accepted regimen involves inserting seven pellets, each with 36 mg of quinacrine dihydrochloride dihydrate, into the uterus using a modified intrauterine device (IUD) inserter. A single procedure delivers a total of 252 mg of quinacrine; a second procedure is done 1 month after the first to ensure a high rate of tubal sclerosis and occlusion.

In 1988, the Vietnamese government began offering quinacrine nonsurgical sterilization in select Ministry of Health programs [4]. An estimated 50,000 women sought and received quinacrine services in Vietnam before the program was halted in 1993 [5]. The program was stopped by the Vietnamese government because of safety issues, including a concern voiced by World Health Organization that quinacrine might be a carcinogen [6]. Quinacrine had

* Corresponding author. Tel.: +1 919 544 7040x232.
E-mail address: dsokal@fhi.org (D.C. Sokal).

0010-7824/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2008.02.011

been used in substantially higher doses prior to and during World War II for both long-term prophylaxis and treatment of malaria, so it had been presumed that the smaller doses and limited exposure in the uterus were safe. Since Vietnam halted its quinacrine program, mutagenicity studies and a neonatal mouse carcinogenicity study have been completed [7,8]. In the mutagenicity studies, quinacrine was found to be mutagenic in three of the four test systems. The results of the neonatal mouse study were difficult to interpret because the study found an increase in benign uterine polyps in female mice but not in any other types of tumors among either male or female mice.

The primary objective of this report is to provide cumulative safety estimates over 10 years for a variety of end points; our previous interim report provided 5-year results [9]. A companion article on contraceptive efficacy is published with this report.

2. Materials and methods

We recruited participants for this observational study from rural, northern provinces in Vietnam. A description of the recruitment, sampling and data collection methods, study populations, calculation of sampling weights and estimation of age at time of insertion is presented in the interim publications [5,9]. Briefly, we selected quinacrine acceptors and a frequency-matched sample of IUD acceptors (matched on province, district and 5-year age cohort) from contraceptive records from a 1994 retrospective survey. Although the1994 survey focused on issues of regret and informed consent, it did include limited information on health problems, which we used in the present analysis. In 1995, we began the long-term follow-up study consisting of women selected for the retrospective study. We had considered comparing quinacrine acceptors to a group of women who had had surgical tubal occlusion procedures; however, at that time, very few women in Vietnam had had surgical procedures. Thus, it would have been difficult if not impossible to identify women who had had surgical sterilizations in the same time frame as women who had had quinacrine insertions. The groups would have differed significantly in (1) time from the procedure to first interview and (2) length of follow up, potentially introducing various biases.

In addition to the women who had been in the 1994 survey, we included an expanded sample of women who had received only one insertion. We added this group because of concerns that women who had only one quinacrine insertion might experience increased risks of ectopic pregnancy and we wanted more statistical power to detect this difference. The expansion group consisted of all remaining one-insertion women in the sampling frame. The participants received quinacrine or an IUD between 1989 and 1993; thus, this report encompasses cumulative experiences that occurred over a period of 9 to 13 years for 2735 quinacrine and 1623 IUD users.

Since establishing the cohort, we attempted yearly interviews (1995–2002, inclusive) with each participant to review pregnancies and health problems. At each interview, participants (or their next of kin in the case of death) provided information on any health problems since the previous interview. The definition of a health problem was any problem that led a woman to see a health care provider or kept her from her usual activities for 2 days or more. Many of the reported health problems were minor. For serious health problems or health problems related to the reproductive system in which the diagnosis was unclear, Family Health International (FHI) staff (blinded to study group) requested that site physicians conduct follow-up interviews. For cases of ectopic pregnancy, hysterectomy, pelvic/abdominal operations, cancer or death, we requested any available medical records. We translated Vietnamese text describing health problems into English, and we coded medical problems using a dictionary of medical terminology developed by the FDA, Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART). Recently, COSTART was replaced by the Medical Dictionary for Regulatory Activities (MedDRA).

We compared IUD users to quinacrine users (both single and double insertions) with regard to the following primary safety end points: ectopic pregnancy, cancer and hysterectomy. As planned, we compared the risk of ectopic pregnancy for quinacrine acceptors who had received one vs. two insertions; for completeness, we compared these groups on the other two primary end points as well. Death was an end point for the interim analysis and is a planned secondary end point here. Pelvic/abdominal surgery was a post hoc secondary end point.

We made two changes in the definition of these end points since the interim analysis: (1) hysterectomy was redefined to exclude hysterectomies performed only because of pregnancy complications, for example, at the time of cesarean delivery; and (2) pelvic/abdominal surgery was redefined as surgery involving entry into the lower peritoneal cavity and not including hysterectomy, pregnancy-related surgery such as cesarean delivery or upper abdominal surgery such as cholecystectomy or gastric surgery. Some unblinding occurred before we narrowed our definitions of qualifying events for hysterectomy and pelvic/abdominal surgery.

We conducted a medical review of available data to determine end point status. We used data items, including text fields suggestive of end points, as identified from blinded clinician review, to select participants for review. Two physicians (KN and DTH) then independently reviewed all available data (including medical records) from these participants to determine if the end point had occurred. The medical review team assigned to this task was blinded to study group status; however, in few cases, quinacrine was mentioned in the clinical histories that they reviewed. During this review, we discovered that three cases of hysterectomy (all in the quinacrine group) were performed only because of pregnancy complications; in these instances, the events were

not considered hysterectomies for purposes of the end point analysis because of our desire to study the direct effects of quinacrine use.

Previously, we reported evidence of information bias: women in the one-insertion "expansion" group reported significantly fewer health problems than one-insertion women interviewed in the retrospective study [9]. This may have been due to differences in data collection and resulting recall of events. For the present analysis, we addressed this problem by evaluating, separately by end point, whether the risk of end point differed between women interviewed in the retrospective study vs. those who were not, controlling for group. If the differences were significant ($p \leq .20$, two-tailed), we adjusted for retrospective study participation in the primary analysis of the end point.

We computed cumulative life-table event probabilities (with 95% confidence intervals) and estimated standard errors using Greenwood's method [10], modified to account for differential sampling probability, nonresponse, and stratification. Quinacrine and IUD groups, and one- vs. two-insertion groups, were compared on the cancer and hysterectomy end points using discrete proportional hazards regression, controlling for age at insertion (the "improved" age measure that takes into account animal year of birth; see Ref. [5]). Because the retrospective study did not capture dates of ectopic pregnancies for IUD users, we used logistic regression and added length of follow-up as a covariate in the analysis comparing the quinacrine and IUD study groups. In comparing ectopic pregnancy for women with one vs. two insertions, we used Cox regression, controlling for age. We controlled for participation in the retrospective study, if necessary. We never planned to statistically compare groups on the secondary end point (death) because we anticipated few events. We could not statistically compare groups on the post hoc event category (pelvic/abdominal surgery) because the events were not reported in the first retrospective survey.

To put the risks of ectopic pregnancy in perspective, we compared our ectopic rates with published ectopic pregnancy rates of women who underwent tubal sterilization in the United States, as reported by the US Collaborative Review of Sterilization (CREST) [11]. We used two different published rates from CREST: any tubal sterilization technique and the subset who underwent bipolar electrocoagulation. In these comparisons, we did not manipulate or test for possible differences. It is important to note that an improvement in the bipolar electrocautery technique has been identified that could reduce its failure rate since the initial CREST data were published [12].

For other reported health problems that were not study end points, we reviewed 51 distinct events in the urogenital system and reported on a subset of those problems according to the following criteria: experienced by at least 1.0% of either study group or could arguably be sequelae of intrauterine exposure to quinacrine. In reporting these results, we did not do any statistical tests in comparing proportions by study group, that is, IUD vs. quinacrine. It should be noted that in our previous publication [9], we found quinacrine acceptors reported a higher rate of all types of medical problems, including many not plausibly related to quinacrine.

We used SAS software version 9.1 (SAS Systems, Cary, NC) and SUDAAN version 8.0.1 (Research Triangle Institute, Research Triangle Park, NC) to account for sampling design for all analyses. The analysis assumed stratified random sampling, with replacement (see previous publication for additional details). Percentages are weighted to account for differential sampling and nonresponse. P values are not adjusted for multiple comparisons.

3. Results

The present analysis is based on 4358 participants who were interviewed at least once (directly or by proxy). Of these, 1335 had received two quinacrine insertions, 1400 had one quinacrine insertion, and 1623 were in the IUD group. These groups differ slightly from those in the interim analysis because of new data (e.g., previously lost-to-follow-up participants who were interviewed or new information that affected participants' eligibility status and/or classification for number of quinacrine insertions). In some cases, missing or invalid dates of insertion precluded calculation of time to event.

Most of the study participants were between 30 and 39 years of age at the time of receiving the contraceptive method; age distribution was similar among the different study groups (Table 1), as expected by the sampling design that matched on age. Using the improved age value, the quinacrine group was older than the IUD group (median age of 35 vs. 33, respectively) (data not shown). Average length of follow-up was 10 years for each group, and marital and education statuses were also similar. Quinacrine users had had more live births than IUD users. Over 90% of participants in each study group were successfully interviewed during the final round in 2002–2003, and completion rates were comparable across groups.

With 28,697 cumulative person-years of observation, the quinacrine group experienced 36 hysterectomies, 23 cancers and 27 ectopic pregnancies. With 17,382 person-years of observation, the corresponding numbers of events for the IUD group were 12, 13 and 12 (Table 2). For secondary end points, the quinacrine group experienced 28 deaths and 41 pelvic/gynecologic operations compared to 11 of each event for the IUD group. Among the women with pelvic/gynecologic surgery, the most common indications for operations were ovarian cysts, appendicitis and fibroids (data not shown).

We found significant evidence of information bias for the ectopic pregnancy end point ($p < .0013$). Women who participated in the retrospective study were nearly six times more likely to report an ectopic pregnancy than

Table 1
Participant characteristics[a] by study group

	Study group							
	Quinacrine: two insertions (*n*=1335)		Quinacrine: one insertion (*n*=1400)		Quinacrine: total (*n*=2735)		IUD (*n*=1623)	
	n	(wt %)	n	(wt %)	n	(wt %)	n	(wt %)
Age at insertion[b]								
20–24	0	(0.0)	8	(0.5)	8	(0.1)	0	(0.0)
25–29	139	(10.2)	129	(9.0)	268	(9.9)	180	(10.1)
30–34	483	(36.2)	444	(31.9)	927	(35.1)	618	(35.2)
35–39	525	(39.7)	557	(40.1)	1082	(39.8)	684	(39.2)
40+	188	(13.9)	262	(18.4)	450	(15.1)	141	(15.4)
Mean	34.8		35.2		34.9		34.3	
SD	(7.68)		(4.57)		(6.29)		(4.41)	
Median	35		35		35		35	
Min/max	25/48		20/48		20/48		25/40	
Years from insertion to last interview (length of follow-up)								
<6	49	(3.7)	75	(5.4)	124	(4.1)	82	(5.1)
6–7	32	(2.4)	27	(1.9)	59	(2.3)	32	(1.9)
8–9	177	(13.3)	103	(7.5)	280	(11.8)	367	(22.2)
10+	1077	(80.7)	1195	(85.2)	2272	(81.8)	1142	(70.8)
Mean	10.2		9.6		10		10.2	
SD	(3.58)		(2.06)		(2.93)		(2.31)	
Median	11		10		10		10	
Min/Max	0/13		0/13		0/13		0/14	
Marital status[c]								
Married	1324	(99.2)	1343	(95.9)	2667	(98.3)	1592	(98.1)
Not married	7	(0.5)	10	(0.7)	17	(0.6)	23	(1.4)
Unknown	4	(0.3)	47	(3.4)	51	(1.1)	8	(0.5)
Education								
Illiterate	4	(0.3)	8	(0.6)	12	(0.4)	3	(0.3)
Primary school (1–5)	194	(15.0)	152	(11.6)	346	(14.1)	151	(10.4)
Basic school (6–9)	1000	(77.1)	1086	(80.8)	2086	(78.0)	1180	(75.1)
Secondary school (10–12)	77	(6.0)	78	(5.8)	155	(5.9)	147	(9.0)
Technical/vocational	19	(1.5)	14	(1.1)	33	(1.4)	56	(3.8)
College/university	2	(0.2)	2	(0.1)	4	(0.2)	22	(1.5)
Number of live births								
None	3	(0.2)	1	(0.1)	4	(0.2)	1	(0.1)
1	2	(0.1)	6	(0.4)	8	(0.2)	110	(6.5)
2	109	(8.1)	213	(15.5)	322	(10.0)	504	(29.9)
3	503	(37.7)	537	(39.7)	1040	(38.2)	526	(33.2)
4	422	(31.8)	390	(28.9)	812	(31.1)	295	(18.2)
5	191	(14.5)	131	(9.7)	322	(13.3)	119	(7.9)
6+	99	(7.5)	76	(5.7)	175	(7.0)	60	(4.1)
Final status:								
Completers[d]	1230	(92.1)	1301	(92.9)	2531	(92.5)	1486	(91.6)
Withdrew from study	15	(1.1)	14	(1.0)	29	(1.1)	21	(1.3)
Lost to follow-up[e]	90	(6.7)	85	(6.1)	175	(6.4)	116	(7.1)

[a] Percentages, means, medians and standard deviations are weighted for differential probabilities of selection and nonresponse. Frequencies are unweighted. Includes only women interviewed at least once.
[b] As reported in the original logbooks used in the sampling frame.
[c] As reported during the 1994 interview. If not available, then during long-term study.
[d] Interviewed in 2002 or known to be deceased.
[e] Does not include 94 (3%) quinacrine and 34 (2%) IUD users who were selected for the study but never interviewed.

women who had not participated, controlling for study group (Table 2). Further investigation revealed that this result was not necessarily isolated to the one-insertion expansion group and did not appear to be a function of differences in data capture but rather of some difference between the samples of women themselves. Unfortunately, extensive analysis did not uncover the source of these differences within available data (analysis not shown).

Neither hysterectomy nor cancer risks among quinacrine users were significantly higher compared to the IUD groups (Table 3). The 10-year cumulative probability of hysterectomy among quinacrine users was approximately 1.1 events per 100 women [95% confidence interval (CI), 0.7–1.5] vs. 0.7 among IUD users (95% CI, 0.3-1.1); for cancer, the probabilities were 0.8 (95% CI, 0.4–1.1) and 0.7 (95% CI, 0.4–1.1).

Table 2
Number and percentage with given end point, by study group

Event	Study group			
	Quinacrine: two insertions (*n*=1335)	Quinacrine: one insertion (*n*=1400)	Quinacrine: total (*n*=2735)	IUD (*n*=1623)
	n (wt %)	n (wt %)	n (wt %)	n (wt %)
Primary end points				
Hysterectomy	14 (1.1)	22 (1.6)	36 (1.2)	12 (0.8)
Cancer	12 (0.9)	11 (0.8)	23 (0.9)	13 (0.7)
Ectopic pregnancy (total)	15 (1.1)	12 (0.9)	27 (1.1)	12 (0.7)
Women in retrospective study (*n*=3174)[a]	15 (1.2)	8 (2.0)	23 (1.2)	12 (0.7)
Women not in retrospective study (*n*=1184)[b]	0 (0.0)	4 (0.4)	4 (0.4)	0 (0.0)
Secondary end point				
Death	12 (0.9)	16 (1.1)	28 (0.9)	11 (0.6)
Post hoc end point				
Other pelvic or gynecologic operation	22 (1.7)	19 (1.3)	41 (1.6)	11 (0.8)
Person-years of observation[c]	14,294	14,403	28,697	17,382

Percentages are weighted for sampling and nonresponse.
[a] 1268 with 2 insertions, 408 with 1 insertion and 1498 IUD participants.
[b] Women not in the initial retrospective study (67 with two insertions, 992 with one insertion and 125 IUD participants).
[c] Accumulated time between initiation of contraceptive method and last interview.

The risk of ectopic pregnancy was significantly higher in the quinacrine group compared to the IUD group (odds ratio of 2.2, 95% CI of 1.06–4.54), after controlling for participation in the retrospective study (Table 3). When we separated the quinacrine group by number of insertions, women who had had only one quinacrine insertion appeared to have a higher 10-year cumulative probability of ectopic pregnancy (2.2 events per 100 women; 95% CI, 0.9–3.6) than women who had two insertions (1.2 events per 100 women; 95% CI, 0.6–1.8) (Fig. 1); this difference, however, did not reach statistical significance ($P = .079$).

Twenty-one other health problems met the criteria for reporting, and quinacrine users generally reported more problems than IUD users (Table 4). Salpingitis, menstrual disorders and colitis were the most common problems found in both groups. With regard to reported partial or complete intestinal obstruction, two of the seven cases led to surgical interventions, and five resolved with medical treatment. Five of the seven women had had surgical procedures after their quinacrine administration and before the reported obstruction: two for ectopic pregnancies, one hysterectomy for fibroids, one tubal sterilization and one case of pelvic inflammatory disease with peritonitis. The other two women's diagnoses of intestinal obstruction were attributed to *Ascaris lumbricoides*, an intestinal parasite. One of these women had had surgery for *Ascaris*-associated obstruction about 10 years prior to quinacrine insertion and reported persistence of occasional symptoms of obstruction. The other woman was treated medically and recovered without operation.

Table 3
Risks ratios (and 95% CI) of primary safety end points: quinacrine (*n*=2735) relative to IUD users (*n*=1623)

Event	Risk ratio[a] (95% CI)	p Value
Hysterectomy	1.40 (0.63–3.11)	.41
Cancer	1.22 (0.57–2.63)	.60
Ectopic pregnancy	2.2 (1.06–4.54)	.03

[a] For ectopic pregnancy, odds ratio using logistic regression controlling for length of follow-up, age at insertion and participation in retrospective study. For other events, hazard ratio is used, controlling for age at insertion.

4. Discussion

This study suggests that exposure to quinacrine results in a low risk of subsequent health problems. Rates of hysterectomy, cancer, and death among quinacrine users were similar to IUD users. The risk of ectopic pregnancy among quinacrine users was twice that of IUD users, although the 10-year cumulative probability of ectopic (1–2%) was similar to the risks after tubal sterilization

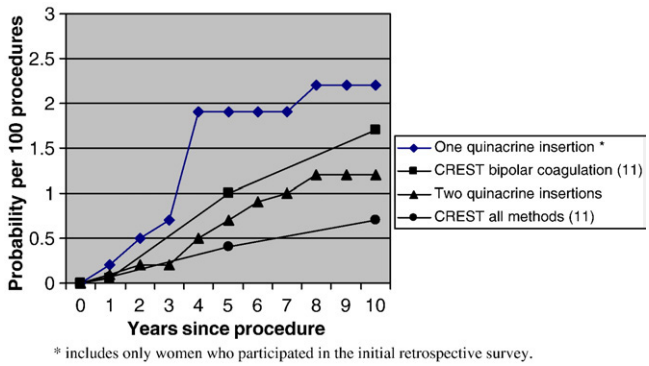


Fig. 1. Cumulative probability of ectopic pregnancy, by type of sterilization. *Includes only women who participated in the initial retrospective survey.

Table 4
Proportion of women reporting selected health problems[a], by study group

Health problem	Quinacrine (*n*=2735)		IUD (*n*=1623)	
	Wt %	*n*	Wt %	*n*
Abdominal pain	0.37	10	0.29	5
Amenorrhea	0.02	1	0.00	0
Appendicitis	0.68	17	0.31	3
Cervicitis	1.91	48	0.85	15
Colitis	2.56	67	1.08	17
Dysmenorrhea	2.11	49	0.63	11
Dyspepsia	0.52	14	0.34	6
Endometritis	1.16	30	0.52	9
Enterocolitis	0.02	1	0.00	0
Gastrointestinal disorder	0.22	6	0.12	2
Hypomenorrhea	0.13	3	0.06	1
Intestinal obstruction	0.35	7	0.00	0
Kidney calculus	1.36	36	0.84	14
Menorrhagia	0.52	15	1.00	15
Menstrual disorder	2.71	66	1.22	20
Pelvic pain	0.23	6	0.11	2
Peritonitis	0.05	1	0.00	0
Salpingitis	3.02	81	1.33	22
Urethritis	1.02	25	0.23	4
Urinary tract infection	2.10	51	1.01	15
Uterine fibroids enlarged	1.83	46	1.15	14

[a] Urogenital health problems that constituted a minimum of 1% in either study group or other health problems that, from clinical judgment, could be associated with quinacrine exposure. Women are counted only once in each category irrespective of the number of episodes they may have reported.

(bipolar coagulation technique), as performed in the United States about 20 years ago. Published estimates from the CREST study (Fig. 1) show that the ectopic risks for bipolar coagulation (as typically performed in the late 1970s and 1980s in the United States) are similar to two insertions of quinacrine, while the CREST estimate that includes all methods of tubal sterilization is lower [11].

Due to limitations in our study, we could not fully evaluate whether quinacrine increases the risk of subsequent pelvic/abdominal operations. We tabulated the frequency of 21 other health problems, most of which were more commonly reported by quinacrine users compared to IUD users. None of these problems were frequent enough to cause alarm over the safety of quinacrine. Since the interim analysis found that women who had had quinacrine were significantly more likely to report all types of medical problems — not just gynecologic problems — the differences between the groups are difficult to interpret and may be attributable to recall bias.

In the interim report [9], we reported the frequency of salpingitis. As others have noted [13] however, salpingitis is difficult to diagnosis correctly and is generally an unreliable clinical outcome for research purposes, especially when it is diagnosed on an outpatient basis, as most of these were. Given that we also found an increased rate of reporting of all types of medical problems by quinacrine users compared to IUD users at the interim analysis, we do not feel that this study provides valid evidence of an increased risk of salpingitis after quinacrine insertion.

This study has two important limitations that make it difficult to generalize the findings to other settings. First, it was an observational study comparing women who chose two very different contraceptive methods: quinacrine, a permanent method, and the IUD, a reversible method. Second, we were not able to obtain hospital records for study end points for many women, and thus some of the data are not confirmed by medical record review. This limitation is also shared by the CREST study. The main strength of this study is its long duration of follow-up and systematic annual interviews, including a second interview to collect more detailed data on study end points.

Although we report cancer rates in this article, prospective cohort studies are not the best tools to evaluate cancer risk. Gynecologic cancers are relatively rare events and require many years of observation to tally a sizable number for analysis. A recently completed case-control study of gynecologic cancers, also conducted in northern Vietnam, is focused on evaluating the potential cancer risks of quinacrine use; results of that study should be available in the coming year. Past research on the association between cancer and quinacrine use in humans found no conclusive evidence of a link [14].

We identified 27 ectopic pregnancies among the quinacrine users; this translates into a rate of approximately 0.9 events per 1000 women-years. Our estimate is about three times higher than that provided in another quinacrine report from Vietnam [15]. In that study, researchers identified cases of ectopic pregnancy by reviewing hospital records, interviewed the patients at their homes to find out if they had been sterilized with quinacrine prior to the ectopic pregnancy and estimated total quinacrine women-years of exposure (including women without ectopic pregnancies) in the participating provinces to derive their estimate of the rate. In that study, the rate of ectopics in quinacrine users was lower than the rate among IUD users. Given the dissimilar approaches to estimating the rate of ectopic pregnancy among quinacrine users, it is not surprising that rates from our study are different from theirs. However, the difference in the relative rates between IUD users and quinacrine users is more difficult to explain and could reflect either an under-ascertainment of ectopics among IUD users in our study, random variation or other unknown biases.

Using a similar methodology to ours, ectopic pregnancy rates among quinacrine users in Chile [16] were estimated to be approximately 30–50% lower than our rates. Age at the time of the sterilization procedure is an important variable determining risk of ectopic pregnancy. Although not reported above, women in our study who were less than 35 years old at the time of the procedure had a sixfold higher cumulative 10-year rate compared to women who were 35 years and older at the time of the procedure, a finding that is similar to the Chilean results.

Given the safety profile of IUDs, the recruitment of IUD users as a comparison group should be considered a conservative, "worst-case" approach in terms of evaluating the safety of nonsurgical sterilization. Many women are dissatisfied with IUDs due to side effects, mostly increased menstrual pain and bleeding, and would prefer a permanent method. However, many women are afraid to undergo surgical procedures due to the potential complications, which may occur more frequently in low-resource settings. Others do not have access to affordable surgical services. A comparison of quinacrine nonsurgical procedures vs. surgical tubal sterilization procedures would probably have shown significant safety advantages for quinacrine over a surgical procedure as suggested by a cross-sectional study by Hieu et al. [4]. However, FHI has decided not to pursue research to support FDA review of a quinacrine method, partly due to concerns from results of a two-year rat carcinogenicity study (unpublished data). Further research is needed on other low-cost approaches to nonsurgical sterilization.

Acknowledgments

This study was supported in part by FHI with funds from an anonymous foundation. The views expressed in this article do not necessarily reflect those of the authors' institutions. FHI is an international not-for-profit organization that supports public health interventions and conducts research to improve health in developing countries. The authors wish to thank the study interviewers and staff of the Research Center for Rural Population and Health in Vietnam, and the District health officials, and the Ministry of Health of Vietnam, without whose help this study could not have been completed. Thanks also to Robert Hanenberg who helped manage the study for FHI and to other FHI staff who worked on this study.

References

[1] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 1980;18:275–9.

[2] Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. Contraception 1996;54:181–6.

[3] Lippes J, Brar M, Gerbracht K, Neff P, Kokkinakis S. An FDA phase I clinical trial of quinacrine sterilization (QS). Int J Gynaecol Obstet 2003;83(Suppl 2):S45–9.

[4] Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong LQ. The acceptability, efficacy and safety of quinacrine nonsurgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases. Int J Gynaecol Obstet 2003;83 (Suppl 2):S77–S85.

[5] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. Fertil Steril 2000;74:1084–91.

[6] Hieu DT. Quinacrine method of family planning. Lancet 1994;343: 1040.

[7] Clarke JJ, Sokal DC, Cancel AM, et al. Re-evaluation of the mutagenic potential of quinacrine dihydrochloride dihydrate. Mutat Res 2001; 494:41–53.

[8] Cancel AM, Smith T, Rehkemper U, Dillberger JE, Sokal D, McClain RM. A one-year neonatal mouse carcinogenesis study of quinacrine dihydrochloride. Int J Toxicol 2006;25:109–18.

[9] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Huu Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. Fertil Steril 2000;74:1092–101.

[10] Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980. p. 14–6.

[11] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of ectopic pregnancy after tubal sterilization. U.S. Collaborative Review of Sterilization Working Group. N Engl J Med 1997;336: 762–7.

[12] Peterson HB, Xia Z, Wilcox LS, Tylor LR, Trussell J. Pregnancy after tubal sterilization with bipolar electrocoagulation. U.S. Collaborative Review of Sterilization Working Group. Obstet Gynecol 1999;94: 163–7.

[13] Jacobson L, Westrom L. Objectivized diagnosis of acute pelvic inflammatory disease. Diagnostic and prognostic value of routine laparoscopy. Am J Obstet Gynecol 1969;105:1088–98.

[14] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. Fertil Steril 2000;74:169–71.

[15] Hieu DT, Luong TT. The rate of ectopic pregnancy for 24,589 quinacrine sterilization (QS) users compared to users of other methods and no method in 4 provinces in Vietnam, 1994–1996. Int J Gynaecol Obstet 2003;83(Suppl 2):S35–S43.

[16] Feldblum PJ, Hays M, Zipper J, Guzman-Serani R, Sokal DC. Pregnancy rates among Chilean women who had nonsurgical sterilization with quinacrine pellets between 1977 and 1989. Contraception 2000;61:379–84.

Contraception 2006 Apr;73(4):433-6.

Sonographic recognition of three cases of septate uteri diminishes failures of quinacrine sterilization

C R C Ferreira[1], D R B Magalhaes, J Lippes
Affiliations expand

- PMID: 16531181
- DOI: 10.1016/j.contraception.2005.09.002

Abstract

Aim: Using sonography, the bicornate and septate uterus as causes of failure of quinacrine sterilization (QS) are explored. Whether QS can be effectively performed on women with a bicornate or septate uterus is a question answered by a presentation of three such cases.

Methods: Three cases presented were part of a prospective nonrandomized study of QS in 205 women requesting sterilization at the Family Planning Clinic, School of Medicine of the Federal University of Minas Gerais, Belo Horizonte, Brazil. Sonography was performed on all patients before, during and after QS. Quinacrine was packaged as seven pellets in a modified Copper-T IUD inserter (Sipharm, Sisseln, Switzerland). Each woman received the first transcervical insertion of 252 mg of quinacrine during the follicular phase of the menstrual cycle, usually immediately after menses. One month later, a second insertion was similarly performed. Patients were advised to use an alternate method of birth control for 12 weeks to allow time for scarring of the oviducts. A blood pregnancy test was done before the QS procedure.

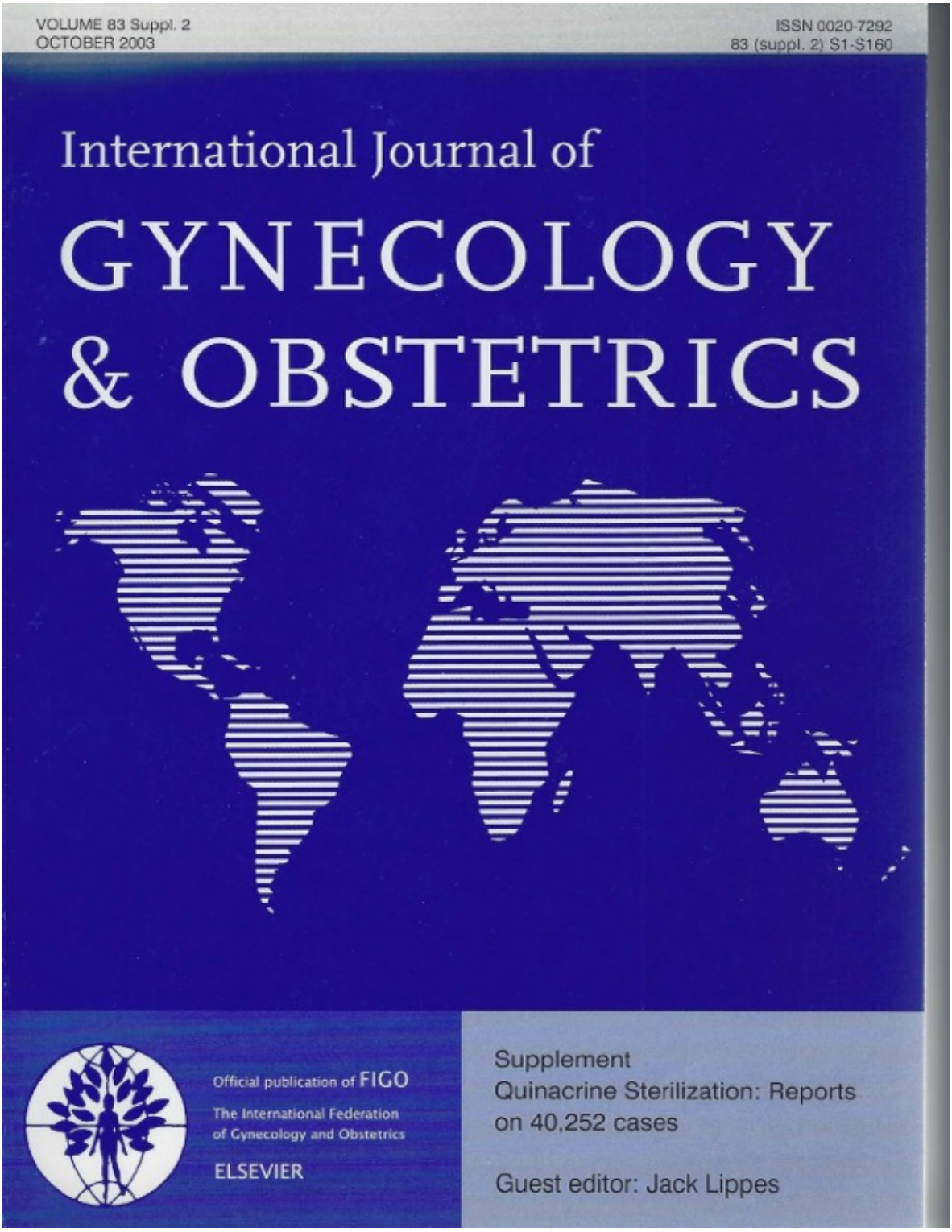
Results: The diagnosis of a septate or bicornuate uterus was made by sonography in three of the 205 patients in the study. It was obvious that quinacrine had to be inserted into the two horns of such an anomalous uterus if the dissolved drug was to enter both fallopian tubes. Quinacrine dissolved into "lakes of quinacrine," and sonographically could be seen at the top of the uterine fundus. For this clinical trial of 205 patients, there were 546 woman-years of follow-up, and the Pearl index was 0.73 per 100 woman-years (95% confidence limits: 0.02, 1.4).

Conclusions: The bicornate or septate uterus can be a cause of failure of QS if undetected. Advantages of sonography prior to, during and after QS are apparent in the three patients with septate uteri. Sonography is advantageous when performing QS by demonstrating an anomaly of the uterus, which required separate insertions of quinacrine into each horn of a septate uterus and helping to direct quinacrine into each horn of these anomalous uteri.

Section 2: Human Studies (2003)

(Review of 40,252 cases)

International Journal of Gynecology and Obstetrics 83 Suppliment; Cover



International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S3–S5

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

Forward

Jack Lippes

Guest Editor

This Supplement provides an update on the extensive quinacrine sterilization (QS) research referenced and reported on in the 25 articles from 15 countries we have included. They reinforce evidence of QS safety, effectiveness and possible innovations to improve efficacy.

Safety, the acid test of initiating trials among rural indigenous practitioners proposed by Zipper and Kessel, is discussed in articles by Pal and Roy revealing the safety of QS in their hands and the advantage of long-term follow-up in rural practices. The ease of dissemination of knowledge of QS in such local communities is also noted. The extended monitoring of Sarin's study among high risk women provides additional evidence of safety of QS while illustrating the need for a nonsurgical method of sterilization.

Hieu offers a rare opportunity to compare safety of three sterilization methods: QS, tubectomy and vasectomy in Vietnam. In an additional report Hieu demonstrates similar rates of ectopic pregnancy for QS and tubectomy. It is clear now that QS is safer than tubectomy and even vasectomy as performed in Vietnam. The question of QS efficacy remains.

The long-term follow-up of Bhatt's trial enables us to be assertive regarding any remaining reproductive risks post-QS concerning safety and efficacy. It appears from this report and others of extended patient monitoring by Sarin, Pal and Roy that late pregnancy failures are less likely for QS than for tubectomy. This brings total lifetime pregnancy risk of QS into a range similar to some accepted tubectomy techniques.

Saroodi-Moghaddam and Alpizar document the fact that hysterosalpingograms (HSG) will increase pregnancy failure of QS and should be avoided.

Hieu explains that the higher than expected pregnancy failure rate of the Vietnam field trial was due to readily available menstrual regulation (MR) procedures, without confirmation of pregnancy. This is important because delayed menses is a common side effect of QS.

It appears from these reports that the involvement of clinicians using QS leads to innovative views for improving efficacy of QS and even challenging discarded techniques. Of considerable interest is the work of Ferreira, visualizing the "lake of dissolved quinacrine" and formation of the intratubal scar by ultrasound. The application of this technique in the FDA-approved phase I trial provided a lead for predicting efficacy by size of the formed scar. The work of Pal in increasing the dose of quinacrine for younger, more fertile women and decreasing dissolution time of pellets are interesting leads for further research toward improved efficacy. The report of Roy suggests deposit of pellets at the cornual areas might improve efficacy.

Lu in China provides comparative data showing improved safety of QS over tubectomy, the similarity in efficacy of the two methods and an innovative approach to reversal of QS for future investigation.

The effect of clinician training in proper insertion technique is dramatically seen in the report of Bashir. This largest single insertion QS experience brings into question whether a second insertion is essential in all circumstances. The use of ultrasound to evaluate the QS scar may eventually determine this decision.

These reports further document the established safety of QS and a better understanding of efficacy issues. But there are many remaining unknowns to be explored. The molecular characteristic of quinacrine that induces inflammation and a scar in only two

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

tissues, the pleura and the mucosa of the fallopian tube, is yet to be clarified. The difference in timing of pregnancy failures between QS and tubectomy is poorly understood. Better knowledge of these basic questions might lead to adjuvants to improve the efficacy of both QS and tubectomy. How relevant is the position of patients after quinacrine pellet insertion to the success of the procedure? Does this depend on different positions of the uterus in the pelvis? Evaluation of the QS scar as a predictor of efficacy is a matter of urgency. While *in vitro* fertilization is still an option for reversal of QS, further research should be addressed to opening its occlusive scar. All this critical research should be a high priority for the improved health of women everywhere.

What we know

- Quinacrine sterilization (QS) is safe, effective, easily performed and low in cost.
- Acceptability is high. When QS is offered simultaneously with surgical sterilization, QS is preferred ten to one over surgical techniques. If you want people to use a service it must be made available. Secondly, they must be aware of it.
- QS scars can be seen on ultrasound.
- Hysterosalpingogram (HSG) to determine tubal patency after QS may blow out the scar, thus defeating the purpose of the sterilization procedure.
- We know zinc plays a role in inhibiting some enzymatic reactions and diminishes the effect of the quinacrine's action on the zinc-rich endometrium.

What we do not know

- How does quinacrine work?
- On a molecular biological basis we do not understand how quinacrine produces inflammation and scars.
- Do the anatomical positions of patients make a difference in efficacy?
  - Standing up.
  - Lying down. Will this reduce failures?
  - Trendelenberg position. Would pillows placed under the patient's hips to elevate the pelvis help to assure that quinacrine flows into the lumen of the oviduct?
  - For patients with a retroverted uterus, would lying on the abdomen facilitate the entrance of quinacrine into the tubal ostia?
- What is the value of ultrasound to QS?
  - Is immediate observation through ultrasound of the lake forming when quinacrine pellets dissolve significant in predicting or improving results?
  - Can the size of the scar as measured by ultrasound be a predictor of possible failure? If so, patients must be warned that a small scar might result in failure.
  - If a small scar is seen, would a third insertion of quinacrine produce a large scar?
  - When using sonography, which way do we see scars more efficiently? By transvaginal ultrasound (TVU), or by transabdominal ultrasound (TAU)? Should we do both routinely when ultrasound is available? Should ultrasound be limited for investigational use only? In the end will sonography be of any help, or make no difference in how we manage QS patients?
  - Is there a compound, to be added to quinacrine, that would make it more echogenic so that scars could be more easily seen on ultrasound?
- Drugs for pain relief?
  - How valuable are nonsteroidal anti-inflammatory drugs (NSAID) for relieving pain and cramps associated with QS?
  - Will an NSAID inhibit the inflammation and thereby inhibit scarring? Might this produce a higher pregnancy rate? Should we then rely on a drug other than an NSAID, such as acetomenophen?
- Is there an adjuvant to be added to quinacrine which would facilitate scar formation more rapidly and be more reliable when pellets are inserted? If such an improvement were forthcoming, will we be able to accomplish sterilization with only a single insertion? Are there better drugs than quinacrine?
- Will a muscle relaxant such as papaverine, taken orally, relax the muscles of the tube, and thereby allow more quinacrine to enter the tube and produce a better, more reliable scar?
- When is it advisable to do a third insertion?
  - Heavy bleeding. How much would indicate the necessity for a third insertion? How do we estimate blood loss?
  - Would a canal going through a scar seen on ultrasound, indicate a requirement for a third insertion? Is an alternate contraceptive indicated until we resolve the problem of recanalization seen on US?
- Can we develop a technique to reverse QS? Could

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S7–S11

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization: a retrospective

J. Zipper[a,*] and E. Kessel[b]

[a]*Department of Obstetrics and Gynecology, Sótero del Río Hospital, University of Chile, Santiago, Chile;*
[b]*Department of Public Health and Preventive Medicine, Oregon Health Sciences University, Portland, Oregon, USA*

Abstract

Objective: To trace development of quinacrine sterilization (QS). *Methods*: Review of published reports. *Results:* The high prevalence of septic abortion among high parity women in Santiago, Chile, motivated Zipper to find a safe, inexpensive method of non-surgical female sterilization. Various cytotoxic drugs were tried in rats. Because quinacrine was already accepted for intrapleural injection it was chosen for the first clinical trial. A slurry consisting of quinacrine and xylocaine was instilled into the uterine cavity with a transcervical syringe. Reasonable efficacy was noted and a limited scar of the intramural tube demonstrated. However, a side effect of cortical excitation and reports of 3 deaths ended this approach. Zipper and Wheeler hypothesized that the difficulty was due to rapid absorption of quinacrine under pressure and designed a pellet form that dissolves slowly and could be delivered transcervically using a modified IUD inserter. A standard protocol of 252 mg in seven 36 mg pellets placed at the uterine fundus on two occasions a month apart has now been widely used with considerable evidence for safety and efficacy. Indeed, protection is greater than 98% at 2 years of use. *Conclusion*: QS is ready for widespread use, especially where surgical sterilization is not safely available or when women are poor candidates for surgery or have such a fear of surgery that they will not seek surgical sterilization.

Keywords: quinacrine sterilization, female sterilization, contraception

1. Introduction

The motivation for developing a non-surgical method of female sterilization was initially the high prevalence of septic abortion seen in government hospitals in Santiago, Chile [1]. A majority of these patients were of high parity; they occupied an important segment of female ward hospital beds and accounted for a significant proportion of maternal mortality in Chile [2], estimated as 38.8% in 1963. In this predominantly Catholic country, contraception was not legalized until 1967, at the time of an International Planned Parenthood Federation conference in Santiago; but abortion remains illegal. Government hospitals to this day cannot accommodate the demand for an elective procedure such as surgical sterilization [3]. As a result, its prevalence in Chile remains low [4]. The same is true for such countries as Indonesia [5], Vietnam [6] and Egypt [7], for religious and political reasons despite their well-developed family planning programs. There is a great need for a less invasive method of female sterilization, especially one that could be safely performed in rural areas of developing countries at an affordable cost.

* Corresponding author. Tel.: 56-2-232-1712; Fax: 56-2-333-0801.

E-mail address: dzipper@entelchile.net (J. Zipper)

Correspondence address: El Comendador 2280, Providencia – Pedro de Valdivia Norte, Santiago, Chile.

2. Early animal experiments

Although transcervical sterilization techniques have been investigated for over a century, using silver

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

nitrate applied to the cornual angles of the tubal ostia [8] and electrocoagulation of the same areas [9], modern methods were initially described by Corfman in 1967 [10]. The experiments of Zipper and his coworkers [11] started with the use of cytotoxic compounds in rats. While some agents studied did have a pronounced effect on fertility, they were also known to be systemically toxic. Their research therefore turned to quinacrine [12] which, at a concentration of 200 mg/ml in distilled water, produced permanent occlusion of the uterine horn of rats. The fact that quinacrine was already clinically accepted for intrapleural injection for the treatment of repeated pleural effusion [13,14] led to a decision to try this compound clinically as a method of fertility control.

3. Quinacrine slurry studies

The first quinacrine slurry trial [15] used two concentrations of quinacrine of 125 mg/ml in 2 ml of distilled water for 85 cases and 250 mg/ml in 4 ml for 37 cases. Instillations were made during the proliferative phase of the menstrual cycle until there was evidence of tubal occlusion by CO_2 insufflation, or hysterosalpingogram. Three instillations were planned for the 125 mg/ml concentration and 2 for the 250 mg/ml slurry. An 88.2% tubal obstruction rate was seen for the 125 mg/ml group with a cumulative life-table pregnancy rate of 1.2% for obstructed cases at 31 months of use. The 250 mg/ml group had tubal occlusion of 84.3% and zero pregnancies among occluded cases. During this period, a few patients had hysterectomies and sections of their tubes were examined. These showed that the occlusive lesion was located in the intramural portion of the tube and extended for 2–4 mm. The muscular layer did not reveal important changes. No permanent damage to the endometrial mucosa was evident. The protective effect of zinc was also noted. A single complication of cortical excitation occurred in 150 quinacrine instillations. A few small quinacrine slurry trials were reported from Miami, Florida [16], Thailand [17], Jamaica [18] and Canada [19]. This experience was encouraging enough to pursue research on a larger scale, with potentiating agents to improve efficacy. Such a clinical trial by Zipper and his coworkers [20] suggested that xylocaine may improve efficacy.

This led them to conduct, in cooperation with the International Fertility Research Program (IFRP) [21], a clinical trial of slurry instillations in xylocaine involving 300 Chilean women. They used 3 instillations, the first two a month apart and the third at six months, with 1.5 g of quinacrine suspended in 5 ml of 2% xylocaine delivered in a 4 mm cannula and 10 cc syringe. Of an initial 300 cases recruited, 114 completed the third instillation and were followed for 13 to 24 months with a pregnancy failure rate of 7.1%; most of these failures (80.4%) occurred before the third instillation. Zipper's 1976 report concluded that a revised quinacrine instillation schedule was needed to improve efficacy and such trials were planned. However, reports of 2 deaths were noted in other experiences and when a third death was reported in Bangladesh, no further cases of the quinacrine slurry method were performed.

4. Quinacrine pellet method

After the decision to discontinue quinacrine slurry instillations, discussions between Zipper and Wheeler of the IFRP led to the hypothesis that cortical excitation and possibly fatalities with the quinacrine slurry method were due to rapid absorption of the slurry through endometrial capillaries and that this could be avoided by preparation of quinacrine in pellet form for its slow release without pressure. Furthermore, they believed that in pellet form, the dose could be greatly reduced, from 1500 mg to 250 mg, which would also lessen the risk of cortical excitation. Wheeler designed a simple method for preparing the pellets [22] which was first used clinically by Zipper [23]. Cortical excitation did not appear with the pellet method. Several prehysterectomy studies confirmed Zipper's previous impression [15] that damage to the intramural tube was limited [24–27]. A further study [28] initiated in 1977 in Santiago, Chile, with pellets made at the Pharmacy Department of the University of North Carolina, showed additional promise by 3 monthly insertions of 252 mg of quinacrine as pellets with a 12-month pregnancy failure rate of 3.1%. Shortly thereafter, a trial was initiated in Baroda, India, with similar encouraging results. This trial, with support of the IFRP, was later reported with 4 years' follow-up [29].

With these encouraging results, three different initiatives were set in motion. The IFRP prepared a proposal

for a United States Food and Drug Administration (FDA) approved trial [30], which included pharmacologic and toxicologic studies [31–34] to be conducted at the Johns Hopkins University in the early 1980s. At the same time, the International Federation for Family Health (IFFH) arranged for manufacture of quinacrine pellets in Taiwan and later in Switzerland. Supported with this supply the IFFH mounted a large number of clinical trials in developing countries [35-41]. The largest of these was conducted by the Ministry of Health in Vietnam [41].

Finally, in a meeting of the authors in the early 1980s in Chapel Hill, North Carolina, it was decided that a field experience was needed in rural regions of a developing country to determine the suitability of QS for areas of greatest need. As IFFH had a long-standing experience with the Indian Rural Medical Association (IRMA) in Calcutta, that organization was encouraged to introduce a network of its active members to the procedure. These were primarily homeopathic physicians practicing outside the urban confines of West Bengal. The training proceeded in 3 phases; first, in IUD insertions, second, in menstrual regulation and finally, in QS. Dr. Biral Mullick, Secretary General of IRMA, an obstetrician/gynecologist who had published [42] his own experience in QS, supervised this preparation. Approximately 100 rural-based clinicians received this instruction, and it is estimated that over 30,000 QS cases were performed in their private practices without a reported mortality. Their early experience was under IRMA-approved protocols [42–45], even before IRMA had accepted a standard protocol [46] for their service programs. Their experience is considered the acid test of QS safety, which was clearly established with no reported deaths or hospitalizations required for complications in over 30,000 cases. A report in 1996 [47] summarized the international experience of the first 100,000 cases of QS. In the same vein, long-term follow-up of early QS experience in Chile showed no evidence of increased cancer risk [48]. The risk of birth defects with QS was also estimated to be remote [49] and ectopic pregnancy risk is not higher than for surgical sterilization [50].

5. Progress in efficacy of QS

The original insertion techniques of quinacrine pellets followed IUD experience using a mid-intrauterine placement as for a Lippes Loop, or a vertical line of pellets from fundus to mid-uterine placement with the Copper T insertion technique. Hieu was the first to publish an insertion technique [41] that would place all pellets at the very top of the uterine fundus. Bairagi and his coworkers provided evidence for the superiority of the Hieu technique [45]. A wide experience since this report shows that almost all published reports using the Hieu technique have pregnancy failure rates below 2% at two years of use. Confusion occurred in the publication of an evaluation of the Vietnam field trial that showed a higher failure rate [51]; this was answered by Lippes in a letter to the editor [52]. It appears that pregnancy failure rates in the Vietnam trial were exaggerated by the availability of menstrual regulation for delayed periods, a recognized side effect of QS [35]. The true failure rate of the Vietnam experience remains unknown.

6. Future prospects

Despite a wide experience of QS demonstrating safety and reasonable efficacy using a standardized protocol [46], the method remains unaccepted by any government. It appears that without US FDA imprimatur of QS there is little chance of such sanction. For this reason, the IFFH and the Center for Research on Population and Security (CRPS) have encouraged FDA-approved trials in the USA, which have now been initiated by Dr. Jack Lippes as principal investigator. The need for QS as an option for American women has been described by Lippes [53], and certain American clinicians have begun to offer QS to their patients [54].

There is also current research [55] suggesting the possibility of identifying tubal closure after QS by ultrasound. This may not only improve efficacy but reduce the need for a second or third insertion in a high proportion of cases.

7. Conclusions

The original QS research in Chile continues to grow [56] and it has been joined by a wide international investigation. QS safety is thoroughly demonstrated

in long-term clinical experience in a wide variety of settings. There is a growing consensus [57] that the method should be made available to women where surgical sterilization is difficult to provide safely. Prospects for improved efficacy matching that of surgical sterilization appear likely. Final approval by the US FDA of QS is now the highest priority for contraceptive development.

References

[1] Hererra M, Rubio R, Krug A. Aborto septico, excluido el producido por el bacilus perfringens. *Rev Chil Obstet Ginecol* 1973; 38:176–186.

[2] Espinoza OM, Montesinos N, Muñoz H, Marchant L. Analisis de la mortalidad materna en Chile de 1981 y sus factores asociados según el certificado de defuncion. *Rev Chil Obstet Ginecol* 1984; 49:71–83.

[3] Menanteau-Horta D. Observations on female sterilization in Chile. *Bull Pan Am Health Organ* 1982; 16:101–110.

[4] Herrera M, Wells W, Araneda L, Moncada M. Female sterilization. Retrospective evaluation and perspectives in the central area of Santiago, Chile. *Rev Chil Obstet Ginecol* 1976; 40:61–71.

[5] Indonesia Central Bureau of Statistics (CBS), State Ministry of Population/National Family Planning Coordinating Board, Ministry of Health, Macro International Inc. (MI). Indonesia Demographic and Health Survey 1994. Calverton, Maryland: CBS and MI. 1995:76 (Table 5.2.2.).

[6] General Statistical Office. 1994 Inter-Censal Demographic Survey. Hanoi: Statistical Publishing House. May 1995.

[7] National Population Council (NPC), Macro International Inc. (MI). Egypt Demographic and Health Survey 1996. Calverton, Maryland: NPC and MI. 1997.

[8] Froriep R. Zur Vorbeugung der Nothwendigkeit des Kaiserschnitts und der Perforation. *Notizen Gebiete Natur Heilkunde* 1849; 211:9–10.

[9] Kocks J. Eine neue Methode der Sterilisation der Frauen. *Centralblatt Gynakologie* 1878; 2:617–619.

[10] Corfman PA. Transcervical Oviduct Occlusion. In: Advances in Planned Parenthood (Vol. 2). Amsterdam: *Excerpta Medica Int Congr Ser 138.* 1967; 183–187.

[11] Zipper J, Medel M, Prager R. Alterations in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. *Am J Obstet Gynecol* 1968; 101:971–978.

[12] Zipper J, Prager R, Medel M. Biological changes induced by unilateral intrauterine instillations of quinacrine in the rat: reversion through the use of estrogen and progesterone. *Fertil Steril* 1973; 24:48–53.

[13] Gellhorn A. The use of atabrine (quinacrine) in the control of recurrent neoplastic effusions. *Dis Chest* 1959; 39:165.

[14] Rochlin DB. The control of recurrent malignant effusions using quinacrine hydrochloride (Atabrine). *Surg Gynecol Obstet* 1964; 118:991.

[15] Zipper J, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil Steril* 1970; 21:581–589.

[16] Davidson OW, Wilkins C. Chemically induced tubal occlusion in human female following a single instillation of quinacrine. *Contraception* 1973; 7:333–339.

[17] Isranckun C, Phaosavadi S, Neuwirth RS, Richart RM. Clinical evaluation of quinacrine hydrochloride for sterilization of the human female. *Contraception* 1976; 14(1):75–80.

[18] Davidson OW. Quinacrine-induced tubal occlusion. In: Sciarra JJ, Droegemueller W, Speidel L, editors. Advances in Female Sterilization. Hagerstown: Harper & Row. 1976: 200–207.

[19] Benoit A, Melancon J, Gagnon MA. Chemically induced tubal occlusion in the human female using intrauterine instillation of quinacrine. *Contraception* 1975; 12(1):95–101.

[20] Zipper J, Stacchetti E, Medel M. Transvaginal chemical sterilization: clinical use of quinacrine plus potentiating adjuvants. *Contraception* 1975; 12:11–21.

[21] Zipper J, Medel M, Goldsmith A, Edelman D, Pastene L, Rivera M. The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization. *Int J Gynaecol Obstet* 1976; 14:499–502.

[22] Wheeler RG. Delivery systems for applying quinacrine as a tubal closing agent. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, editors, Female Transcervical Sterilization. Philadelphia: Harper & Row. 1983:105–115.

[23] Zipper J, Edelman D, Cole LP, Rivera M. Overview of clinical trials with quinacrine. In: Zatuchni, Shelton, Goldsmith, Sciarra, op. cit. pp. 94–99.

[24] Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM. Quinacrine-induced pathologic changes in the fallopian tube. *Fertil Steril* 1980; 33:666–667.

[25] Merchant NR, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40(1):47–54.

[26] El-Kady AA, Mansy MM, Nagib HS, Kessel E. Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. *Adv Contracept* 1991; 7:1–9.

[27] Sarin AR, Mohindroo A, Chandra P, Gill SS. Histologic changes in the fallopian tubes after lower doses of transcervical quinacrine insertion. *Fertil Steril* 1998; 70:Suppl. 1 (abstract p-121), S164.

[28] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:265–269.

[29] Bhatt R, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.

[30] Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. *Contraception* 1996; 54:181–186.

[31] Dubin NH, Parmley TH, DiBlasi MC *et al*. Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In: Zatuchni, Shelton, Goldsmith, Sciarra, op. cit. pp. 60–70.

[32] Blake DA, Dubin NH, Blasé MC, Parmley TM, Stetten G, King TM. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni, Shelton, Goldsmith, Sciarra, op. cit. pp. 71–88.
[33] Dubin NH, Blake DA, DiBlasi MC, Parmley TH, King TM. Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. *Fertil Steril* 1982; 38:735–740.
[34] Dubin NH, Strandberg JD, Craft CF, Parmley TH, Blake DA, King TM. Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry and hematology in cynomolgus monkeys. *Fertil Steril* 1982; 38:741–747.
[35] Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–151.
[36] Arshat H, Suan AE, Kim KS. Nonsurgical female sterilization with quinacrine pellets: Malaysian experience. *Malay J Reprod Health* 1987; 5:61–69.
[37] El Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59:301–304.
[38] El Sahwi S. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization. *Adv Contracept Deliv Syst* 1992; 8:151–159.
[39] Sarin AR. Quinacrine sterilization: experience among women at high risk for surgery. *Adv Contracept* 1999; 15:175–178.
[40] Soroodi-Maghaddam S. Preliminary report on a clinical trial of quinacrine pellet method for nonsurgical female sterilization in Iran. *Int Fam Plann Perspect* 1996; 22:122–123.
[41] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–227.
[42] Mullick B, Mumford SD, Kessel E. Studies of quinacrine and of tetracycline for nonsurgical female sterilization. *Adv Contracept* 1987; 3:245–254.
[43] Roy A. A 22-year experience with quinacrine sterilization in a rural private clinic in Midnapore, India: a report on 5 protocols and 1838 cases. *Int J Gynecol Obstet* 2003; 83 (Suppl 2):S87–S91.
[44] Pal SK. Quinacrine sterilization of 1997 women in Daharpur, Midnapore, West Bengal, India: a comparison of 3 protocols*Int J Gynecol Obstet* 2003; 83 (Suppl 2):S97–S100.
[45] Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization. *Adv Contracept* 1995; 11:303–308.
[46] Institute for Development Training. Female voluntary non-surgical sterilization: The quinacrine method. Module 12 of Training Course in Women's Health. Chapel Hill, North Carolina: IDT, 1996.
[47] Kessel, E. 100,000 quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.
[48] Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1988–1991. *Fertil Steril* 1995; 64:324–334.
[49] Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. *Adv Contracept* 1998; 14:81–90.
[50] Hieu DT, Luong TT. The rate of ectopic pregnancy for 24,589 quinacrine sterilization (QS) users compared to users of other methods and no method in 4 provinces in Vietnam, 1994–1996. *Int J Gynecol Obstet* 2003; 83 (Suppl 2):S35–S43.
[51] Sokal DC, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part 1: interim efficacy analysis. *Fertil Steril* 2000; 74:1084–1091.
[52] Lippes J. What is the future of quinacrine sterilization? (letter) *Fertil Steril* 2001; 75:1244.
[53] Lippes J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2002; 77:1106–1109.
[54] Whitney RB. Quinacrine sterilization (QS) in a private practice in Daytona Beach, Florida: a preliminary report. *Int J Gynecol Obstet* 2003; 83 (Suppl 2):S117–S120.
[55] Ferreira CRC, Magalhães DRB, Ferreira DC, Hanan MZ, Camargos AF. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women.*Int J Gynecol Obstet* 2003; 83 (Suppl 2):S59–S66.
[56] Zipper J, Trujillo V. 25 years of quinacrine sterilization experience in Chile: review of 2,592 cases.*Int J Gynecol Obstet* 2003; 83 (Suppl 2):S23–S29.
[57] Potts M, Benagiano G. Quinacrine sterilization: a middle road. *Contraception* 2001; 64:275–276.

a canula be pushed through the tubal ostia under hysteroscopic guidance and thus reverse the effect of QS?
- Will QS be affected when patients are on concomitant drugs for medical complications such as heart disease, asthma and diabetes?
- Does lactation have an effect on QS results?

The answers to these questions will be found when QS is in the hands of many physicians.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S13–S21

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS): the ethical issues

S. Bhattacharyya

School of Social Science, Philosophy and Religion, Buena Vista University, Storm Lake, Iowa, USA

Abstract

QS has generated debates that are ultimately grounded in various principles, norms, and values. Through a careful analysis of opposing arguments, this paper focuses on two ethical principles claimed by both sides, namely: respect for life and beneficence. Though issues surrounding QS are complex, from the common ground of these two principles, this paper proposes a course of action that addresses many of the concerns from both points of view.

Keywords: quinacrine sterilization, arguments pro and con, beneficence, respect for life, ethics

Fighting behind the banners of protection of women's health and their reproductive rights, overpopulation and poverty, organizations and individuals argue their positions for and against the use of quinacrine as a non-surgical form of female sterilization (QS). QS sparks heated debates rivaling those that accompany the issues surrounding abortion. Similarly, discussions regarding QS are often painted with bold "black and white", right/wrong distinctions. However, the issues themselves are complex and tightly intermingled with various political, sociological, economic and religious agendas. Unfortunately, when discussions are polarized and ideologies are set up against one another, a great deal of energy is often expended in the argument itself and those whose lives are affected continue to suffer. This paper is designed to provoke thoughtful reflections on the ethical issues relating to QS and the plight of women who can be most helped or harmed by its utilization.

* Tel: (712) 749-2181.
E-mail address: bhattacharyya@bvu.edu (S. Bhattacharyya)

Biomedical ethics is an inherently interdisciplinary field of inquiry, where we examine questions of morality: "What is right?" and "What ought to be done?" We also examine underlying principles and values. Ethical discussions and dilemmas highlight conflicts among competing goods, rights, principles and values. For example, proponents claim that QS is an option for reproductive freedom. They work to alleviate the high maternal mortality in the Third World, to address issues of overpopulation and to provide women throughout the world with the choice for non-surgical sterilization. On the other hand, QS opponents assert that their efforts are directed to protecting the rights of poor, often exploited groups, particularly women, and to preserve and maintain what they say is the integrity of medical research. While proponents argue that QS addresses urgent needs with a potential of minimal risk, opponents counter that the risks (not defined) which are associated with QS far outweigh any potential good. Thoughtful bioethical discussions begin with an understanding of the facts and of the various stakeholders[1] involved. Unfortunately, impassioned de-

[1] A stakeholder is any individual, local or international group or organization, that has an interest in, and is in some way involved with, the ethical issue under discussion.

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

bates between stakeholders involved with controversial issues such as abortion and QS often become a barrier to clear perception and determination of the facts.

What the stakeholders view as relevant "facts", and their positions regarding QS, are influenced by: familial, societal, political, economic and religious factors. These also affect the principles, norms and values upon which they ground their arguments for or against QS. In his discussion on sterilization, Robert Veatch observes, "Decisions pertaining to sterilizations, just like all other medical decisions, must be made in the context of a set of fundamental value orientations." [1] Veatch would argue that it is logically impossible to make decisions regarding medical treatments, such as QS, without examining the value orientation of the various stakeholders inherent in their culture and society. The polarizing discussions regarding QS reflect multiple political, religious, economic and other influencing elements, and lead to the possibility of multiple motivations and principles for actions relating to this method.

To comprehend the ethical issues in a situation requires insights regarding the facts and the stakeholders involved. After presenting their differing perspectives on QS, this paper carefully analyzes several arguments, both for and against QS. Both sides in the debates put forth claims ultimately grounded in similar principles, namely: a respect for human life and beneficence. By focusing on this common ground, we are led to an understanding of a range of perspectives and then arrive at a multifaceted solution that attempts to stand between the "ban" vs. "use" positions currently being put forth for QS.

Few, if any, "facts" – even scientific facts – are pure, objective entities. Often the answer to the question "What are the facts?" depends upon the relative position of the individual responding. One's perspective influences not only what are deemed the pertinent "facts" of the case under examination, but also how they are to be interpreted. Thus, prior to discussing the facts associated with QS, it is necessary to consider the stakeholders involved. Examination of the disparate organizations and individuals who are in one way or the other concerned with QS, reveals a complicated web of interconnected lives. They constitute a long list, including all women of the world, particularly impoverished women living in Third World villages with only limited access to and means for healthcare. The existence of these women and their families often gets caught among the ideological arguments regarding overpopulation, reproductive freedom, family planning and human rights. The Pope and the Roman Catholic Church are powerful stakeholders who fight through a commitment to what they term "natural law" to protect "the family" as they perceive it. Physicians working in rural villages, or in industrial cities like New York, represent stakeholders operating under any number of motivations: from a desire to provide female patients with reproductive choices to ambition for recognition in promoting governmental policies regarding the number of children a couple may have. Stakeholders are also found among government leaders, members of international medical organizations, such as the Association for Voluntary Surgical Contraception, the Congress of the United States of America, pharmaceutical companies, non-governmental organizations (NGO) and many others. Those within these groups are concerned about freedom, reproductive choices, and the health of women, their families and communities. This web of stakeholders includes women and men, old and young and individuals from all levels of society.

Such a diversity of stakeholders, not surprisingly, leads to a multitude of perspectives and ideas regarding what are and are not the correct/acceptable facts of QS. Despite all the controversy surrounding this procedure, there is general agreement over the historical development of quinacrine (atabrine, mepacrine hydrochloride) as an anti-malarial drug and the way in which it came to be utilized for non-surgical female sterilization [2]. Additionally, both those who support and those who oppose the utilization of QS agree that it is inexpensive, simple to administer, and does not require surgical facilities or the expertise of physicians. However, these three facts, along with others emphasized or ignored, are at the heart of the ethical controversies surrounding QS. Perceiving a need for an inexpensive, non-surgical form of sterilization, physicians from a number of countries conducted clinical trials (to date approximately 140,000 women have undergone QS). They concluded that QS is a safe and effective option for women who want no more children [3–7]. On the other hand, opponents, keenly aware of the historical abuse of sterilization, specifically in developing countries, are highly suspicious of QS. Abuse of anything can occur anywhere. Opponents question QS' primary use where the world's most vulnerable populations live.

They claim the success rate of QS is low, its side effects daunting, and that the potential for its abuse is simply too overwhelming to allow its use [8–10]. Although there is agreement that QS is inexpensive, easy to utilize and requires neither specialized equipment nor intensive training, there are a variety of disputes concerning the implications of these facts.

So here is a situation rife with disagreements regarding the facts associated with the method. Respected, peer-reviewed journals such as *Contraception*, *Fertility and Sterility*, the *International Journal of Gynecology & Obstetrics* and *Lancet*, have published the results of a number of QS clinical trials. The conclusions of Drs. Zipper, Hieu, Bhatt and others, all indicate that QS is successful in preventing pregnancies, with minimal side effects [11,12]. But Drs. Carignan and Pollack, journalist Alix Freedman, and others view the clinical trials with great suspicion. They insist that this research is invalid due to what they consider irregularities. They question the manner in which data were calculated, and take exception to the ability of the investigators to conduct adequate follow-up programs. According to them, "It is not possible to conclude quinacrine pellets are a safe, effective non-surgical method of female sterilization", because the results varied too widely. Questions have been raised regarding lack of informed consent and inability to conduct follow-up studies because the women are from rural areas and difficult to find. These opponents claim that QS has not yet been approved by the US Food and Drug Administration (FDA) and call for a halt in its use in humans until questions regarding QS safety and efficacy can be answered, and it receives FDA authorization. However, the FDA has approved a phase I trial of QS which was completed as of 30 April 2003. Ultimately, medical concerns aside, these individuals argue that the potential for abuse is simply too high to support the method.

Kessel, Mumford, Lippes and others, however, point out that quinacrine has been prescribed as an antimalarial for over 70 years and has been ingested in large doses by over 100 million people. In all these years, there has been no report of long-term side effects or any increase in cancer. They argue that quinacrine is in fact an FDA-approved medication, and utilizing it for QS is considered an "off-label" use. The toxicology testing and clinical trials available in the 1942 Winthrop Corporation publication indicate the safety of the drug. Proponents apply the results of these earlier tests to QS, arguing for its safety. Opponents reject this assumption and insist that the tests for the oral consumption of quinacrine are not applicable to its transcervical uterine administration for QS. In order to gain FDA approval specifically for the procedure, Family Health International estimates it would require eight years and eight million dollars [13]. Pharmaceutical houses usually provide the financial backing for drug testing. However, quinacrine is in the public domain and cannot be patented, thereby decreasing, if not removing altogether, the profit incentive. Perhaps it is for this reason, and the fear of litigation, that many of these companies are unwilling to conduct the studies and have even abandoned further research and development for contraceptives [14].

While Pollack, Freedman and others claim QS clinical trials lack follow-up studies, Suhadi, Soejoenoes, Bhatt, Sokal and others have conducted, and published, studies that monitored patients anywhere from 6 months to over 19 years following the procedure. Some of these studies reported a success rate of 97%. All the research has found that QS was a safe, effective, non-surgical form of female sterilization [15–17]. While proponents of QS maintain that past testing and current clinical trials are applicable and reliable, opponents reject these conclusions. These are but a few examples of the disputes concerning the facts relating to QS and how the positions of the stakeholders influence both their presentation and interpretation.

Having discussed the various stakeholders and facts, let us now examine several arguments for and against QS. Arguing against QS, Brinda Karat, general secretary of the All India Democratic Women's Association, claims that her group is fighting to assure respect for the lives of poor, uneducated Indian women by attempting to protect them from the possible harms of QS. According to Ms. Karat, QS in India is the product of white, imperialist men who are "motivated by a political agenda that smacks of racism", whose "politics are questionable" and whose bottom line is to control, if not exterminate the poor, vulnerable Third World populations, all for the better good of this planet. Ms. Karat led the call that resulted in India's governmental ban on QS. According to her, "Indian women are not guinea pigs to be used ... I don't think any doctor could ever believe that a drug without adequate testing should be used on human

beings." [18] This opposition to QS may be indicative of several influencing elements, political, economic and perhaps religious, to name a few. However, the opinion itself may be reflecting a sincere concern of many who fight to protect the lives of those often abused and overlooked, the poor and uneducated. Opponents maintain that past governmental actions regarding sterilization are deplorable and caution needs to be exercised as sterilization methods are proposed.

Dr. Naseem Rahman, a gynecologist who has performed over 3,000 QS procedures on women in Bangladesh, also fights for the lives of poor, uneducated women. However, her conclusions regarding QS are the antithesis of Ms. Karat's. Motivated by the urgency of the high rate of maternal mortality, overpopulation and the need for an accessible, inexpensive, non-surgical method of sterilization, she enthusiastically supports QS. When asked about the possible cancer risks with QS, Dr. Rahman responded: "She's [women living in the villages] probably going to die next year or the year after in childbirth. Do you still think she's bothered about cancer, which can take place – may or may not – after twenty or forty years? She won't live that long." [18] Due to the critical circumstances in which she functions, Dr. Rahman's response is pragmatic: perhaps additional FDA pharmaceutical testing could be done, but she is satisfied with the already published results. Her patients are suffering under a multitude of burdens and have requested sterilization. Because the current situation is characterized by insufficient funds, lack of trained surgeons and proper facilities (operating room, anesthesia etc), tubal ligations, the method of choice for women seeking sterilization in industrialized societies, are not feasible. According to Dr. Rahman, QS is a method of choice. If there was a full FDA approval, we would no longer need clinical trials or put another way – to gain FDA approval, we must have clinical trials.

Ms. Karat and Dr. Rahman are both stakeholders from the Indian subcontinent's elite; Ms. Karat is a politician and Dr. Rahman is a physician. Undoubtedly their positions regarding QS are influenced by various elements. Dr. Krishna Jafa, a physician working with others who support the use of QS, considers Ms. Karat's position a political reaction. Dr. Krishna Jafa admits she was skeptical about QS at first. However, after interviewing over one hundred women who underwent QS, discussing the side effects and their experiences, she concluded that QS was an appropriate option. She is convinced that the rationale for India's ban on QS was purely political and had nothing to do with science. When asked if QS may have had a different fate had it been distributed by an Indian woman's movement and not by two white American men, Dr. Krishna Jafa answered with a definite, "Yes, that's a forgone conclusion!" [18]

While Ms. Karat's position is criticized on political grounds, Dr. Pollack, president of EngenderHealth (formerly known as Association for Voluntary Surgical Contraception – AVSC), charges Dr. Rahman and others in favor of QS with setting a dangerous precedent regarding healthcare. Doing a risk/benefit analysis, Drs. Kessel and Mumford (the two above-mentioned "white, imperialist men") argue that developing nations "with low contraceptive prevalence, high population growth and high maternal mortality benefit greatly from increased contraceptive prevalence." Dr. Kessel, along with many others, cites the statistics: worldwide 500,000–600,000 women die each year from pregnancy-related complications. According to the World Health Organization (WHO), 98% of these deaths occur in developing countries [19]. With every maternal mortality, another fifteen women, men and children are left handicapped in some way. In view of the magnitude of these losses, Dr. Kessel argues that the benefits provided by QS far outweigh the possible potential risks. As far as Dr. Kessel is concerned the risks are minimal to nil. Dr. Pollack disagrees with this conclusion insisting "that [QS] sets up a big double standard for how we live in this world. It's like saying 'that's another world ... we don't have to be worried about quality or safety or efficacy over there'." [18] According to her, performing QS prior to its full FDA approval is unethical and setting a double standard of healthcare.

Dr. Pollack's comments indicate a disregard of the numerous published clinical studies on QS. Her comments also imply that there is equity in healthcare and its distribution. Although her desire for a worldwide healthcare system that is equal in its availability and distribution is a noble and ethical goal, her arguments against QS fail to acknowledge the realities of the great disparities in that care around the world. Consider the statistics cited above, that, while maternal deaths are rare in industrialized countries, they are a major

cause of mortality for women of childbearing age in the Third World [20]. In this context, is supporting QS promoting a double standard or addressing different realities? In the majority of situations world-wide, if individuals are gainfully employed, have some means and health insurance, then they have a greater access to healthcare than those who are unemployed, and have neither money nor coverage. Combining elements of Kant's categorical imperatives and agent-centered utilitarianism, Denise Cooley posits that there are certain situations where it is morally permissible to support something like the distribution of QS even if it is lacking full FDA approval [21].

Drs. Malcolm Potts and Giuseppe Benagiano, two physicians directly involved with pharmaceutical clinical trials in developing countries, understand how QS could be misinterpreted as promoting a "double standard". However, they suggest that the "differences are quantitative not qualitative." [22] According to them, QS is a safer choice over surgical sterilization for women living in the United States as well as in India. It is safer than surgery for women who are heavy smokers, anemic or otherwise not appropriate candidates for surgical, voluntary sterilizations. QS could also be a method of choice for those who desire sterilization but are afraid of surgery [23].

Drs. Kessel and Mumford agree that overpopulation is an issue they are attempting to address. During the 1994 Cairo conference, direct connections were made between population growth, reproductive health strategies and economic and environmental conditions. Many speaking from a Malthusian perspective, see the reduction of population growth as the panacea for poverty. Advocates of this position believe QS is an answer to a nation's overpopulation concerns. However, many Third World nations see the "Western focus on population control as a way to avoid discussing such causes of underdevelopment as inadequate access to capital, exploitative investment strategies and unfair trade practices." [24] It is well known that while industrialized nations contain only 25% of the world's population, they consume 75% of the earth's energy and 85% of its forest products. This same 25% is responsible for generating 75% of the world's pollutants and wastes.

Bonnie Johnson, in her article "Overpopulation and Reproductive Rights", claims that contraceptive technologies do not provide solutions to poverty, overpopulation or even the subordination of women. As she sees it, one needs to look at economic inequities, women's roles in economic and political decisions, traditional roles in the relationships between the sexes, food production and the healthcare delivery system [25]. In Dr. Mahmoud Fathalla's estimation, the focus needs to shift away from the "problems of overpopulation" to the goal of empowering women. Increase a woman's level of education and improve her status, and she will most likely bear fewer children if given the opportunity to curtail her fertility. Working to improve the child survival rates, as well as providing care and protection for the elderly, would also go a long way in decreasing the need for having many children [20]. These are arguments that must be taken seriously as individuals work to provide all women with the option of QS. The need for amelioration of these problems is recognized by many, and most are in favor of solving them.

Drs. Kessel and Mumford have taken up Ms. Karat's challenge, where she implored them to "experiment on their white women first and then come tell us its for our good." [18] Dr. Kessel admits that perhaps they committed a tactical error in not pursuing FDA approval in the USA prior to taking QS around the world. The two pioneers, along with Dr. Lippes and others, have worked toward obtaining FDA approval and to making QS accessible to women in the United States of America[2]. In 1999, the Planned Parenthood Federation of America (PPFA) convened an ad hoc committee meeting to discuss QS. This committee voted to recommend PPFA's involvement in a clinical trial. Paradoxically, opponents of QS have militated to prevent QS testing in the United States. Judith A.M. Scully argues that the United States trials should be banned so as to not affirm previous studies [26]. However, others, like Potts and Benagiano, look forward to these FDA clinical trials there. By the end of April 2003, Dr. Lippes had completed a Phase I clinical trial with 10 women at the Children's Hospital, Buffalo Medical School, in Buffalo, New York.

Ms. Karat and Dr. Pollack accused Drs. Kessel and Mumford of acting unethically toward the poor, uneducated women of India and out of particular

[2] Interview with Dr. Elton Kessel.

political agendas. Mumford claims Ms. Karat and Dr. Pollack's objections to QS are motivated more by a desire to promote their own political and economic ideologies, rather than to protect the lives of the poor and uneducated. According to Mumford, Ms. Karat's crusade against QS provided her husband's communist party with a controversial platform issue. Mumford also suggests that Dr. Pollack's objections stem from the need to defend the interests of her organization, EngenderHealth, and he has presented his position in detail [27]. Undoubtedly, all the positions mentioned regarding QS are influenced by a variety of political, economic and religious elements.

Despite their conflicting opinions and the mutual attacks on each other's probity, one can find that their claims share a commitment to common ethical principles. One can propose that the unfavorable attitudes of Ms. Karat, Dr. Pollack and others arise from a commitment to respect for human life and beneficence. According to their point of view, all lives, poor, rich, educated or not, deserve safe, effective, healthcare. They raise questions and voice concerns that originate from their firmly held beliefs, so the good thing to do, the beneficent action, for Ms. Karat and Dr. Pollack, is to prevent QS from being performed. One can also propose that Drs. Rahman, Kessel, Mumford and others desire only to relieve the suffering associated with high maternal mortality. Their position in favor of QS may also be grounded in a commitment to respect for human life and beneficence. According to these doctors, the beneficent action is to provide a safe, effective method of sterilization for those women who would desire no more children. Taking all the above arguments at face value, one could contend that although their positions regarding QS are antithetical, the two camps share the principles of a respect for life and beneficence.

Having discussed the complex web of stakeholders and facts, and pointed out two ethical principles upon which all the above arguments can be based, let us now consider potential courses of actions. After all, ethics is about making decisions and acting toward what is good and right, for the individual and for society. First, one could do nothing. In terms of QS, this would mean the continuation of debates and controversy with little or no actual change in the way things were done, or in the lives of individual women and men who are suffering the most. In a broader scope, inaction is not only accepting mediocrity, it is allowing the inequities and injustices in the world to continue. Societies world-wide continually evolve and develop as they rise to meet the challenges placed before them. Inaction is an inappropriate response, for ultimately too much is at stake.

A second course of action could be to call for an absolute, international ban on QS. For those ideologically opposed to the method, or for that matter any other form of contraception, this is the only ethical option. No number of tests and studies, and no amount of money would ever make QS acceptable to the Roman Catholic Church or others who are firmly against any form of artificial contraception. However, the very attributes that make quinacrine attractive, and at the same time feared, make banning it impractical. It is inexpensive, easy to make, to obtain and to administer. Banning it may make it illegal, but not unavailable. Also, if QS is banned, protocols, policies and reviews for its use and distribution would neither be developed nor enforced. Although some would argue this action could feasibly protect women from the potential harms of QS, it definitely leaves them with fewer legal reproductive choices. This alternative, along with the first, does not positively address their contraceptive needs.

Another alternative along the above course of action, is to ban QS, but present a different, proven, safe, effective, inexpensive, accessible, non-surgical method of sterilization. This is a good idea, but again highly unrealistic. As already mentioned, pharmaceutical companies are backing away from the research and development of new forms of contraception. Also, although the voices of the opponents to QS are loud and firm, they are not offering a comparable alternative. If such research were actually implemented, then perhaps the reproductive needs of individuals could be met. However, QS is much farther along in testing, development and acceptability than any new idea for non-surgical sterilization.

If one's primary focus is overpopulation, then one may propose a third option: an immediate approval for world-wide distribution and use of QS. This same course of action may be chosen by those whose primary concern is poverty and reproductive freedom. Statistics demonstrate that poverty and overpopulation go hand in hand. Many studies indicate that sterilization is the contraceptive of choice in many countries, thus a

reason to support this alternative. Because of its cost, need for expertise and facilities, surgical sterilization alone cannot meet the demands [28]. QS could be an answer for overpopulation and poverty. However, with over-arching goals such as these, individual desires and choices can too readily be overlooked. Focusing exclusively on goals such as overpopulation almost invites abuse. Additionally, this narrow emphasis on contraception ignores other very powerful causes of overpopulation and poverty.

Among the options mentioned is a full range of other possible alternatives. Perhaps a foundation or government could provide the necessary funding and facilities with which to perform the required FDA drug studies. This action would directly address the fears related to the risks of cancer, effects on the fetus, and the like. One needs to remember that quinacrine itself has had FDA approval for decades; it is the "off-label" use that has not been officially approved. If money and time were not an issue, additional trials could be conducted – following FDA protocols to the letter. This could answer the questions and criticism of the studies already completed. However, time and money are important issues for those stakeholders dealing with the reality of high maternal mortality in developing countries and concerns with the results of overpopulation.

An ideal ethical alternative would address the concerns discussed above, and the actual needs of those living in the present and future. Since a multi-faceted issue such as QS requires a multifarious response, this final alternative incorporates a variety of elements and by its very nature is complex. This alternative has long- and short-term goals, mindful of both the fears and abuses associated with the history of sterilizations, as well as the years of research already conducted on QS. This view implements an ethical policy that works towards justice, safety and protecting from, even preventing, abuses. Influenced by conclusions reached at international conferences such as the 1994 Cairo International Conference on Population and Development and the fourth UN World Conference on Women held in Beijing in 1995, the focus of this alternative is to improve and ensure the health of all women, their children and families. Thus, it is called the "*whole family health*" ethical alternative. This focus ensures the ethical principles of respect for human life and beneficence [29].

The focus of this option must be on the well-being of the whole family, not exclusively on the reproductive health of women or men, which may obscure the whole picture. Sterilization is not always *the* answer. Sterilizing a woman does not inevitably protect her or provide the basic needs for her family's survival. Unfortunately, in cases where the focus has been exclusively on sterilization, the basic health needs of the family are not always met [29]. Thus, this alternative would present a *whole family health* package. A comprehensive healthcare program would include access to nutrition, clean water, safe general medical assessments for children, adults and the elderly, as well as reproductive/contraceptive care for women and men.

A serious problem in most, if not all, societies is that women have had to carry the primary responsibility of contraception (and its failures) without the power to make their own reproductive decisions [30]. This is unacceptable. As a long-term goal, this *whole family health* alternative respectfully challenges religious, cultural, societal and political systems. As Fathalla stated, "No society, primitive or advanced, no culture, no religion, and no legal code has been neutral about reproductive life. The health of women is to no small extent determined by certain males of the species, moralists, politicians, lawyers and others ..." [31] Women and men have equal rights within the society and the family, and they should share the responsibility of contraception. It is unacceptable that women carry the primary responsibility for contraception, but do not have the power to make their own choices regarding reproduction and contraception. Even policy experts at the 1994 Cairo Conference realized that empowering women was the primary means to achieving their central goal of stabilization of the world population growth. Again, the focus would not be population reduction. That may be a by-product of empowering women, but it is not the focus of this alternative. Another goal involves increasing the level of education in the society. Once the focus is on the stories of the lives of women, their children and men, patterns of subordination can be uncovered and corrected [32].

The *whole family health* package offers QS as one of its many services. Women requesting permanent sterilization are to be fully informed of the risks and benefits of QS and provided with other long-term contraceptives options such as Norplant and condoms.

Only after informed consent is given, is QS to be administered. Additionally, to guard against abuse and coercion, the offer of QS is to be totally independent of any other needed medical assistance. It is not to be a condition for receiving medical assistance with pregnancy, childbirth, or any other medical need. This approach provides healthcare for the whole family.

This *whole family health* alternative also accepts the facts associated with QS. Drs. Malcolm Potts and Giuseppe Benagiano go so far as to say that "the unreasoned passion about QS is making evidence-based decisions difficult to reach." In their article "Quinacrine Sterilization: A Middle Road," they acknowledge that while they have had different stances regarding QS policies, they now "wish to help broaden the range of fertility control options available, especially for low income women around the world." They demonstrate an understanding of the complexities involved with the testing of new drugs or devices and they understand the desire for certainty. However, they are mindful that "the introduction of any new drug must necessarily take place on the basis of balanced judgment and, almost inevitably, incomplete information." They also recognize that "as with all new family planning methods at this stage of development, there are insufficient data to answer all possible questions about rare but potentially important long-term risks." Nonetheless, they argue "the experience to date has shown that QS has a low risk of serious, immediate side effects. We deplore hasty judgments and biased comments, and we ask all those who are interested in the welfare of women around the world to recognize the difficulty and inevitable uncertainty surrounding the introduction of any new method of fertility regulation." They conclude that QS should be available for "women who ask for sterilization and for whom existing methods are not available or present unacceptable risks." [22]

The *whole family health* approach is clearly the action of choice. It is mindful of the concerns raised by an examination of the historical context of sterilization in developing countries. By moving forward with an emphasis on the health of the entire family, it addresses the legitimate concerns regarding abuse, and takes into account the data obtained from the clinical trials conducted over the past twenty years. The primary values, principles and concerns critical for QS are incorporated. It is a compromise between doing nothing and a complete ban or full-scale implementation. Its central focus is the health of the individual, not merely reproductive health of women, but the general health of the whole family. This broader perspective calls for the enhancement of the lives of the whole community. It allows us to go behind Rawl's "veil of ignorance", where, based on respect, care, and concern for others, we make decisions that will affect us all.

References

[1] Veatch R. Sterilization: its socio-cultural and ethical determinants. In: Advances in Voluntary Sterilization: Proceedings of the Second International Conference. New York: American Elsevier. 1974; 138–150.

[2] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[3] Bhuiyan SN, Begum R. Quinacrine non-surgical female sterilization in Bangladesh. *Contraception* 2001; 64:281–286.

[4] Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. *Int J Gynecol Obstet* 1995; 51 (Suppl 1):S58–S69.

[5] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342: 213–217.

[6] Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–151.

[7] Kessel E, Zipper J, Mumford SD. Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy. *Fertil Steril* 1985; 44:293–298.

[8] Carignan CS, Rogow D, Pollack AE. The quinacrine method of nonsurgical sterilization: report of an experts meeting. *AVSC Working Paper,* 6 July, 1994.

[9] Pollack AE, Carignan CS. Association for Voluntary Surgical Contraception: a technical statement on quinacrine pellets for nonsurgical female sterilization. *Adv Contracept* 1994; 10:43–50.

[10] Freedman AM. Americans Export Chemical Sterilization to the Third World. *Asian Wall Street Journal* June 19–20, 1998.

[11] Bhatt R, Waszak CS. Four-year follow up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.

[12] Suhadi A, Anwar M, Soejoenoes A. Four-year clinical evaluation of quinacrine pellets for non-surgical female sterilization. *Adv Contracept* 1998; 14:69–77.

[13] Family Health International. FHI Quinacrine Studies. *Contraceptive Update* 1995; 16:27.

[14] Lippes J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2002; 77:1106–1109.

[15] Mumford SD. A response to Alix Freedman's Wall Street Journal article on QS. Downloaded from http://www.quinacrine.com/news6.htm#n1962. October 16, 1998.

[16] Suhadi A, Soejoenoes A. One year experience using quinacrine pellets for non-surgical female sterilization. *Indonesian J Obstet Gynaecol* 1996; 20:39–43.
[17] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: update through 1996. *Fertil Steril* 2000; 74:169–171.
[18] CBS 60 Minutes. Quinacrine. Program aired 18 October, 1998.
[19] Kessel E. Risk/benefit criterion vs. single standard for QS trials, *Quinacrine Sterilization*. Downloaded from http://www.quinacrine.com/news6.htm#n1962. October 16, 1998.
[20] Fathalla MF, Gruskin S, Heise LL, Gilbert, Capelon R. The impact of reproductive subordination on women's health. *Amer Univ Law Rev* 1995; 44:1179–1189.
[21] Cooley D. Good enough for the Third World. *J Med Philos* 2000; 25:427–450.
[22] Potts M, Benagiano G. Quinacrine sterilization: a middle road. *Contraception* 2001; 64:275–276
[23] Sarin AR. Quinacrine sterilization: experience among women at high risk for surgery. *Adv Contracept* 1999; 15:175–178.
[24] Hartmann B, Pramik MJ. The Double Challenge. *Whole Earth Rev* 1995; 88:14–17. Downloaded from Journal Express – UMI (tm) 1986 – present.
[25] Johnson B. Overpopulation and reproductive rights. *Free Inquiry* 1994; 14:13–16. Downloaded from Journal Express – UMI (tm) 1986 – present.
[26] Scully JAM. Maternal mortality, population control, and the war in women's wombs: a bioethical analysis of quinacrine sterilization. *Wisconsin Int Law J* 2001; 19:103–151.
[27] Mumford SD. Quinacrine sterilization: Letters to the Editor. *Lancet* 1994; 344:1434.
[28] Mumford SD, Kessel E. Sterilization needs in the 1990s: the case for quinacrine nonsurgical female sterilization. *Am J Obstet Gynecol* 1992; 167:1203–1207.
[29] Hartmann B. Cairo consensus sparks new hopes, old worries. In: *Forum for Applied Research and Public Policy* 1997; 12:33–40. Downloaded from http://firstsearch.oclc.org/:next=NEXTC August 11, 1999.
[30] Martin S. A woman centered approach to laws on human reproduction. In: Mahoney KE, Mahone P, editors, Human Rights in the Twenty-First Century: A Global Challenge. Boston: Martinus Nijhoff Publishers. 1993:911.
[31] Fathalla MF. Women's health: an overview. *WIN News* (Women's International Network) 1995; 21:23–26. Downloaded from Journal Express – UMI (tm) 1986 – present.
[32] Cook R. Women's health from Cairo to Beijing and beyond. *Lancet* 1995; 346:8978.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S23–S29

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

25 years of quinacrine sterilization experience in Chile: review of 2,592 cases

J. Zipper[a], V. Trujillo[b,*]

[a] *University of Chile, Sótero Del Río Hospital, Santiago, Chile*
[b] *San José Hospital, Santiago, Chile*

Abstract

Objectives: To assess short-term side effects, long-term risks and efficacy of quinacrine sterilization (QS) in Chile. *Methods*: Review experience of 2,592 cases sterilized with 2 or 3 transcervical insertions of 252 mg quinacrine as pellets since 1977; review the Chilean pre-clinical experience and epidemiological studies on cervical, endometrial and other cancers. *Results*: Among 2,592 women who underwent QS, the total number of pregnancies was 119 (4.6%); 59 (49.5%) were carried to term with no birth defects related to QS. Nine cases were ectopic pregnancies. The ectopic pregnancy risk per 1,000 woman-years was 0.41, similar to that for surgical sterilization. The cumulative life-table pregnancy rates per 100 women at 10 years varied from 5.2 to 6.9. Mild and transient side effects were reported in 13.5% of quinacrine intrauterine insertions and pelvic inflammatory disease was diagnosed in 4 cases (0.15%). Long-term follow-up of quinacrine-sterilized patients shows no increased risk of cervical, endometrial or other cancer. *Conclusions*: QS efficacy at 10 years is comparable to widely accepted tubal clip and single point bipolar electrocoagulation laparoscopic procedures. QS has a low risk of serious, immediate side effects. No long-term risks have been identified after 25 years of use.

Keywords: quinacrine sterilization, non-surgical female sterilization

1. Introduction

In the 1960s Dr. Jaime Zipper initiated a study of reproductive physiology in Chile. Using rabbits, he demonstrated that, by placing a copper wire in the lower portion of the uterus, he was able to totally prevent pregnancy implantations. Rabbits have a double uterus and on the side with no copper, implantations were normal. This discovery led to the development of the copper IUD that once generated controversy but is now recognized as one of the safest and most effective reversible methods of birth control. At that time, IUDs were mistakenly associated with a carcinogenic potential, especially cervical cancer, but long-term controlled studies finally disproved this theory [1,2]. Similar controversy engages our attention today with Quinacrine Sterilization (QS).

QS began in Chile in the mid-1960s. Zipper and his colleagues were searching for a contraceptive method that could curtail the alarming increase in septic abortion cases and their related deaths. They tested various agents. Using the rat as an experimental animal, they evaluated the effect of intrauterine administration of such compounds on fertility [3]. Quinacrine had been extensively used in humans orally as an efficient antimalarial therapy and prophylactic. It is still used in the treatment of lupus erythematosus and giardiasis [4–7]. Previous knowledge of quinacrine action in pleural and peritoneal cavities, where it produces adhesions, led the

* Corresponding author. Tel: 56-2-341-7416; Fax: 56-2-341-5774.
E-mail address: vtrujillo@netline.cl (V. Trujillo)
Correspondence address: Jorge Washington 210, Dp. 606-Nunoa, Santiago, Chile

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

group to choose it for the first clinical trial for transcervical sterilization in 1970 [8]. Because a quinacrine slurry was the form used for treatment of neoplastic effusions, a slurry was used in this trial. The instillations consisted of 1.5 gm quinacrine in 5 ml of xylocaine. After the first instillation, this was repeated one and 6 months later. Instillation was done under syringe pressure, unexpectedly resulting in entry of quinacrine through endometrial capillaries directly and rapidly into the bloodstream. The high pregnancy rate and a 2% incidence of cortical excitation led to a halt in the trial.

In 1975, Dr. Zipper and Robert Wheeler of the International Fertility Research Program in North Carolina, devised a quinacrine pellet to eliminate the problems associated with the liquid preparation. Five years later, a preliminary report on quinacrine pellets was published [9]. Pellet use resulted in the total elimination of cortical excitation and a significant reduction of pregnancy rates.

Since Chilean women sterilized with quinacrine pellets have the longest experience of any patients worldwide, pathologic conditions or abnormalities attributable to quinacrine would be detected first in this primary group. One could ostensibly consider QS experience a completed phase III study because more than 100,000 cases have been documented with no deaths and no complications requiring surgery [10].

Recent studies of Chilean subjects show no increased risk of reproductive tract cancers for this method [11–13]. Review of these cases provides considerable evidence that the frequency of ectopic pregnancies is no higher in QS cases than in surgical sterilization. Also, amenorrhea, uterine lesions and fetal exposure are acceptable risks [14–19]. Sokal and his colleagues, in a recent long-term follow-up study of quinacrine acceptors in Vietnam, demonstrated another advantage to QS, i.e., that the number of hysterectomies in a period of 5 years is much higher (8%) in patients surgically sterilized than in women with QS (0.5%) [20].

The present study reviews the Chilean experience with QS as it relates to gynecologic cancer in Chilean women.

2. Materials and methods

Three hospitals in Chile were recruited for QS: Sótero del Río Hospital and San José Hospital in Santiago, and Valdivia Hospital. They initiated their quinacrine programs on different dates: 1977, 1989 and 1979, respectively. At first, the sterilization technique was the same in all centers: transcervical application of 7 quinacrine pellets (36 mg each, 252 mg total dose) in the proliferative phase of the menstrual cycle, using an inserter similar to a copper-T IUD inserter. The procedure was carried out under aseptic conditions two to three times, with a monthly interval between each quinacrine placement. After performing hysterometry, the inserter was introduced as far as the uterine fundus. However, at San José Hospital, Dr. Trujillo noted that the technique was difficult since the pellets formed a row and sometimes one of them could be placed next to the cervix. After discussion with Dr. Zipper, a new approach was initiated. The inserter was withdrawn 0.5 cm and the pellets were pushed into the uterine cavity. This technique was not described as a standard in all hospitals. It was not until 1993, after publication of Hieu's paper, that the other hospitals adopted his recommended technique. The dissolution time of pellets was 30 minutes (Sipharm, Sisseln, Switzerland). In two series an anti-inflammatory drug (diclofenac 25 mg–50 mg) was administered with quinacrine into the uterine cavity.

Women had revisits at 3, 6 and 12 months after the last insertion and every 6 months thereafter. At Sótero del Río Hospital, insertions were performed by two midwives; at San José and Valdivia Hospitals two gynecologists were the operators.

Only women who requested sterilization for family planning reasons, with a previous informed consent and completed follow-up, were included in this study. In each hospital a committee reviews all applications for sterilization. National regulations at the time of the study required that, for approval of tubal sterilization, a woman must be 30 years old and have 4 living children, or 35 years old with 3 living children. Women suffering from a serious illness would qualify for approval.

One group of 1,061 women from Santiago, Chile, who had requested quinacrine sterilization since 1977, were evaluated for possible cytologic changes in their Pap smears. Papanicolaou tests were carried out before and after QS.

Table 1 shows the experience in Chile with QS. A total of 2,592 patients were sterilized from 1977 to 1998. Two groups of women received 3 insertions of quinacrine pellets, containing 252 mg and no intrauterine diclofenac. Three other groups received

Table 1
2,592 patients sterilized with quinacrine pellets: 252 mg at hospitals in Chile, between 1977 and 1998

Hospitals	Patients (*N*)	Period	Insertions (*N*)	Use of NSAIDs
Sótero del Río	733	1977–1989	3	no
Sótero del Río	508	1977–1989	2	no
Valdivia	151	1979	3	no
San José	445	1989–1994	2	50 mg IU diclofenac
Sótero del Río	755	1995–1998	2	25 mg IU diclofenac
Total	2,592			

Table 2
Efficacy and ectopic pregnancy risk among 2,592 quinacrine sterilization acceptors, Chile 1977–1998

	(I) Sótero del Río 1977–1989	(II) Valdivia 1979	(III) San Jose 1989–1994	Sótero del Río 1995–1998	Total (*N*)
Patients: all	1,241	151	445	755	2,592
Pregnancies *N* (%)	68 (5.5)	9 (6.0)	19 (4.3)	23 (3.0)	119 (4.6)
EP[a] *N* (%)	4 (0.32)	3 (1.98)	2 (0.44)	0	9 (0.34)
WY[b] follow-up	15,756	2,416	2,330	1,284	21,786
EP risk per 1000 WY	0.25	1.24	0.85	0	0.41
Pearl-Index	0.43	0.37	0.81	1.79	0.54
Cumulative life-table pregnancy rates per 100 women and (SE)	5.2[d] (0.87)[c] *N* = 733 6.9[e] (1.24)[c] *N* = 508 at 10 years	5.9 (1.7)[c] at 10 years	5.5 (1.41)[c] at 5 years NSAID	4.9 (1.22)[c] at 2 years NSAID	

[a] EP, ectopic pregnancies.
[b] WY, woman-years.
[c] SE, standard error.
[d] 3 insertion data set.
[e] 2 insertion data set.

2 insertions, and two of these groups were also given 50 mg or 25 mg of IU diclofenac. Although the groups presented in Table 1 are not strictly comparable, they summarize the global Chilean experience with QS, representing the group with the longest follow-up.

The inclusion criteria were: The subject is between 21 and 45 years of age; has three or more living children, the youngest of whom is at least 3 years old; is generally healthy; is sexually active; is not using another contraceptive method; has had a recent and normal Pap smear; is not known to be infertile or sterile. The patient must carefully read and sign an informed consent, freely agreeing to participate in the study. She must find it convenient to return for follow-up visits. The hospital sterilization committee grants authorization for the procedure.

The exclusion criteria were: The subject suspects she may be pregnant; has abnormal uterine bleeding; has gynecologic anatomical abnormalities such as myomas or cervical synechia; has any serious illness; has pelvic inflammatory disease (PID), acute or chronic; is allergic to quinacrine; is taking any drug that alters fertility, i.e., anticoagulants, furosemide, methotrexate, etc.; has had previous pelvic surgery; has a seizure disorder; is amenorrheic; and/or has gynecologic cancer.

3. Results

Table 2 shows that a total of 2,592 women were sterilized at three hospitals in the following groupings: 1,241 (from 1977–1989) and 755 (from 1995–1998) at Sótero del Río Hospital; 151 at Valdivia Hospital (1979); and 445 (from 1989–1994) at San José Hospital.

Table 3
Patients' complaints and complications[a] by insertions, hospitals and period of years, Chile 1977–1994 ($N = 1837$)

	(I) Sótero del Río 1977–1989	(II) Valdivia 1979	(III) San José 1989–1994)	Total
Patients	1241	151	445	1837
Insertions	3215	450	890	4555
Complaints/Complications N (%)				
Vaginal bleeding	6 (0.2)	5 (1.1)	19 (2.1)	30 (0.7)
Feverishness	57 (1.8)	–	15 (1.7)	72 (1.6)
Headache	107 (3.3)	3 (0.6)	20 (2.2)	130 (2.9)
General discomforture	74 (2.3)	–	10 (1.1)	84 (1.8)
Vomiting	3 (0.1)	1 (0.2)	10 (1.1)	14 (0.3)
Lower abdominal pain	175 (5.4)	45 (9.9)	23 (2.6)	243 (5.3)
Vulvovaginitis	6 (0.2)	2 (0.4)	8 (0.9)	16 (0.4)
Myalgia	–	1 (0.2)	–	1
Emotional reaction	–	1 (0.2)	–	1
Fever	–	1 (0.2)	8 (0.9)	9 (0.2)
Cervical synechia	2 (0.1)	–	2 (0.2)	4 (0.1)
Amenorrhea	–	–	4 (0.4)	4
Back pain	–	–	1 (0.1)	1
Allergic reaction	–	–	1 (0.1)	1
PID[b]	3 (0.1)	1 (0.2)	–	4 (0.1)
Hepatitis[c]	–	1 (0.2)	–	1
Total	433 (13.4)	61 (13.2)	121 (13.5)	615 (13.5)

[a] One or more events can be reported by each patient. There was one uterine perforation.
[b] Pelvic inflammatory disease.
[c] Probably in incubation at insertion.

Table 2 also shows the efficacy and ectopic pregnancy risk among the 2,592 acceptors from 1977–1998. The groups with longer follow-up (I, II, III) have a pregnancy rate that varies from 5.2% following 3 insertions to 6.9% following 2 insertions at 10 years. Intrauterine diclofenac had no apparent effect on efficacy. In all groups, two-thirds of all pregnancies occurred during the first 2 years after QS. There was a total of 3 pregnancies between insertions; 2 resulted in induced abortions and one in a spontaneous abortion.

The ectopic pregnancy risk per 1000 woman-years (0.41) is similar to that for IUD users (0.3) [21], lower than for surgical sterilization (0.7–0.8) [22] and much lower than for non-contraceptive users (2.6) [23]. All such cases were surgically resolved with no serious post-operative complications or deaths. The 9 ectopics correspond to 7.5% of the 119 pregnancies.

Table 3 shows complaints and complications reported by QS patients. Headache and lower abdominal pain are most frequent. All complaints, except amenorrhea, PID and hepatitis, were mild and transitory, did not require hospitalization and disappeared in the first 3 days. The patient in distress presented with an emotional reaction with sadness and weeping. The problems for four patients with cervical synechia were resolved by hysterometry with no further complications. One case with hematometra was easily treated with a uterine sound. Patients with amenorrhea started their menstrual cycle before the third month after their last insertion. The allergic reaction was reported as a mild sun-burn sensation that remained for less than 8 hours. One woman with PID had a previous undiagnosed chronic adnexial disease and should have been excluded from the study. All of these patients were treated successfully without surgery. The case of hepatitis A, an endemic disease in Chile, probably was in its incubation period before the woman was sterilized. The uterus of one patient was perforated by the inserter, but pellets

Table 4
Comparison of the number of *in situ* carcinomas and woman-years of exposure by age[a] among 1,061 quinacrine sterilized women between March 1977 and October 1990 and the general female population in Santiago, Chile

Age group	Quinacrine *in situ* cancer	Woman-years	Comparison *in situ* cancer	Woman-years	Chile 1970 female population[b]
30 to 34	3	729	13	4,951	299,200
35 to 39	3	975	5	3,374	259,400
40 to 44	1	1,046	1	2,309	248,100
45 to 49	1	535	3	1,721	200,200
Total	8	3,285	22	12,355	1,006,900

[a] Age-standardized rates: quinacrine, 2.62 per 1000 woman-years; control, 1.56 per 1000 woman-years (RR: 1.62, CI: 0.73–3.61).
[b] Population used for age adjustments.

Table 5
Incidence of cancer in women sterilized with quinacrine pellets (QS) and controls, Chile, 1977–1996 ($N = 1514$)

Type of cancer	Number of cases		Rate per 100,000		Relative risk
	QS	Control	QS	Control	
All cancers	17[a]	217.2[b]	134.5	124.2	1.1
Endometrial	0	9.1	–	2.2	–

[a] 1514 women (17,450 woman-years).
[b] 215,171 woman-years among patients over 30 years of age.

were not introduced into the abdominal cavity. No hospitalization or specific therapy was needed. A rate of 13.5% of adverse events was reported.

One group of 1,061 women from Santiago, who had requested sterilization since 1977, were evaluated for possible cytological changes in their Pap smears [24]. Some grade of a cervical lesion was observed in 75 women (7.1%). The prevalence was 3.4% (36 women) and the incidence was 1.1% (34 women) in a total of 3,654 woman-years between the first and the last Pap smear. From this group, 30 patients were found with low grade intraepithelial cervical lesions, and 8 with high grade cancer *in situ* (CIS). One patient with squamous cell carcinoma was surgically treated in 1986 (Table 4). After standardizing the incidence rates, the results were compared with a control group of women in Santiago. The incidence of CIS, precursors of cervical carcinoma, in patients treated with quinacrine (2.62%) was not higher than that found in other areas of Santiago (1.56%, $P > 0.05$).

A retrospective cohort study of 1,514 women sterilized with quinacrine was carried out between 1977 and 1996. Seventeen cancer cases of any location were diagnosed after quinacrine insertion. Prior to sterilization, 12 cases of CIS were diagnosed. No endometrial cancer was found in QS patients. The latest up-date in 1996 found no endometrial cancer in the QS group, with a follow-up of 12,468 woman-years [25]. The cohort members provided 17,450 woman-years of follow-up. No evidence of increased cancer risk was found to be associated with QS (Table 5) [26].

Fifty percent of 119 pregnancies were carried to term. Most of them were vaginal deliveries (42 of 59). All ended in normal births. No birth defects related to quinacrine and no macroscopic uterine pathology were detected at the time of delivery. Premature deliveries were not considered abnormal pregnancies. Forty-one pregnancies (34%) ended in abortions; 16 of them (13%) were spontaneous. One case of hydatidiform mole was reported (Table 6).

Patients with QS failures were scheduled for surgical sterilization or other contraceptive methods because we assume that for some anatomical reason quinacrine did not reach the tubal ostium. Also most patients reject a second quinacrine sterilization after a failure.

Table 6
Outcome of pregnancies in women sterilized with quinacrine pellets (QS) in Chile, 1977–1996 ($N = 119$)

Outcome	*N*
Normal pregnancies	59
42 vaginal deliveries	
17 cesarean deliveries	
Ectopic pregnancies	9
Spontaneous abortion	16
Induced abortion	25
Hydatidiform mole	1
No information	9
Total	119

Hysterosalpingograms (HSG) were routinely performed only in the group from Valdivia Hospital, where 80% of patients underwent this examination 3 months after the first quinacrine insertion in order to confirm occlusion. Hysteroscopies were performed in 5 patients from San José Hospital who wanted to reverse the sterilization. Fibrotic tissue blocking the tubal ostium was noted. Attempts to unblock the tubes through pressure of HSG were not successful.

4. Discussion

The Chilean experience with QS encompasses more than 30 years of basic and clinical research and numerous scientific publications. This group of Chilean women who have had QS have been closely monitored and constitute the first cases with this non-surgical method. Data presented in this study amply support the initial concept of QS, i.e., it is a simple, safe and highly acceptable ambulatory method of non-surgical sterilization. Is there another reasonable option that could help to meet the increasing demand for sterilization, especially in developing countries?

The anti-inflammatory drugs were used in an attempt to diminish the mild side effects associated with intrauterine insertion and theoretically to potentiate quinacrine tubal occlusive action. No additional contraceptive method was used in any group. Intrauterine quinacrine produces a fibrotic and granulomatous tissue in the tubal ostium that obstructs the oviductal lumen. Failure rates of QS can be compared to those for IUD users. QS efficacy at 10 years is comparable to widely used surgical procedures such as laparoscopic tubal sterilization by clip or by bipolar single point electrocoagulation [22]. In surgical sterilization, one-third of the failures are an ectopic pregnancy [27]. In this series, only group II follows this trend. With the Progestasert® IUD, one half of failures are ectopic pregnancies [28].

Since the contraceptive potential of quinacrine has become known, controversies have arisen, based mainly on its mutagenic activity in Ames test (*in vitro*) and its theoretical carcinogenic effect in humans. *In vitro* tests cannot be extrapolated to humans. They have low specificity, 67% false positives [19] when nitrogen organic compounds (i.e., quinacrine) are tested and only 60% valid extrapolation to rodents [29]. Also frame-shift mutations induced by amino acridines are inhibited when glucose, cAMP or adenosine derivatives are present in the cell medium [30–31]. There is no evidence that quinacrine can be carcinogenic in humans or rodents. Data on the *in vivo* genotoxicity of quinacrine (micronucleus cytogenetic assay in mice) represent evidence that quinacrine lacks *in vivo* genotoxic activity [32].

Although the efficacy of QS is lower than surgical sterilization, the absence of deaths and serious complications is a great advantage of QS, especially for high risk patients [33]. One examines the results with QS and notes that abnormal uterine lesions or damage have not been detected. In the pregnancies carried to term after QS, we have seen no fetal abnormalities. The rate of ectopic pregnancies with QS is similar to those with IUD use and surgical sterilization, but far lower than for non-contracepting women. Long-term follow-up of QS cases in Chile shows no increased risk of gynecologic or any other type of cancer associated with QS in this population [24].

5. Conclusion

After 30 years of research, we firmly believe that there is no scientific reason to consider QS an experimental or dangerous procedure. There is no evidence to believe that QS may increase the incidence of cancer. Acceptance of QS could help to reduce the maternal mortality in developing countries. It may be the safest option for women at high risk for surgery who desire to limit family size by sterilization.

References

[1] Li HQ, Thomas DB, Jin SK, Wu F. Tubal sterilization and use of an IUD and risk of cervical cancer. *J Womens Health Gend Based Med* 2000; 9:303.

[2] World Health Organization. Mechanism of action, safety and efficacy of intrauterine devices. *WHO Tech Rep Ser* 1987; 753:1–91.

[3] Zipper JA, Prager R, Medel M. Biologic changes induced by unilateral intrauterine instillation of quinacrine in the rat and their reversal by either estradiol or progesterone. *Fertil Steril* 1973; 24:48–53.

[4] Fitzhugh OG, Nelson AA, Calvary HO. The chronic toxicity of quinacrine (Atabrine®). *J Pharmacol Exp Ther* 1945; 85:207–221.

[5] Shannon JA, Earle DP, Jr, Brodie BB, Taggart JV, Berliner RW. The pharmacological basis for the rational use of atabrine in treatment of malaria. *J Pharmacol Exp Ther* 1944; 81:307–330.

[6] Dubois EL. Effect of quinacrine (Atabrine®) upon lupus erythematosus phenomenon. *Arch Dermatol* 1955; 71:570–574.

[7] Bassily S, Farid Z, Mikhail JW, Kent DC, Lehman JS. The treatment of Giardia lamblia infection with mepacrine, metronidazole and furazolidone. *J Trop Med Hyg* 1970; 73:15–18.

[8] Zipper JA, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil Steril* 1970; 21:581–589.

[9] Zipper J, Cole LP, Goldsmith A, Wheelera R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[10] Kessel, E. 100,000 quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.

[11] Sokal DC, Zipper J, Guzman SR, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. *Fertil Steril* 1995; 64:325–334.

[12] Dabancens A, Sokal DC, Pruyas M, Rivera M, Zipper J. Prevalence and standardized incidence rates of preclinical cervical pathology among 1,061 women sterilized with transcervical quinacrine hydrochloride pellets. *Fertil Steril* 1995; 64:444–446.

[13] Dabancens A, Pruyas M, Rivera M, Zipper J. Seguimiento de cánceres en una cohorte de mujeres esterilizadas con pellets de quinacrina. *Ginecol Reprod* 1998; 6:21–26.

[14] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[15] Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. *Int J Gynecol Obstet* 1995; 51 (Suppl 1):S57–S69.

[16] Kessel E, Zipper J, Mumford SD. Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy. *Fertil Steril* 1985; 44:293–298.

[17] Blake DA, Dubin NH, Diblasi MC, Parmley TM, Stetten G, King TM. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, editors, Female Transcervical Sterilization. Philadelphia: Harper and Row. 1983:71.

[18] Guzman-Serani R, Bernales A. Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. *Contracept Deliv Syst* 1984; 5:131–135.

[19] Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. *Adv Contracept* 1998; 14:81–90.

[20] Sokal D, Hieu DT, et al. Long-term Follow-up Study of Quinacrine Acceptors in Vietnam. Presented to the Medical Committee of the Planned Parenthood Federation of America: St.Louis, Missouri. December 2, 1998.

[21] Sivin I. Dose- and age-dependent ectopic pregnancy risks with IU contraception. *Obstet Gynecol* 1991; 78:291–298.

[22] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from The US Collaborative Review of Sterilization. *M J Obstet Gynecol* 1996; 174:1161–1170.

[23] Franks AL, Beral V, Cates W, Hogue CJR. Contraception and ectopic pregnancy risk. *Am J Obstet Gynecol* 1990; 163:1120–1123.

[24] Dabancens A, Pruyas M, Rivera M, Sokal D, Zipper J. Standardized rates of incidence and prevalence of cervical preclinical pathology in 1,061 women sterilized with intrauterine quinacrine. *Rev Chil Obstet Ginecol* 1994; 59:181–184.

[25] Dabancens A, Pruyas M, Zipper J, Rivera M, Velasco V. Intrauterine quinacrine and risk of endometrial cancer. *Ginecol Reprod* 1998; 6:21–26.

[26] Sokal D, Dabancens A, Guzmán-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. *Fertil Steril* 2000; 74:169–171.

[27] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussel J. The risk of ectopic pregnancy after tubal sterilization. *N Engl J Med* 1997; 336:762–767.

[28] Zador G, Nilsson BA, Nilsson B, Sjalberg NO, Westram L, Wiese J. Clinical experience with the uterine progesterone system (Progestasert®). *Contraception* 1976; 13:559–569.

[29] Tennant RW, Margolin BH, Shelby MD, Zeiger E, Haseman JK, Spalding J, et al. Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* 1987; 236:933–941.

[30] Ames B, Swirsky L. Too many rodent carcinogens: mitogenesis increases mutagenesis. *Science* 1990; 249:970–971.

[31] Kopsidas G, MacPhee DG. Frameshift mutagenesis by 9-aminoacridine: antimutagenic effects of adenisine compounds. *Mutation Res* 1996; 352:135–142.

[32] Clarke JJ, Sokal DC, Cancel AM, Campen DB, Gudi R, Wagner VO, et al. Re-evaluation of the mutagenic potential of quinacrine dihydrochloride dihydrate. *Mut Res* 2001; 494:41–53.

[33] Sarin AR. Quinacrine sterilizations: experience among high risk women. *Acta Obstet Gynecol Scand* 1997; 76(Supl) 167:16 (Abstract).

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S31–S33

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine nonsurgical female sterilization in Baroda, India: 23 years of follow-up of 84 women

R.V. Bhatt

Department of Obstetrics and Gynecology, B.D. Amin Hospital, Baroda, India

Abstract

Objectives: Evaluate the long-term effectiveness and safety of transcervical insertion of quinacrine hydrochloride pellets for nonsurgical female sterilization (QS). *Methods*: During the period June 1979 through January 1980, 84 women were admitted to a study at the Baroda Medical College and Hospital, Baroda, India. Our protocol called for three transcervical insertions of 252 mg of quinacrine hydrochloride to be deposited in the uterus of each patient. Follow-up was scheduled at 6, 12 and 48 months after the last administration. *Results*: These women were 25 to 39 years of age at the time of the QS procedure and now, 23 years later, have completed their reproductive years. There were 4 pregnancies subsequent to the completion of QS, all prior to their 4-year follow-up. Thus, the life-time failure rate for these women was 3.7%. Complaints were minor, especially when compared to surgical sterilization. There were no long-term effects suspected of being attributable to QS. *Conclusions*: QS appears to be a reasonably effective method that is much safer than surgical sterilization.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

For decades, surgical sterilization has been the most effective and the most popular method for limiting family size. It has also been the most widely used. Surgical methods are difficult to provide, thus limiting access. Furthermore, there are life-threatening and other serious complications associated with surgical sterilization and many women fear surgery. Consequently, experimentation with a nonsurgical modality has been considered vitally important for decades. Zipper, of Santiago Chile, who has led the effort to produce such a method from the beginning, designed one that uses quinacrine in the form of pellets. From January 1977 to June 1978, 139 women, under Zipper's direction, gave informed consent at an outpatient clinic in Santiago. They received three transcervical intrauterine insertions of 250 mg of quinacrine pellets [1]. By late 1978, results of this study were found to be promising.

Zipper's first trial of quinacrine pellets had been partially funded by Family Health International (FHI), earlier called the International Fertility Research Program (IFRP), then led by Elton Kessel, and supported by the United States Agency for International Development. In the Fall of 1978, FHI decided to expand this research by undertaking a larger clinical trial that would include centers around the world. With approval from its Human Subjects Committee, FHI chose 4 collaborators, among them the Indian Fertility Research Programme, which appointed the author to conduct this study on its behalf.

Research of the quinacrine pellet method (QS) continued in India until August 14, 1998. It is estimated

* Tel. (91-265)-334302/313182 Fax. (91-265)-334302

E-mail address: gsbt@satyam.net.in (R.V. Bhatt)

Correspondence address: Department of Obstetrics and Gynecology, 1 Shivani Society, Vasana Road (off Old Padra Road), Baroda 390015, India

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

that nearly 30,000 cases were carried out in that country. Indian researchers contributed significantly to the development of the currently recommended protocol for performing QS. But on that date, the government banned QS, criminalizing the procedure. This decision was made without any input from Indian obstetrician-gynecologists or other scientists involved in contraceptive technology. With this in mind, the author decided that, since the patients in his original study would have nearly all entered menopause after 23 years, this would be an appropriate time to do an additional follow-up.

2. Materials and methods

This study was conducted at Baroda Medical College in Baroda, India. The subjects were 84 women who gave informed consent from June 1979 through January 1980. The criteria for admission were that they requested sterilization for family planning reasons and had no history of medical or psychiatric problems. Women who had pathologic pelvic conditions (except mild cervicitis) were excluded. A 252 mg dose of quinacrine hydrochloride, in the form of seven cylindrical pellets, 3.3 mm in diameter, each 4 mm in length, was deposited in the uterus of each patient with the use of a modified Cu-T-200 IUD inserter using a technique similar to the one for CuT placement. Three insertions were made, 4 weeks apart.

The insertions were done on an out-patient basis, without any premedication, during the proliferative phase of the menstrual cycle in interval women (who were not pregnant within the last 42 days). They were observed for 2–3 hours before allowing them to go home. All were sexually active and they were not permitted to use any contraception after the first insertion. Follow-up was scheduled at 6, 12 and 48 months after the last insertion. These patients were also asked to return at any time there were complications or complaints.

In October of 2002 another follow-up visit was requested. This monitoring was completed in March, 2003. Out of 84 women who had QS, 74 were available for follow-up. These patients were asked about any medical problems they might have experienced since QS. Complete physical and gynecological examinations were performed at clinic visits. A Papanicolaou smear was taken on all the subjects who appeared for this follow-up. Ultrasound examinations were performed in 20 cases. Nine other women, with whom we corresponded but did not see at the clinic, were asked to report any pregnancy or illness since QS and whether they had had any physical examination elsewhere since undergoing QS.

3. Results

Results of the study through the 4-year follow-up have been previously reported in detail [2,3]. The mean age of the women admitted was 31.3 years, ranging from 25 to 39. The median number of years of education was 4.4 years and 77.4% were from urban areas. The number of live births was 3.9, with a range of 2 to 6. The last pregnancy outcome before sterilization for over 80% of the women was a live birth, and the mean time interval between the end of their last pregnancy termination and first insertion was 18.5 months. A majority of patients reported that either they or their husbands were the most important person involved in their decision to request sterilization. Over half cited the undesirable side effects of other contraceptive methods as the reason for choosing sterilization.

Three women became pregnant before their third insertion. Their pregnancies were terminated by suction evacuation and they were then excluded from the study. The remaining 81 patients completed all three insertions, with only one requiring analgesia during the procedure. Mild pain was experienced by 10 subjects (11.9%) during the first insertion. Five (6.1%) complained of mild or moderate pain during the second insertion, while 4 women (4.9%) reported pain during the third one.

Follow-up in this study was excellent. All 81 women were seen at a four year follow-up visit. Three pregnancies were diagnosed at 23, 25 and 26 months after the completion of the last insertion. The cumulative life-table pregnancy rate at 48 months was 3.7/100 women.

The most serious complication reported during the first four years was a case of menorrhagia in a 37-year-old patient. An abdominal hysterectomy was performed 3 years after the sterilization procedure. Two women who complained of abdominal pain were examined at

48 months. In one there was a thickening in the right fornix, and in the other tenderness was elicited in the left fornix but no mass was felt. Other follow-up complaints included leukorrhea, backache, hypertension, and amenorrhea – one to four cases each. None of these complications or complaints appeared to be related to the sterilization procedure itself. A comparison of the menstrual cycle length and the duration of menstrual flow between pre and poststerilization data indicated no significant differences.

The follow-up rate after 23 years was even more remarkable – 88% (74 of 84 women). Sixty-five women were examined and 9 were followed-up through correspondence.

No further pregnancies occurred after the four-year follow up. Therefore, the life-time pregnancy rate is 3.7/100 women. Their ages at the time of follow-up ranged from 43 to 60. Except for three women, the rest had entered menopause. Three more had undergone hysterectomy – two for uterine prolapse and one for dysfunctional uterine bleeding. The histology of the specimen did not show any cancer. Two women died due to causes unrelated to QS – one was bitten by a snake and the other was in a motor accident. Six years after QS insertion, one patient suffered from hepatitis Type A. She is now in good health. Four subjects complained of leucorrhoea and six had symptoms suggestive of a urinary tract infection. Three women sustained fractures due to accidental falls. Menopausal symptoms were seen in 9 of the group. Ten had blood pressures greater than 140/90 mm mercury. Breasts were atrophic in 24 cases and looked normal in the rest. No breast lump or any abnormality was noted. Abdominal palpation did not reveal any abnormality. Four women needed hysterectomies; one was recorded at the 4 year follow-up and three more since then. Indications for hysterectomy were uterine prolapse and menorrhagia. Senile vaginitis was seen in 6 women. Two subjects had a monilial vaginal infection. Ultrasound examination was performed in 20 cases. Two patients had small fibroids of 1 cm size on the anterior uterine wall, which did not cause any symptoms.

A Papanicolaou smear was taken in every examined woman. It showed inflammatory changes in 8 of them. Malignant cells were not seen in any smear. Genital malignancy was not seen in any woman.

The patients who came for follow-up were asked if they were satisfied with QS. All except those who conceived were satisfied with the method. They liked its simplicity and reputation for no morbidity or mortality associated with QS. They had heard of complications and even death after surgical sterilization.

4. Conclusions

The long term follow-up of the QS technique shows that it is a simple, inexpensive and effective method of female sterilization. The pregnancy rate is within acceptable limits. Women are largely satisfied with the procedure. There were minimal initial side effects and long-term follow-up does not show any serious adverse effect. The method is simple, cost-effective and is acceptable to women. We strongly feel that QS is a good alternative to surgical sterilization. We do not have data on chances of success for reversing fertility when pregnancy is desired. At present QS should be considered for women who desire no more children.

We feel it is now necessary to review the ban of the QS method in India by the Drug Controller. It would be appropriate for the Drug Controller of India to consult gynecologists in India who have some experience with the method. The US FDA has given permission for a QS trial and it should not happen that India is the last country in the world to recognize the value of this simple, inexpensive and reasonably effective method.

References

[1] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[2] Bhatt RV, Jariwala KM, Bhiwandiwala P, Laufe L. Chemical female sterilization using quinacrine pellets. In: Proceedings of the third international seminar on maternal and perinatal mortality. Hingorani V, Pandit RD, Bhargava VL, editors, Pregnancy Termination and Sterilization. New Delhi, October 3–5, 1980; 370–373.

[3] Bhatt RV, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S35–S43

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

The rate of ectopic pregnancy for 24,589 quinacrine sterilization (QS) users compared to users of other methods and no method in 4 provinces in Vietnam, 1994–1996

D.T. Hieu[a,*], T.T. Luong[b]

[a]*Director (retired), Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi, Vietnam*
[b]*Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi, Vietnam*

Abstract

Objective: To determine the rates of ectopic pregnancy with the use of quinacrine sterilization (QS) compared to other methods and no method (non-users). *Methods*: Four provinces were selected for their above average numbers of women who had undergone QS: Nam Dinh, Nam Ha, Hai Duong and Hung Yen. Case histories related to surgical treatment of all ectopic pregnancies in these 4 provinces from 1994 through 1996 were collected from all hospitals by researchers from the Ministry of Health in June 1997. Using a questionnaire designed for this study, 120 physicians interviewed every woman in her home who had had an ectopic pregnancy during this period. If deceased, a family member was consulted. All interviews were completed in September 1998. The numbers of users of each method and nonusers were calculated from service statistics and demographic data. *Results*: Based on 2,551,355 woman-years of exposure, the rate of ectopic pregnancy among users per 1000 woman-years was calculated to be: 0.26 with QS; 0.42 with surgical sterilization (TL) and IUD; 0.45 with the Pill; 0.50 with condoms; 0.78 relying on withdrawal; and 1.18 among non-users. *Conclusion*: Ectopic pregnancy rates for QS, TL, IUD and the Pill were similar and much lower than the rate for non-users of contraception.

Keywords: quinacrine sterilization, ectopic pregnancy, tubal ligation, female sterilization, IUD

1. Introduction

Ectopic pregnancy is a serious complication in Vietnam where communication and transportation in rural districts are poor. These conditions contribute to the high mortality due to ectopic pregnancy complications found there. Laparotomy remains the only method for treatment. Understandably, ectopic pregnancy is much feared in Vietnam, especially in the countryside.

In recent years, rumors about the likelihood of ectopic pregnancy following sterilization have become widespread. These rumors have been damaging to both surgical sterilization (TL) and quinacrine sterilization (QS). The result: acceptability of TL among women plummeted in recent years. [1]

QS has not been offered in Vietnam since December 1993. The program was halted when the World Health Organization Human Reproduction Program (WHO HRP) sent a letter to Vietnam stating: "WHO experts and FDA officials have said that they would be very surprised if quinacrine did not turn out to be carcinogenic." [2] Neither WHO HRP nor any other institution has offered any evidence to support this claim since it was made. Sokal reported in 2000 that,

* Corresponding author. Tel/Fax: 84-4-943-3207;
E-mail address: ngaquan2000@yahoo.com (D.T. Hieu)
Correspondence address: 41 Tran Quoc Toan Street, Hanoi, Vietnam

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

after 19 years of follow-up and 13,444 woman-years of experience with QS, patients in a Chilean study showed: "Rates of cancer among women exposed to intrauterine quinacrine are not significantly different from population-based rates." [3] Since December 1993, a surgical procedure has been the only sterilization option in Vietnam. However, QS users continue to account for a large fraction of sterilized women in some provinces.

In a study of 31,781 QS cases in Vietnam, we examined ectopic pregnancy in a small subset of women. We found the incidence to be 0.89 per 1000 woman-years. This was higher than the rate reported in the United States after surgical sterilization (0.32 per 1000 woman-years) but lower than among American women not using contraception (2.6 per 1000 woman-years). [4]

However, to counter the rumors we decided to undertake a definitive study to determine the rates of ectopic pregnancy among users of both QS and surgical sterilization, temporary contraceptive methods, and non-users of contraception. Since QS is no longer offered, this study would necessarily be retrospective.

2. Methods

This retrospective study was initiated in June 1997. To insure that an adequate number of QS patients were included, four provinces known to have larger numbers of cases were chosen: Nam Dinh, Nam Ha, Hai Duong and Hung Yen. Researchers from the Ministry of Health obtained permission to collect and copy every single case history related to the treatment of ectopic pregnancy in all district and provincial hospitals in these 4 provinces during the 1994–1996 period. A first analysis was carried out to confirm that only women with a correct diagnosis of ectopic pregnancy would be included in this research.

Each ectopic patient identified by the researchers would be interviewed by one of 120 medical doctors. They are on the staff of one of 15 provincial and district hospitals or of one of the provincial Maternal and Child Health/Family Planning Centers, and provide family planning services in these provinces. A questionnaire was developed by the International Federation for Family Health for this study and modified by the Department of Maternal and Child Health/Family Planning of the Ministry of Health after a pretest of 20 cases.

To minimize potential biases, all interviews took place in the homes of the women who had experienced an ectopic pregnancy. Finding these homes was the most difficult phase of this study because the address recorded in the hospital record was often inadequate. In most cases, a local guide was necessary. This interviewing phase was completed in September 1998.

To calculate and analyze the rates of ectopic pregnancy, we needed to know the number of users of each of the contraceptive methods and no method in the 4 provinces under study. The number of users was determined in the following way: The 4 provinces all lie within the 7-province Red River Delta Region, near Hanoi. This region has the largest population of the 7 regions of the country. Its population is also the most knowledgeable about contraception, with the highest proportion of users of modern methods of contraception of any of the 7 regions. [5] This practice is substantially higher than for the country as a whole. For this reason, it was decided that regional contraceptive prevalence survey data would produce more accurate results than the national statistics. However, QS and TL were combined in the prevalence survey which simply asked the question "female sterilization yes/no." As a result, we decided to use program data to determine the number of QS and TL users in these four provinces.

3. Results

Among 1,654 medical records collected from provincial and district hospitals, 1,582 were chosen for interview. Following a preliminary analysis, the other 72 records were excluded because they were not related to ectopic pregnancy. Table 1 shows the distribution of ectopic pregnancies by age group and province. They are widely distributed across the age groups, reflecting the distribution of all pregnancies by age. Nearly three-fifths occurred to women 30–39 years of age. Lower abdominal surgery resulted in a significantly increased risk of ectopic pregnancy (Table 2) in all provinces studied. About one ectopic pregnancy out of 20 occurred in a woman who had not previously given birth.

The fertility history of women prior to ectopic pregnancy was remarkably similar among the 4 provinces (Table 3). Death of a child from birth until this follow-up among these women was remarkably low

Table 1
Ectopic pregnancy by province and age group, 1994–1996, Vietnam

Province	Age group							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Hai Duong	4	33	122	206	151	97	8	621
Ha Nam	3	18	28	36	44	21	3	153
Hung Yen	2	15	43	76	64	34	3	237
Nam Dinh	6	49	105	178	163	63	7	571
Total *N*	15	115	298	496	422	215	21	1582
(%)	(0.9)	(7.3)	(18.8)	(31.4)	(26.7)	(13.6)	(1.3)	(100.0)

Table 2
History of lower abdominal surgery and pregnancy prior to ectopic pregnancy by province, 1994–1996, Vietnam

Province	Lower abdominal surgery prior to EP[a]		One or more pregnancies prior to EP	
	N	%	*N*	%
Hai Duong	50	8.1	594	95.7
Ha Nam	9	5.9	137	89.5
Hung Yen	21	8.9	223	84.5
Nam Dinh	39	6.8	553	96.8
Total	120	7.6	1,507	95.3

[a] EP = ectopic pregnancy.

at 0.06 children per couple, or about one child lost per 17 couples. Table 4 shows that abortion does not increase the risk of ectopic pregnancy. Women using QS and TL ($N = 13{,}487$) who had not had an ectopic pregnancy [1] had experienced a similar mean number of abortions as the ectopic pregnancy patients (0.92 and 1.07, respectively).

Three deaths were identified in this series (1994–1996), 2 in Nam Dinh Province and 1 in Hung Yen Province (Table 5). The cause of death for all three was the same: severe bleeding without a blood transfusion. None of the deaths were QS or TL patients. Of the 1,582 ectopic pregnancies, 24 were initially misdiagnosed and treated for another condition such as PID. Most underwent surgery immediately (91.5%) and 110 women (7.0%) were observed for a period before surgery. While the diagnosis was confirmed by laparotomy in 97.2% of the cases, a pathology exam was required in the remaining 2.8%. Nearly half of the ectopic pregnancy patients chose to have surgery on both tubes during the ectopic pregnancy operation for permanent contraception (Table 6). All women were asked about their outcomes with these procedures. The gross failure rate for surgical sterilization among

Table 3
Fertility history prior to ectopic pregnancy diagnosis, by province, 1994–1996, Vietnam

Province	Pregnancies (mean *N*)	D&Cs[a] (mean *N*)	MRs[b] (mean *N*)	Spontaneous abortions (mean *N*)	Births (mean *N*)	Living children (mean *N*)
Hai Duong	3.40	0.59	0.40	0.20	2.33	2.17
Ha Nam	3.53	0.45	0.51	0.20	2.47	2.40
Hung Yen	3.37	0.52	0.35	0.16	2.43	2.39
Nam Dinh	3.40	0.38	0.53	0.27	2.35	2.31
Total	3.42	0.48	0.44	0.20	2.37	2.31

[a] D&C, induced abortions.

[b] MR, menstrual regulation (early abortion).

Table 4
Mean number of abortions and menstrual regulations among ectopic pregnancy patients ($N = 1,582$) compared to women using quinacrine sterilization (QS) and tubectomy (TL) ($N = 13,487$)[a] in the Red River Delta, Vietnam, in the 1990s

	Pregnancies (mean N)	Induced abortions (mean N)	MRs[b] (mean N)	Abortions (total mean N)
Ectopic patients	3.2	0.56	0.51	1.07
Non-ectopic patients (QS and TL users)	4.6	0.48	0.44	0.92

[a] See reference [1] for source of these QS and TL data. Note: data on ectopic pregnancy comes from 4 provinces in the Red River Delta: Hai Duong, Ha Nam, Hung Yen and Nam Dinh. Data on non-ectopic pregnancies are from the same 4 provinces and Thai Binh.
[b] MR = menstrual regulation (early abortion).

Table 5
Outcome of ectopic pregnancy by province, 1994–1996, Vietnam

Province	Treatment at admission									
	Deaths within 42 days of LMP[a]		Immediate surgery		Follow-up first		Medical treatment first		Diagnosis confirmed by laparotomy	
	N	%	N	%	N	%	N	%	N	%
Hai Duong	–	–	560	90.2	55	8.9	6	1.0	589	94.8
Ha Nam	–	–	146	95.4	5	3.3	2	1.3	150	98.0
Hung Yen	1	0.4	222	93.7	12	5.1	2	0.8	223	94.1
Nam Dinh	2	0.4	519	90.9	38	6.7	14	2.5	566	99.1
Total	3	0.2	1,447	91.5	110	7.0	24	1.5	1,537	97.2

[a] LMP = last menstrual period.

Table 6
Health outcomes as measured by subsequent serious complications or pregnancy of women who had a tubectomy at the time of ectopic pregnancy surgery vs. women who did not, by province, 1994–1996, Vietnam

Province	Tubectomy, N (%)			No tubectomy, N (%)				Ectopics total N (%)
	Total	Pregnancy	Complications	Total	Pregnancy	Complications	Both	
Hai Duong	330 (53.1)	6 (1.8)	9 (2.7)	291 (46.9)	71 (24.4)	49 (16.8)	7 (2.4)	621 (100.0)
Ha Nam	48 (31.4)	–	1 (2.1)	105 (68.6)	12 (11.4)	20 (19.0)	–	153 (100.0)
Hung Yen	120 (50.6)	4 (3.3)	4 (3.3)	117 (49.4)	21 (17.9)	16 (13.7)	5 (4.3)	237 (100.0)
Nam Dinh	275 (48.2)	8 (2.9)	3 (1.1)	296 (51.8)	80 (14.0)	62 (10.9)	4 (0.7)	571 (100.0)
Total	773 (48.9)	20 (2.6)	17 (2.2)	809 (51.1)	184 (22.7)	147 (18.2)	16 (2.0)	1,586

[a] TL, tubal ligation.
[b] EP, ectopic pregnancy.

these women was 2.6% by the time of the interview. Among those who elected not to be sterilized, 22.7% had become pregnant by the time of the interview. However, patients who had not wished to be sterilized had experienced a much higher rate of serious complications subsequent to their ectopic pregnancy operation (20.2%) than those who were sterilized (2.2%).

Women who had an ectopic pregnancy following TL (Table 7) or QS (Table 8) were carefully studied to determine the distribution of the ectopics over time. Most ectopics, like most uterine pregnancies, tend to occur earlier rather than later, with the majority occurring within the first 3 years. However, in this study 2 cases are reported among TL users even after

Table 7
Time interval between sterilization and ectopic pregnancy (EP) diagnosis for tubectomy (TL) users in 4 provinces, 1994–1996, Vietnam ($N = 27$)

Patient (initials)	Sterilization date	EP diagnosis date	Time interval (months)
1. TTD	05/13/96	05/21/96	same month
2. VTT	07/01/94	03/14/95	8
3. TTT	09/01/93	06/10/94	9
4. BTK	08/19/95	05/03/96	9
5. TTL	01/01/94	01/27/95	12
6. DTT	08/23/94	08/11/95	12
7. NTD	03/13/95	05/18/96	14
8. PTL	03/01/95	06/25/96	15
9. PTH	08/01/93	01/04/95	17
10. NTT	07/01/93	12/13/94	17
11. NTH	03/30/94	09/08/95	18
12. TTH	10/01/94	08/21/96	22
13. VTG	08/01/93	07/19/95	23
14. NTL	04/01/94	03/11/96	23
15. BTL	04/29/94	05/15/96	25
16. PTL	05/06/94	08/14/96	27
17. DTG	05/10/93	12/30/95	31
18. PTL	04/01/93	12/24/95	32
19. KTT	09/23/93	06/21/96	33
20. HTT	09/10/93	06/10/96	33
21. LTQ	01/01/91	01/21/94	36
22. TTN	04/12/92	06/22/95	38
23. P TN	01/01/93	05/03/96	40
24. NTO	01/01/89	08/27/95	79
25. VTL	01/01/87	10/18/94	100
26. HTO	01/01/87	08/18/95	103
27. NTO	07/01/86	06/17/96	119
Mean months			33.1

8 years and one after 10 years and 4 cases are reported after 5 years among QS users. The mean number of months from the time of the sterilization procedure until ectopic pregnancy was 38.5 for QS and 33.1 for TL.

Table 9 shows the contraceptive method in use at the time of the ectopic pregnancy or non-use. There is a remarkable consistency across the 4 provinces. With a few minor exceptions, the ranking of each province for each method is consistent with the total number of ectopics in that province.

Table 8
Quinacrine sterilization users ($N = 17$): time interval between the second insertion of quinacrine and ectopic pregnancy (EP) diagnosis

Patient (initials)	Sterilization date	EP diagnosis date	Time interval (months)
1. NTH	03/15/94	01/21/95	10
2. NTX	07/25/93	07/21/94	12
3. LTH	07/01/93	12/05/94	17
4. LTH	05/02/92	05/09/94	24
5. VTN	12/28/93	12/13/95	24
6. BTV	05/26/90	06/16/92	25
7. DTL	02/04/94	04/05/96	26
8. TTG	08/18/92	04/11/95	32
9. HTH	11/15/92	11/03/95	36
10. LTT	05/20/92	05/03/95	36
11. VTT	09/15/93	09/05/96	36
12. VTT	01/03/93	02/25/96	37
13. HTL	04/07/91	10/29/94	42
14. DTN	08/30/91	03/11/96	55
15. NTN	04/10/90	04/23/95	60
16. NTT	02/09/90	03/03/95	61
17. VTX	03/03/91	06/02/96	63
18. TTN	01/01/90	08/01/95	67
19. DTQ	03/10/92	11/09/97	68
Mean months			38.5

The number of QS and TL procedures performed in each province over time is given in Table 10. All surgical sterilizations are tubectomies performed by minilaparotomy. No laparoscopic procedures were performed in these provinces at that time. A downward trend in the number of tubectomies is evident in all provinces. Since all QS procedures had been carried out prior to the study period, each of the 24,589 QS patients was exposed to the risk of ectopic pregnancy (as a QS user) for the full 3 years (1994–1996). However, only the TL patients who had been operated on before January 1, 1994 were exposed to this risk for the full three years. On average, women who had surgery in 1996 were exposed to 0.5 years of risk, while in 1995, an average of 1.5 years of risk and in 1994, an average of 2.5 years of risk. For this analysis we must, of course, make an assumption that an equal number of procedures are performed each month of that year. Knowing the number of QS and TL procedures

Table 9
Users of each contraceptive method or none at time of ectopic pregnancy, by province, 1994–1996, Vietnam ($N = 1582$)

Province	QS	Tubectomy	Vasectomy	IUD	Condom	Pill	Withdrawal	Other[a]	Non-use	Total
Hai Duong	5	10	–	250	23	8	56	5	264	621
Ha Nam	2	–	–	32	10	1	6	5	97	153
Hung Yen	4	9	–	85	19	7	43	2	68	237
Nam Dinh	8	8	1	188	37	9	89	12	219	571
Total *N*	19	27	1	555	89	25	194	24	648	1582
(%)	(1.2)	(1.7)	(0.1)	(35.1)	(5.6)	(1.6)	(12.3)	(1.5)	(40.9)	(100.0)

[a] Includes periodic abstinence.

Table 10
Quinacrine sterilization (QS) and tubectomy (TL) by province, 1994–1996, Vietnam

Province	Year	QS	TL
Hai Duong	Until 1994	10,227	3,541
	1994	0	3,322
	1995	0	2,769
	1996	0	2,692
	Total	10,227	12,324
Ha Nam	Until 1994	3,296	1,384
	1994	0	1,278
	1995	0	1,065
	1996	0	882
	Total	3,296	4,609
Hung Yen	Until 1994	3,221	1,779
	1994	0	1,660
	1995	0	1,384
	1996	0	1,345
	Total	3,221	6,168
Nam Dinh	Until 1994	7,845	2,771
	1994	0	2,558
	1995	0	2,132
	1996	0	1,764
	Total	7,845	9,225
Total		24,589	32,326

performed each year as shown in Table 10 allows the calculation of the number of years of exposure to the risk of ectopic pregnancy. The number of woman-years of exposure for QS patients (24,589) times 3 years equals 73,767 woman-years. The number of woman-years of exposure for TL patients was determined by multiplying the number of women exposed by the length of exposure and adding the products. The total amounts to 64,836 woman-years.

These numbers of years of exposure, 73,767 for QS and 64,836 for TL, are used in Table 11 to calculate the rate of ectopic pregnancies. Since there were 19 ectopics during the 1994–1996 period of study and 73,767 woman-years of exposure, the QS rate per 1000 woman-years is 0.26. The formula for calculating the rate of ectopics per 1000 woman-years is a division of their number by the number of years of exposure times 1000. Similarly, the rate for TL is 0.42. For the remaining methods shown in Table 11, as well as no method or "none," survey data for the Red River Delta was used to determine the prevalence of use of each method and no method. There are an estimated 844,800 married women in the 4 provinces under study. The number of users is calculated by multiplying the prevalence by the number of married women. The number of woman-years of exposure is determined by multiplying the number of users by 3 years since women were exposed from 1994–1996. This, of course, assumes that the contraceptive mix is static for the 3-year period. The same formula is then applied to calculate the rate of ectopics for each method and no method.

The rate for vasectomy was based on a single ectopic pregnancy and 15,206 years of exposure and may not be reliable. The rates found for the remaining methods and no method were as follows: IUD 0.42/1000 woman-years, Pill 0.45, condom 0.50, withdrawal 0.80, and no method 1.53.

The 1,582 ectopic pregnancy patients were asked

Table 11
Rate of ectopic pregnancy for quinacrine sterilization (QS), tubectomy (TL), other contraceptive methods and no method in 4 provinces in the Red River Delta, Vietnam, 1994–1996

Contraceptive method	Prevalence of method (proportion)	Users[a] (*N*)	Woman-years exposure (*N* users × 3 years)	Ectopics (*N*)	Ectopics (rate per 1000 woman-years)
QS	0.050[b]	24,589	73,767	19	0.26
TL		32,326	64,836	27	0.42
Vasectomy	0.006	5,069	15,206	1	0.07
IUD	0.516	435,917	1,307,751	555	0.42
Pill	0.022	18,586	55,758	25	0.45
Condom	0.070	59,136	177,408	89	0.50
Withdrawal	0.096	81,101	243,303	194	0.80
Others	0.075	63,368	190,080	24	0.13
None	0.167	141,082	423,246	648	1.53
Total	1.000		2,551,355	1582	

[a] Number of users based on an estimate of 844,800 married women in these 4 provinces from the Department of Maternal and Child Health/Family Planning, Government of Vietnam, Hanoi 1995.
[b] Survey data do not distinguish between QS and TL female sterilization. The questionnaire reads "Female Sterilization Yes/No." Service program data were used instead. Estimated number of female sterilizations using prevalence survey data was 42,240 (0.05 × 844,800) vs. 56,915 at the end of 1996, using service program data (6,683 cases were performed in 1996).

Table 12
Opinions of 1,582 ectopic pregnancy patients on currently available contraceptives in 4 provinces during study period June 1997 – September 1998[a], Vietnam

Opinion	Method					
	IUDs (%)	Surgical sterilization (%)	Pills (%)	Injectables (%)	Condoms (%)	Traditional (%)
Very good	30.7	73.9	22.7	30.4	35.9	19.6
Good	38.3	6.2	30.7	53.5	25.8	28.8
Acceptable	31.0	19.9	46.6	16.1	38.3	51.6

[a] Quinacrine sterilization was not available during this period.

during the interview what their opinion was of the currently available contraceptive methods in the 4 provinces. QS was not available during the June 1998–September 1998 period. As shown in Table 12, surgical sterilization was overwhelmingly the method of choice. When this question was asked, 97.1% of the respondents had not yet sought sterilization.

4. Discussion

There was a substantial difference in the ectopic pregnancy rate for QS (0.26) and for TL (0.42). It is possible that this difference is an artifact. The incidence of ectopic pregnancy is not constant over time after either QS or TL. More occur in the first few years following these procedures. Over time they occur less and less until menopause. This shortcoming could not be overcome. Our QS program was initiated in 1989 and halted in December 1993. On average, QS patients had already been exposed to the risk of ectopic pregnancy for 2 years before this study was initiated, which is 2 years of the highest risk for ectopics. The ectopics that occurred during 1989–1993 do not appear in this study. To have included them would have more than tripled the investment needed to conduct this study. On the other hand, 70.7% (calculated from

Table 10) of the TL patients had less than 3 years of exposure to ectopic pregnancy following their sterilization, again the period when the risk is highest.

This same artifact accounts for some of the differences in the ectopic pregnancy rate we reported in 1993 [4] of 0.89 ectopics/1000 woman-years in Nam Ha Province now subdivided into two of the provinces reported on here, Ha Nam and Nam Dinh. All of these procedures had been performed over the previous 3 years, when, as is already noted, the risk of ectopic pregnancy is the highest. As the years since the procedure increase then the risk per year concurrently falls, as does the overall risk per 1000 woman-years. Had we followed this same group of women from our earlier report, the long-term risk would probably have also approached 0.26/1000 woman-years.

There is a second factor contributing to the rate of ectopic pregnancy following sterilization. The higher the overall failure rate, the greater the risk of ectopic pregnancy. We believe the rate of failure with QS was higher than the rate seen in this TL series. Unfortunately, it is not possible to accurately determine the QS failure rate for reasons described in a companion paper [1]. We will not be able to determine the magnitude of the effect of this second factor on the ectopic failure rate for QS. In any case, the QS ectopic rate is comparable to TL and far lower than the rate seen with non-use of contraception (1.53/1000 woman-years).

Also, the mean number of months from the time of the sterilization procedure until ectopic pregnancy was different for QS (38.5 months) compared to TL (31.1 months) as seen in Tables 7 and 8. The same artifact described above accounts for this difference. These two findings provide further evidence to support this conclusion that time of the procedure versus the period of the follow-up accounts for the difference in rates reported in Table 11 for QS and TL.

The temporary methods fared well compared to the sterilization methods. In particular, it was important to establish that the IUD was comparable (0.42) to sterilization and far lower than no use of contraception (1.53) because IUDs currently dominate our family planning program, accounting for 51.6% of all married women in Vietnam and 78% of all users of modern methods of contraception. Condoms and withdrawal are the least effective (0.50 and 0.80, respectively), failing more often than the other temporary methods reported on here. Nevertheless, both condoms and withdrawal substantially reduce the risk of ectopic pregnancy compared to non-use of contraception.

Only 3 ectopic pregnancy deaths are reported in this series. All 3 occurred at the district level. We believe the actual number to be far greater. All too often, death occurs before a woman arrives at a hospital, either in the woman's home, on the road or in her local clinic. Death from ectopic pregnancy in Vietnam is a function of how well the communication and transportation systems are developed. The majority of ectopic pregnancy patients come to health facilities only when the clinical symptoms are very clear. Very few cases are diagnosed early using sonography, laboratory tests and/or laparoscopy because of their unavailability. Drug therapy or conservative surgery were never used for treatment. Removal of the pregnant tube is performed at both the provincial and district levels. Of the 1,581 ectopic pregnancy patients, 24 were treated with medicine alone because they had been misdiagnosed as infections around the uterus, such as pelvic inflammatory disease or colitis. The low rate of death once women arrive at the hospital is encouraging.

The risk of ectopic pregnancy following QS and TL does not completely disappear until menopause. Women seeking sterilization should be made thoroughly aware of this at counseling. Symptoms should be stressed as a part of the counseling process. All clinic staff must be similarly informed.

Currently, there are rumors circulating in Vietnam that the use of IUDs and induced abortion are the main causes of ectopic pregnancy. Abortion does not increase the risk of ectopic pregnancy. It is clear from Table 11 that IUDs do not increase the risk of ectopic pregnancy. Quite to the contrary, IUDs reduce the risk of ectopic pregnancy by nearly three-fourths, compared to non-users of contraception, who face the greatest risk of ectopic pregnancy. This study shows that, in the long run, sterilization, either QS or TL reduces the risk of ectopic pregnancy most of all.

The very favorable attitude toward sterilization found in this study (Table 12), shows a clear preference for sterilization, among women who had had an ectopic pregnancy. This leaves little doubt that a large proportion of women in Vietnam would accept QS if this method is offered again. This finding is consistent with a retrospective study conducted by Family Health International in 1994 reporting that 86% of QS users felt QS

to be a good choice of contraception for them. Furthermore, 88% had already recommended the method to someone else [6]. The low infant and early child mortality found in this study give couples confidence that their children will survive, making sterilization a most acceptable and more attractive option. Our program has been plagued by rumors, often from the international press, that QS, TL, IUDs and abortions cause ectopic pregnancy. This study, which included 2,551,355 woman-years of exposure to the risk of ectopic pregnancy (Table 11), should lay those rumors to rest.

References

[1] Hieu DT, Luong TT, Anh PT, Ngoc DH, Duong LQ. The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases. *Int J Gynecol Obstet* 2003; 83 (Suppl 2):S77–S85.

[2] The editors. Death of a study: WHO, what, and why. *Lancet* 1994; 343:987–988.

[3] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: update through 1996. *Fertil Steril* 2000; 74:169–171.

[4] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[5] National Committee for Population and Family Planning. Demography and Health Survey 1997, Vietnam Government Printing Office, Hanoi, March 1999.

[6] Hieu DT, Vinh DQ, Tong NK, Waszak C, Katz K, Hanenberg R, Sokal DC. A retrospective study of quinacrine sterilization in Vietnam. Unpublished report prepared by Family Health International for presentation at the Quinacrine Sterilization Dissemination Meeting In Hanoi, Vietnam February 1995; www.quinacrine.com/archive/chie95-1.pdf.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S45–S49

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

An FDA Phase I clinical trial of quinacrine sterilization (QS)

J. Lippes*, M. Brar, K. Gerbracht, P. Neff, S. Kokkinakis

School of Medicine, State University of New York at Buffalo Buffalo, New York, USA

Abstract

Objective: To review the significance of a United States Food and Drug Administration (FDA) approved Phase I clinical trial of a new use for an old drug, quinacrine. To discover whether ultrasound may have utility in quinacrine sterilization (QS). *Method*: This clinical trial began on 16 September 2000 at the Women's and Children's Hospital of Buffalo (WCHOB) in Buffalo, New York. Ten patients volunteered to have QS. These subjects were carefully followed with regularly scheduled examinations, including extensive laboratory blood tests. In addition, each patient had a trans-abdominal ultrasound examination six weeks or later past the date of the second insertion of quinacrine. The trial was completed on 30 April 2003. *Results*: Laboratory results fell within normal limits, thus providing additional evidence to affirm the lack of toxic effects of QS. With ultrasound, we were able to see scars in both oviducts on all of our patients. One patient with a small scar as seen on ultrasound became pregnant. *Conclusion:* QS was found to be safe and effective. Ultrasound holds the promise of reducing the failure rate.

Keywords: quinacrine sterilization (QS), FDA, oviducts, ultrasound

1. Introduction

Quinacrine has been safely used for over 70 years to treat malaria. More than a 100 million people have taken this drug and no toxicity of any major importance has been reported. The drug is still being used for treating other diseases including giardiasis, rheumatoid arthritis, lupus and tapeworm. In 1942, the Winthrop company published a 71-page bibliography with 171 toxicology articles attesting to the safety of quinacrine [1].

QS now has a history spanning more than 30 years of continuously improving results attesting to its safety and effectiveness [3–7]. Kessel reported on 100,000 documented cases of QS without a death and without a major adverse event (AE) requiring surgery [7].

This paper describes an FDA-approved Phase I clinical trial of QS. It was directed and managed at the Women's and Children's Hospital of Buffalo (WCHOB), in Buffalo, New York. The protocol for this study was approved by the Investigational Review Board (IRB) of WCHOB. The investigators took the on-line course and exam for the protection of human subjects offered by the United States National Institutes of Health (http://ohsr.od.nih.gov/cbt). This hospital is one of the main teaching institutions of the School of Medicine of the State University of New York at Buffalo.

2. Materials and methods

An important concern of any clinical investigation

* Corresponding author. Tel. 716-633-6663; Fax 716-633-5664.
E-mail address: jlip@acsu.buffalo.edu
Correspondence address: 31 Hampton Hill Drive, Buffalo, NY 14221, USA

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

is protection of human subjects. For this trial, the investigators read and became familiar with the Belmont Report, The Helsinki and International Harmonic Conventions, a requirement of the IRB of the WCHOB for any research involving human subjects.

Recruitment of patients was accomplished by posting notices in various hospital clinics and advertising in local newspapers, with the prior approval of the IRB of WCHOB. Each patient was informed about quinacrine sterilization when she made an inquiry. She was provided with written materials and watched a video describing the technology. Patients, who were all Caucasian, were then given an informed consent document to take home for one month or longer if needed. This enabled them to read it at their leisure and consult with relatives, spouses, friends and advisors, as they deemed necessary. At the second clinic visit, they signed the informed consent, keeping a copy for themselves. At this visit, a medical history was obtained and a complete physical examination, including a pelvic exam, was performed. All except one of these women had regular menses. Extensive laboratory work was done at this visit as well as on subsequent visits. Laboratory tests included a urinary pregnancy test (UPT), a urine analysis (UA) and a complete blood count (CBC) with a differential count. Other tests administered were electrolytes, a blood urea nitrogen (BUN), creatinine, blood glucose and glucose-6-phosphate dehydrogenase (G6PD). Quinacrine is contraindicated in patients with a G6PD deficiency.

A Pap smear of the cervix and vagina was done, and cultures were obtained for gonorrhea and chlamydia. These were repeated every six months. Patients who demonstrated pathology either on physical exam, laboratory tests or with the cultures were either treated or referred to an appropriate clinic for further therapy. They were readmitted into the program when these conditions were cleared and the appropriate laboratory tests came within normal limits. Timing of the third visit was determined by the patient to have QS performed within three days of the end of the next menses.

At the time of this first quinacrine insertion, a UPT was done and patients were given a choice of a backup contraceptive to be used for three months to prevent pregnancy during the scar-forming period. Depot medroxyprogesterone acetate (DMPA) was one convenient way to provide the desired three months of protection. Other contraceptives were offered with the choice being left to the patient. A second insertion of quinacrine was set to follow four weeks after the first one. At each visit, a UPT was done before the procedure to avoid inserting quinacrine into a pregnant uterus. Follow-up visits were scheduled at 3, 6, 12 and 15 months after the second visit. To manage pain and cramps we used Tylenol® and/or Tylenol® with codeine, and avoided relying on non-steroidal anti-inflammatory drugs (NSAID). AEs were carefully recorded at all patient contacts, including telephone calls. Fifteen months of follow-up of each subject were summarized to allow at least one year of exposure to QS for analysis.

3. The use of ultrasound

After initiating our clinical trial, we learned about the value of pelvic ultrasound (US) as applied to QS from Dr. Claudia Ramos Ferreira of Belo Horizonte, Brazil [8]. We were impressed by Dr. Ferreira's pictures demonstrating, for the first time, scars in the oviducts. US was then used to evaluate oviductal scar formation on all our ten patients. An ATL-5000 ultrasound machine with three-dimensional software enabled us to obtain an in-depth view of the pelvis. Utility was found with a 5 to 4 MHz transducer and on those occasions where endovaginal examination was done, a 7 to 10 MHz endovaginal transducer was used. All US pictures were taken with the transducer viewing the pelvis transabdominally. Results of this are presented in Figs. 1 through 4.

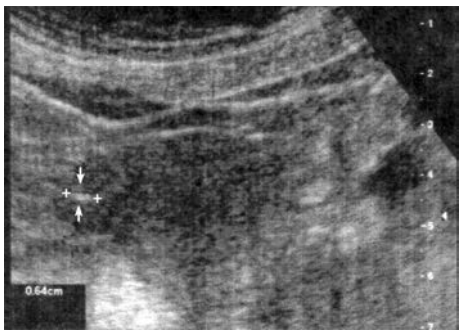


Fig. 1. Scar in right oviduct measuring 0.64 cm. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

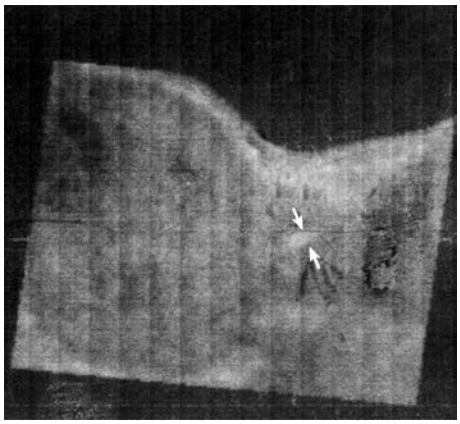


Fig. 2. Scar in left oviduct. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

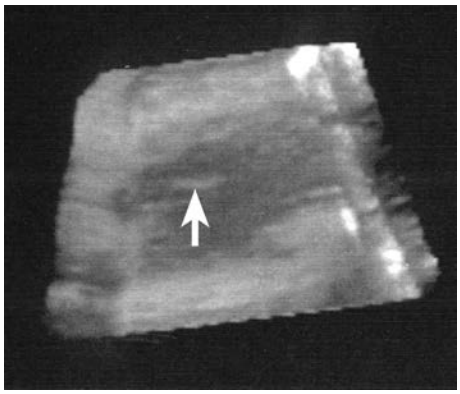


Fig. 3. Scar in oviduct. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

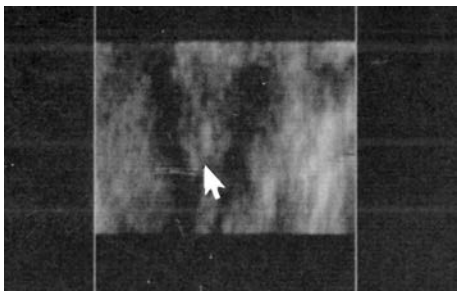


Fig. 4. Scar in oviduct. Note: Canalization through this 3 mm scar. Women's and Children's Hospital of Buffalo. Buffalo, New York, 2002.

4. Results

Ten patients had volunteered for QS in this FDA approved study. Admission and follow-up of these women provided data summarized in Table 1, which also shows the demographic characteristics of the study population. The primary goal of a Phase I FDA study is safety, and this was demonstrated when none of the patients suffered any serious AEs, Pap smears showed no adverse cytologic changes and all laboratory tests fell within normal limits. One exception was a patient who had a hematocrit slightly lower than normal. She was placed on iron with vitamin C and her family doctor was notified about the mild anemia.

Since the FDA had requested that the majority of our subjects should be at high risk, eight of the ten were so recruited. In this high-risk definition is obesity and heavy smoking. Four patients were diagnosed as obese and four were known to be heavy smokers. One also had hypertension. Another had suffered degenerative lumbar discs and vertebrae which necessitated surgical placement of a spinal prosthesis. As she was unable to lie on her back for more than ten minutes, she was considered a high risk for general anesthesia and/or surgery. Two patients were normal.

Some of the women suffered minor AEs, e.g., abdominal cramps, mild pain, nausea, yellow vaginal discharge and pruritis. One had nausea and emesis the evening after a quinacrine insertion. After the first patient complained of yellow discharge and pruritis, we recommended that they all douche once a day as soon as they see the discharge. This eliminated the annoying side effect of pruritis for the remainder of our group. Minor complaints were easily managed.

The second part of this trial involved the use of transabdominal ultrasound of all patients. Oviductal scars could be seen in all ten cases. Typical US pictures are shown in Figs. 1–4. Scars varied in size from 3 mm to 15 mm. There was one pregnancy failure which occurred 18 months after the patient had received her second insertion of quinacrine. Interestingly, the smallest measured scar of 3 mm was observed in this patient, and US examination was repeated for her at 12 weeks' gestation. A canal could be seen coursing through this small 3 mm scar (Fig. 4). Scanning, which is a motion picture of the pelvis, is frequently necessary to ascertain that a scar is definitely present and a snapshot can be taken but may not be persuasive, as exemplified in Figs. 3 and 4.

Table 1
Summary of 10 patients receiving intrauterine quinacrine sterilization (QS). Women's and Children's Hospital of Buffalo, Buffalo, New York. September 16, 2000 – May 1, 2003

Patient #	Age	Parity	Gravida	Medical complications	Menses	1st Visit EDU	2nd Visit H&P	3rd Visit 1st Insert	Phone Call	Lab Work	Contra-ception	4th Visit 2nd Insert	2nd Phone Call	Adverse Events	WM
1	33	5	5	Smoker	Reg	9/16/00	10/17/00	10/26/00	11/3/00	WNL	DMPA	11/29/00	12/6/00	None	18.0
2	29	1	1	Obesity, 181 lbs.	Irreg	12/4/00	1/8/01	3/5/01	3/12/01	WNL	DMPA	4/2/01	4/9/01	Severe cramps and emesis after 1st insert	36.5
3	40	2	2	None	Reg	1/8/01	2/7/01	2/21/01	2/28/01	WNL	OC	3/21/01	3/28/01	Slight bleeding; Slight Cramps, 1st Insert	37.5
4	45	7	9 2 AB	Smoker, 1 small fibroid	Reg	2/1/01	2/21/01	4/20/01	4/27/01	WNL	Condoms	5/17/01	5/24/01	Slight cramps, 1st insert and pruritis	32.5
5	38	3	6 2 spont AB 1 ectopic	3 degenerative discs Walks with cane. On methodone	Reg	2/16/01	4/4/01	6/6/01	6/13/01	Low hct 1st visit	Condoms	8/27/01	9/3/01	Mild cramps 1st insert Moderately severe cramps 2nd insert	27.0
6	30	2	2	None	Reg	3/5/01	4/20/01	5/8/01	5/15/01	WNL	OC	7/6/01	7/13/01	Slight cramps	30.5
7	32	2	3	Obesity, 176 lbs.	Reg	3/12/01	5/3/01	5/29/01	6/5/01	WNL	OC	6/27/01	7/4/01	None	31.0
8	36	4	4	Smoker, Obesity 169 lbs.	Reg	4/19/01	5/30/01	6/5/01	6/12/01	WNL	Condoms	7/6/01	7/13/01	Night sweats after each insertion	30.5
9	41	3	4	Smoker	Reg	8/17/01	9/11/01	11/19/01	11/26/01	WNL	DMPA	12/19/01	12/26/01	Mild cramps Slight vaginal discharge 1st insert	19.0
10	41	1	1	Obesity	Reg	9/27/01	11/12/01	12/4/01	12/11/01	WNL	DMPA	1/16/02	1/23/02	Slight vaginal discharge each insert	17.0
Mean	36.8	3.0	3.5												28.0
															Total[a] 279.5
															Range 17–45 months

Abbreviations:
EDU, Educational visit
WNL, Within normal limits
DMPA, Depot medroxyprogesterone acetate
AE, Adverse event
WM, Woman-months
H&P, History & physical examination
OC, Oral contraceptive

[a] 1.5 months subtracted from each case after date of 2nd insertion. During this time, alternate contraception was used to allow for scar formation.
Race: all patients were Caucasian.

5. Discussion

This paper adds to the volume of literature on the safety and effectiveness of QS. It is important to note that this study was carried out with the approval of the United States Food and Drug Administration (FDA) as well as the IRB of the WCHOB. The concern that intrauterine quinacrine might cause cancer is now seen to be remote. Long clinical experience in many countries has revealed no evidence of an increase in the incidence of uterine or any other cancer associated with QS [9]. Furthermore, the National Cancer Institute, in its annual report of 1994, lists quinacrine as an anti-carcinogenic compound [10]. Previously, the FDA had approved a pre-hysterectomy study of QS [2].

For pain or cramps patients received or were prescribed Tylenol® or Tylenol® with codeine. We avoided using nonsteroidal anti-inflammatory drugs (NSAID). Our rationale for this is that pre-hysterectomy studies of QS have shown it to produce inflammation followed by sclerosis and scarring [2]. As inflammation preceded scarring, it seemed reasonable to expect that an anti-inflammatory drug might inhibit the effect of quinacrine. QS produced no changes in extensive laboratory tests performed repeatedly on all ten patients. In this small series, QS has proved to be both safe and effective as is already well documented in the world's medical literature [2–6].

The ability to see the oviductal scars with ultrasound was reassuring to both patients and staff. The observation that the one failure coincided with the smallest fallopian tube scar presents a potential practical application of ultrasound for QS. A thesis is suggested that the size of the scar may correlate with failures of QS, i.e., the smaller the scar the greater the chance for a failure or pregnancy. Will we arrive at the day when the gynecologist will be able to recommend a third insertion of quinacrine because the scar in the oviduct is too small? This knowledge can only be acquired when QS is in the hands of many clinicians and we can collect and analyze data from a large number of collaborative studies.

References

[1] Winthrop. Atabrine hydrochloride, Annotated Bibliography 171 Refs. From the National Research Council, Division Medical Sciences, Office of Medical Information 1942 (QV 58--791A).
[2] Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. *Contraception* 1996; 54:181–186.
[3] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.
[4] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 871 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.
[5] Bhatt RV, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.
[6] Thakur PS. Quinacrine sterilization in Tripura, India. *Contraception* 2001; 64(5):277–279.
[7] Kessel E. 100,000 quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.
[8] Ferreira CRC, Magalhães DRB, Ferreira DC, Hanan MZ, Camargos AF. Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women.*Int J Gynecol Obstet* 2003; 83 (Suppl 2):S59–S66.
[9] Lippes J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2002; 77:1106–1109.
[10] National Cancer Institute, Chemoprevention Research, NCI, Division of Cancer Prevention and Control – Annual Report. 1994; http:://dcp.nci.nih.gov/reports/ar/94/CPRP.html.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S51–S58

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

A comparison of quinacrine sterilization (QS) and surgical sterilization (TL) in 600 women in Guizhou Province, China

W. Lu[a,*], J. Zhu[b], C. Zhong[b], Y. Zhao[b]

[a]*Center for Research on Population, Guizhou University, Guiyang 550025, China*
[b]*Guizhou Provincial Research Institute for Family Planning, Guiyang 550025, China*

Abstract

Objectives: Compare the safety and efficacy of quinacrine sterilization (QS) and surgical sterilization, also known as tubal ligation (TL). *Methods*: 300 women accepted QS in Guiyang, China during the period from July 1995 to September 1997. Each patient was scheduled for follow-up at 3, 6, 12 and 24 months. In March 1998, a comparison group of 300 women electing TL during the same time period was systematically chosen. Researchers visited the village of every woman and conducted a structured interview. Each candidate was given a general health and pelvic exam at a clinic in her village. All interviews and exams were completed in August 1998. *Results*: Of the 289 QS patients interviewed (a follow-up rate of 96.3%), 265 had had 2 insertions. There were 3 pregnancy failures for a cumulative life table failure rate of 1.2 per 100 women at 24 months. The 299 TL patients (a follow-up rate of 99.7%) had a similar rate of 0.7. There were no life-threatening side effects or deaths in either group. QS was less disruptive, more easily tolerated, required fewer resources and was viewed more favorably than TL by women and their spouses. *Conclusions*: Both methods were found safe and very effective. However, QS was considered to be more acceptable than TL.

Keywords: quinacrine sterilization, nonsurgical sterilization, tubal ligation

1. Introduction

Guizhou is a province of more than 36 million people. It has the second-lowest per capita income in China. As in most countries, there is a great demand for simple, safe, effective and inexpensive sterilization services. When the leadership in Guizhou Province learned of quinacrine sterilization (QS) in 1993, tens of thousands of cases had already been performed in Vietnam and elsewhere [1]. Reports on QS in China were limited to a single 18-month follow-up study of 100 cases by Dr. Ding Juhong in Nanjing, Jiangsu Province [2]. In 1993, QS was adopted by the Guizhou Provincial Science Commission (GPSC) as one of its Eight Five-Year Key Research Projects. That same year, the Guizhou Provincial Research Institute for Family Planning was chosen to conduct research on this new method. During the course of our information gathering process, we received assistance from the Center for Research on Population and Security (CRPS) in the United States. With the approval and support of the Guizhou Provincial Family Planning Commission and the GPSC, we conducted a clinical trial of 300 cases between July 1995 and September 1997. In March 1998, the State Family Planning Commission of China in Beijing requested that a retrospective study be undertaken that would compare the experiences of the

* Corresponding author. Tel: 86-851-699-1403; Fax: 86-851-699-1403.
E-mail address: luweiqun@public.gz.cn (W. Lu)

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

QS patients to those of 300 women who had chosen surgical sterilization at a similar time. This report focuses on that comparison.

2. Materials and methods

The QS protocol for this trial used quinacrine hydrochloride in the form of pellets. Each pellet is 3.5 mm in diameter and 5 mm in length and contains 36 mg of quinacrine. All pellets were provided by CRPS. Seven pellets (252 mg) were deposited using a modified CuT intrauterine device (IUD) inserter from 3 to 7 days after menstruation ended and/or 6 weeks after the last delivery or abortion. A second insertion was performed 4 weeks later. This group included 300 women of child-bearing age who meet the following criteria: volunteer to receive this permanent sterilization and to participate in post-procedure follow-up scheduled at 3, 6, 12 and 24 months. Those who have post-procedure amenorrhea would submit to pregnancy tests as well as pelvic and ultrasound exams. Excluded from the study were women with a history of ectopic pregnancy, psychosis, other serious systemic diseases and reproductive system diseases. For inclusion in the study, her uterine cavity should measure between 5–8 cm in length. Three study sites were chosen in suburban Guiyang. These were the family planning stations in the districts of Huaxi, Baiyun and Wudeng. All women were asked to remain in a supine position for 2 hours immediately after each insertion before leaving the clinic. Each patient was instructed to use a temporary method of contraception for 3 months from the time of the first insertion.

The comparison or control group consisted of 300 women who had undergone tubal ligation (TL). The protocol consisted of a tubectomy procedure involving a small abdominal incision and removal of approximately 1.5 cm of the fallopian tube. These patients had been sterilized in a routine service program and had not agreed in advance to any long-term study protocol. Only women who volunteered to participate were included. Each of the 3 clinics chosen for the QS study also maintained a registry of all TL cases performed at that clinic. Focusing on the portion of the registry for the period from July 1995 to September 1997, a systematic sample was taken from each clinic, to approximate the number of QS procedures performed there. There were about 3 times as many TL cases as QS procedures at each clinic. Therefore, every third TL case on the registry was selected in each clinic until the requisite number for the study had been identified.

Both groups of women had a general health exam, including a battery of liver and kidney function tests, and a pelvic exam, including a cervical smear. Also, subsets of QS patients underwent an endometrial biopsy and/or a battery of reproductive hormone tests. This battery included: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2) and a prolactin (PRL) measurement. Twenty-five women who were relying on condoms for contraception were systematically selected from 2 of the clinics (Huaxi – 13 women and Baiyun – 12 women) to serve as a control group. The women in the condom group were registered in each clinic. Then, for the purpose of identifying a representative sample, every third woman on the list was chosen until the appropriate number was reached. The QS study group was similarly chosen from these same 2 clinics by selecting every third woman on the list of QS patients in each clinic until 15 women were chosen from each clinic. Blood samples were collected from both cases and controls for the hormone study during days 3 to 7 after menstruation. The subset of QS patients who underwent an endometrial biopsy was limited to those women who agreed to this invasive procedure when asked during the interviews for the retrospective study.

Between March and August 1998, researchers visited the villages of the QS patients and the TL controls. The structured questionnaire was administered and the general health and pelvic examinations were performed at a clinic in their village.

3. Results

A total of 289 QS patients of the 300 were located, interviewed and examined for a follow-up rate of 96.3%. A biopsy had not been mentioned at the time of recruitment for the QS study. When asked to do so as a part of this retrospective study, 58 women agreed to an endometrial biopsy. Similarly, they had not been informed beforehand about the battery of reproductive hormone tests and only 30 subjects were randomly chosen to participate in this testing.

All 300 TL patients of the sample were contacted;

Table 1
Cumulative life-table failure rates for 100 women for 2 insertions of quinacrine ($N = 265$) versus tubal ligation ($N = 299$) in Guizhou Province, China, 1998

Months	Failures	At risk	Rate	SE
Quinacrine sterilization (QS)				
3	1	265	0.4	0.38
6	0	264	0.4	0.38
9	1	264	0.8	0.54
12	1	252	1.2	0.69
15	0	194	1.2	0.69
18	0	165	1.2	0.69
21	0	147	1.2	0.69
24	0	105	1.2	0.69
Tubal litigation (TL)				
3	2	298	0.7	0.47
6	0	297	0.7	0.47
9	0	294	0.7	0.47
12	0	281	0.7	0.47
15	0	256	0.7	0.47
18	0	241	0.7	0.47
21	0	219.5	0.7	0.47
24	0	161.5	0.7	0.7

299 were interviewed and examined for a follow-up rate of 99.7%. One woman refused to participate in this retrospective study.

One of the more important ways in which these two groups differed was the mean length of time between their sterilization procedure and the follow-up visit. The mean length of follow-up for QS patients was 20.8 months while it was 25.8 months for TL patients, a full 5 months' difference. This had much to do with the way the TL sample was taken.

Women receiving 2 insertions numbered 265, and 3 of them became pregnant. Table 1 shows the cumulative life-table failure rates of the two groups through 24 months. The rate at 2 years was 1.2 per 100 women for QS users who had 2 insertions and 0.7 for TL patients. There were 2 pregnancies among the 24 women who had a single insertion for a gross pregnancy rate of 8.3%. Table 2 compares QS users to TL users with respect to demographic and physiological characteristics. QS patients were 1.7 years older

Table 2
A comparison of demographic and physiological characteristics of women who chose QS ($N = 289$) versus TL ($N = 299$)

Parameter	QS (mean)	TL (mean)
Age (years)	30.7	29.0
Husband's age (years)	32.6	30.8
Living children (no.)	2.06	2.08
Births (no.)	2.10	2.12
Pregnancies (no.)	2.8	2.4
Induced abortions (no.)	0.6	0.3
Age of youngest child (years)	2.5	2.7
Weight (kg)	49.6	49.1
Height (cm)	155.7	156.5
Systolic pressure (mmHg)	100.7	99.4
Diastolic pressure (mmHg)	70.4	67.7
Menstrual cycle length (days)	29.0	28.7
Menstrual period length (days)	4.5	4.8

QS: quinacrine sterilization; TL: tubal ligation

than women who had obtained a TL and their husbands were likewise older. This age difference is significant and may account for other small differences seen between the 2 groups. Child loss was exceedingly low, a mean of 0.04 children for both groups. "Child loss" is defined as the death of a child from birth until the mother came to the clinic to be sterilized.

The number of TL users was similar to the QS users at each of the three clinics (Table 3). QS patients had a little more schooling on the average but they were far more likely to have used a temporary contraceptive method (47% compared to 20%). However, the majority in both groups had never used such a method. Discussion of sterilization with their husbands was all but universal (99% for QS users and 100% for TL users). Husbands were much more supportive of QS. The greatest difference found between the two groups was in the counseling before the procedure. In the QS group, one woman had not been counseled by her clinician prior to the procedure, while 89.3% of the TL cases reported that they had received no counseling.

Before discussing side effects, it should be noted that women who have a TL usually are not hospitalized, but return home for a few days of complete bed rest. Then they are given light duty for 30 days. Women who have QS usually return to work immediately. None of

Table 3
QS ($N = 289$) versus TL ($N = 299$): a comparison of environmental factors, Guizhou Province, 1998

Parameter	QS (%)	TL (%)
Clinic site		
Baiyun	47.8	42.5
Huaxi	41.5	47.2
Wudeng	10.7	10.4
Education		
No school	3.5	6.4
Elementary school	34.3	38.5
Middle school or above	62.3	55.2
Ever used contraception before sterilization		
Yes	47	20
No	53	80
Discussed sterilization with husband		
Yes	99	100
No	1	0
Husband's attitude		
Supportive	91.0	60.9
Wife should make the decision	8.3	39.1
Disagree	0.3	0.0
Unknown	0.3	0.0
Counseled by clinician prior to procedure		
Yes	99.7	10.7
No	0.3	89.3

QS: quinacrine sterilization; TL: tubal ligation.

these women experienced complications or side effects during either the QS or TL procedures. Furthermore, Table 4 shows that 73.7% of the QS cases and 49.8% of the TL cases experienced no side effects during the first week after the procedure. A similar proportion complained of lower abdominal pain. Women who had chosen TL were much more likely to report that their general health status had deteriorated during the period since the procedure (48.5% as opposed to 22.5% among QS users). As can be seen in Table 4, TL users reported more frequently that they now lack energy (21.0% and 2.8%, respectively) and got feverish easily far more often than QS users (13.0% vs. 0.3%). None

Table 4
Side effects following QS ($N = 289$) and TL ($N = 299$) procedures, Guizhou Province, 1998

Side effect	QS (%)	TL (%)
Discomfort within first week of procedure		
None	73.7	49.8
Lower abdominal pain	18.7	19.4
Yellow discharge	1.4	1.0
Headache	0.3	1.0
Pruritis	4.2	10.7
Fatigue	1.4	18.1
Lumbago	0.3	0.0
Post-procedure assessment of health status		
Unchanged	77.5	51.5
Worse than before	22.5	48.5
In what way is health worse		
Weight increased	2.1	0.0
Weight decreased	0.7	0.7
Headache and dizziness	5.2	6.0
Pelvic pain	3.5	10.0
Infection	0.3	0.7
Gets feverish easily	0.3	13.0
Lack of energy and weakness	2.8	21.0
Lower back pain	6.2	0.0
Other	1.4	0.0
Post-procedure working ability		
Same as before	92.0	48.8
Easily fatigued	8.0	51.2
Post-procedure menstrual cycle		
Same as before	72.7	65.5
Shorter than before	18.3	18.7
Longer than before	8.3	15.7
Ammenorrhea	0.7	0.0
Post-procedure menstrual flow		
Same as before	63.7	60.2
Scantier than before	29.1	24.1
More than before	6.6	15.7
-	0.7	0.0
Pap smear results		
No specific abnormal cells	69.2	83.6
Atypical cell, no cancerous signs	30.4	16.4
Abnormal growth	0.3	0.0
Liver function tests normal	100.0	100.0
Kidney function tests normal	100.0	100.0

QS: quinacrine sterilization; TL: tubal ligation.

of the side effects experienced by either group of women required treatment.

QS patients overwhelmingly (92%) confirm that working ability is unchanged since the procedure, while 51.2% of TL patients reported that they are now easily fatigued. Although both groups (nearly two-thirds) informed us that their menstrual cycles are largely unchanged (see Table 4), more QS patients experienced less flow and more TL patients reported a greater flow. One woman using QS reported continuous amenorrhea at follow-up 2 years after the procedure. Pap smears revealed no specific abnormal cells in most women but the proportion showing atypical cells was higher among QS cases (see Table 4). This came as no surprise since quinacrine does cause temporary inflammation of the endometrium. The findings of the liver and kidney function tests were normal in all women.

A total of 58 QS patients agreed to have an endometrial biopsy. None showed any abnormal findings. No differences were observed between the QS patients and the unmarried women controls in levels of FSH, LH, E_2 and PRL [3].

As noted above, there were 5 pregnancies in this QS series. Two women became pregnant after obtaining but a single insertion and both decided to carry that pregnancy to term. Three women became pregnant after obtaining 2 insertions of quinacrine pellets and one of them chose to carry that pregnancy to term. All 3 of these women gave birth to sons. Two of them had never used a temporary contraceptive. The third had used both the IUD and the Pill and she had previously become pregnant while on the Pill. During follow-up visits in 2002, when the three boys were 4, 4 and 6 years of age, all three were found to be happy and healthy, both mentally and physically. The boy whose mother became pregnant after one insertion, is shown at age 4 with his mother in Fig. 1. These 3 women reported that their quinacrine insertions were uneventful; that their health and sex life remained unchanged after QS. During these follow-up visits, protocol violations other than having but a single insertion were identified. Of these 3 patients who became pregnant, none had remained in a supine position for the required 2 hours or used contraception for 3 months following the first insertion. Furthermore, one woman had her only insertion on the 15th day following menses rather than during the 3 to 7 days following the end of menstruation as recommended in our protocol.

There was one attempt at reversal of QS in this series. This woman gave birth to twins in February 1997 at age 23. Four months later she obtained her first insertion of quinacrine. Before she was due for the second, one of the twins died of hydrocephalus. She did not pursue another QS procedure. On 6 April 2000, she came to the Guizhou Research Institute for Family Planning to meet with the first author, and requested that an attempt be made to reverse her QS. She explained that she had not had any problems, except infertility, and that her menses had been normal since QS. She had completed her menstrual period 2 days before. A hysteroscopic examination was performed. First, the doctor inserted a number 7 Hegar's bougie under hysteroscopic guidance into her uterine cavity with a camera attached. At the same time, distention liquid (10% glucose) flowed slowly into the uterine cavity from the bougie. The uterine cavity appeared as a cylinder and the tunica intima of the uterine cavity was smooth and both yellow and white in color. Most of the endometrium was red and smooth. There were some tunica intima adhesions which were not serious. They were dissected by the flowing distention liquid. The scar tissue filling the orifices or ostia of the fallopian tubes was white (see Fig. 2). Then the doctor moved the number 7 Hegar's bougie into both orifices of the fallopian tubes and infused distention liquid (10% glucose) with methylene blue added. This was difficult, as resistance was encountered (Fig. 3). The doctor felt that the pressure was high when he tried to infuse distention liquid into the fallopian tube. If the tube was patent, the methylene blue would flow freely into the fallopian tube and out through the fimbria. However, in this case, the methylene blue did not seem to flow into the tube at all. But the bougie pressed through the scar tissue at the ostia. When the bougie was withdrawn, the opening to the tube was filled with methylene blue distention liquid (Fig. 4). After completing the hysteroscopy, ultrasonography seemed to show a little methylene blue in the Pouch of Douglas but the finding was not pronounced. This suggested that the pressure from the distention liquid alone may have been sufficient to open a tube.

On 8 May 2000 she was diagnosed as pregnant in a local hospital. Unfortunately, she had a spontaneous

Fig. 1. A healthy boy conceived after QS.

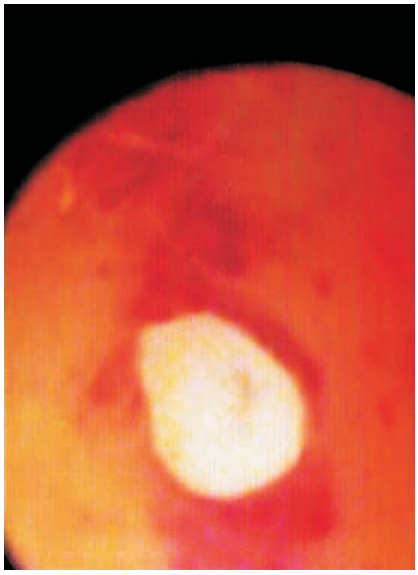


Fig. 2. Scar tissue fills the tubal ostia.

abortion on 13 July 2000. She became pregnant again on 30 May 2001. But on 2 August 2001, an ectopic pregnancy was diagnosed in the left fallopian tube. She was operated on the next day in the Guizhou Provincial Hospital. The ectopic pregnancy was removed from the left tube and the tube repaired. The surgeon found that the right tube was completely blocked. A TL was performed on the right tube to insure that she would not later be faced with another ectopic pregnancy in the right tube. This patient wants to have another child but has continued to use the Pill because she fears another ectopic pregnancy.

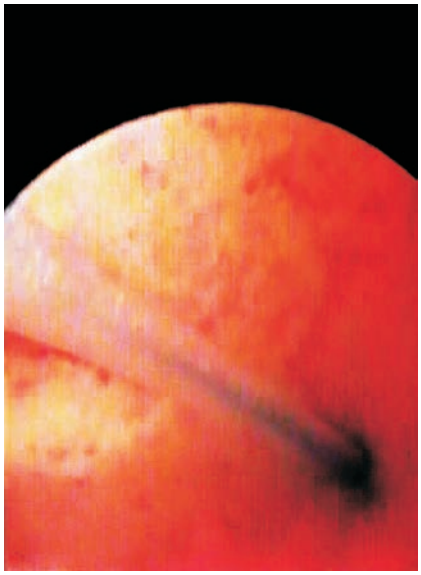


Fig. 3. Bougie filled with methylene blue pressing through scar tissue at ostia.

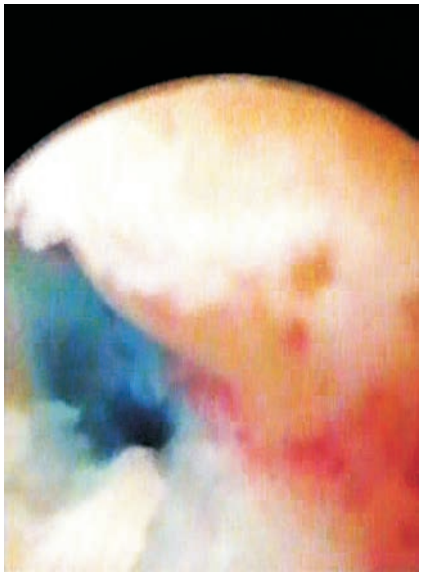


Fig. 4. Backflow of methylene blue from tube.

4. Discussion

The two groups of women differed in length of follow-up: a mean of 20.8 months for the QS group and

25.8 months for the TL group. This difference is largely due to the essentially stable numbers seeking TL during the study period while requests for QS were increasing throughout the patient intake period. Thus, a greater proportion of QS cases were performed later in the July 1995–September 1997 study enrollment period, as can easily be seen in Table 1. However, this difference in length of follow-up does not appear to have had any effect on the outcomes of the monitoring. If there are any, they are not apparent.

There is a significant difference in ages between the 2 groups. The QS group was on the average 1.7 years older. It is not possible to say with certainty why this difference in age exists. However, given the preference for QS found in this study, a plausible explanation is that some of the women had considered TL for a time and then rejected it, even though they wanted to be sterilized. When this new option for sterilization came along, they acted, seeking out QS – at a slightly older age. That 47% of QS users had at some time used a temporary method of contraception compared to only 20% of TL users supports this explanation. It is possible that this increase in age accounts for the higher blood pressure and weight and the slightly greater number of pregnancies and abortions. However, on the whole this significant difference in age did not change the outcome of this study in any substantive way.

The exceedingly low rate of child loss prior to seeking sterilization is remarkable. Only 1 in 25 couples in both groups had lost a child. This reassurance of child survival makes sterilization a more attractive option.

A total of 24 women had received but a single insertion. The gross pregnancy rate was 8.3%, much higher than the rate with 2 insertions. The majority of these single insertions occurred when there was a single logistics breakdown. The supply of quinacrine pellets to clinics was temporarily disrupted and this can be avoided in the future. In the case of the one child loss in this series (discussed above), the woman chose not to have her second insertion because she wanted to have another child. It is possible that a few of the women were simply not sufficiently self-motivated to seek the second insertion. However, there may have been some among them who did not fully understand that they needed to return for a second insertion or recognize its importance, or they were misinformed by a friend or relative who had chosen to have a single insertion. Aside from always placing the pellets at the fundus, nothing has more effect on the failure rate than insuring that the woman has 2 insertions of pellets. Good counseling and visiting the woman if she fails to return for her appointment for her second insertion will help lower the failure rate with this method.

There were other protocol violations and they too may have contributed to a higher failure rate. Performing the insertion at or just after the time of ovulation is known to increase the risk of pregnancy. Also, there are many documented cases in other countries of pregnancies occurring during the period between the first and second insertion. In our province this is particularly important because such a high proportion of women never used any temporary contraceptive method prior to seeking sterilization. Only 47% of QS users and 20% of TL users had done so. This is particularly challenging for the counselor.

Both QS and TL had excellent results in this series. There were no deaths, serious complications or side effects of great consequence in either group. While deaths with TL are occasionally reported, no deaths have been reported with QS anywhere. Although none were found in this series, there are occasionally serious complications reported with TL. Usually 3–7 days of hospitalization are needed with TL, followed by light duty for 30 days. After QS women can return to work immediately. Compared to TL, only a fraction of medical resources are needed with QS. Thus its cost is commensurately much lower than for TL. Most important, this study showed that there is a preference for QS over TL. Women sought QS after having delayed requesting surgical sterilization. They were 50% more likely to report a side effect following TL. Two years after the procedure, those who chose QS were much more apt to have a positive assessment of their health status (77.5% versus 51.5% respectively). Two years later, among women who had undergone QS, only 8% felt that their ability to work had changed for the worse compared to 51% among TL users. Also, husbands showed a preference for QS, although not necessarily for the most altruistic of reasons. QS was found to inconvenience husbands considerably less because the procedure does not affect its users' routine work and life, including her normal sexual activities.

We found, during the course of the interviews, that many recipients are willing to promote QS and had recommended this procedure to their relatives and

friends. These recipients were responsible for its rapid acceptance in Guizhou Province. The good counseling they had received was evidently critical (99.7% of them reported that they were well informed by their clinician before the procedure as compared to only 10.7% of TL users). Our counseling also no doubt, in part, accounted for our low failure rate in this series even though these were the very first 300 cases of QS in this province.

This study has shown that QS has many advantages over surgical sterilization. It is safe, reliable, simple to perform, does not use anesthesia. Health providers who perform IUD insertions can carry out this procedure. It is well suited for our frontier and underdeveloped areas. In short, QS helps implement the family planning policies set by our government.

References

[1] Hieu DT, Tran TT, Do NT, Pham TN, Pham T, Dao QV. 31 781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[2] Ding JH, Ding WH, Shen SQ, Yi MZ. Clinical evaluation of 100 cases of non-surgical female sterilization with quinacrine pellets. *Reprod Contracept* (in Chinese) 1996; 16:375–377.

[3] Zhu J, Lu WQ, Zhao YR. The influence of quinacrine sterilization on reproductive hormones of women. *J Guizhou Medical College* 2003; 28:41–42.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S59–S66

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women

C.R.C. Ferreira*, D.R.B. Magalhães, D.C. Ferreira, M.Z. Hanan, A.F. Camargos

Department of Obstetrics and Gynecology, Federal University of Minas Gerais, Belo Horizonte, Brazil

Abstract

Objective: Investigate effectiveness, safety and endometrial pattern after QS. *Method*: This study began in March 1999 and ended March 18, 2003; 128 women received transcervical insertions of quinacrine. Follow-up visits with ultrasound were scheduled at 1, 3, 6, 12-month intervals. *Results*: Two pregnancies occurred, one at 25 months, the other at 37. Adverse events (AE) were: yellow vaginal discharge, headache, mild abdominal pain, vaginal pruritus, nausea and transient decrease in endometrial thickness. One patient had allergic reaction. A third insertion was done in case of vaginal bleeding (16.4%). One year after QS 10% still had amenorrhea, which may be the result of the fact that 73% of our patients had received DMPH. Once inside the uterus, the dissolved quinacrine could be seen within seconds, via ultrasound as a "Lake of Quinacrine" which stays for up to two hours. Frequently, a transverse vaginal ultrasonographic view of the uterine cavity showed plug-like echogenic points at the cornua. *Conclusion*: Quinacrine sterilization is safe and effective. The echogenic points need to be more thoroughly studied in order to affirm whether ultrasonography may identify the blockage of the tubes. Since early pregnancy is due to imperfect tubal closure, the use of ultrasound may prevent failure. However, pregnancy due to later recanalization cannot be avoided.

Keywords: quinacrine; nonsurgical female sterilization; endometrial assessment after QS

1. Introduction

It has been estimated that in Brazil in the year 2003 the female population of a reproductive age (15 to 49 years) will reach 49 million. Less than 20% of this total has access to family planning information and procedures [1]. The official statistical maternal mortality in Brazil during 1999 was 55.7 deaths per 100,000 live registered births. In some regions, the actual incidence might amount to as many as 150 deaths per 100,000 live births. About 50% of the deliveries, between 1990 and 1995, were from unplanned pregnancies [2]. Unplanned and unwanted pregnancies often end in voluntary abortion (illegal in Brazil), and are an important cause of the increased ratio of maternal mortality.

Women with medical conditions like cancer, stroke, hypertension, obesity, diabetes, heart disease, thromboembolic events, varicose veins, smoking addiction etc, needed a definitive and secure contraceptive.

In Brazil, the need for family planning of an elderly multipara is different from that of an older affluent primigravida [3]. Women entering the perimenopausal years have many menstrual irregularities due to anovulatory cycles. This often confuses patients about the fertile phase of the menstrual cycle. Effective and safe family planning methods are needed in this age group as well as in the young. Pregnancy for the elderly

* Corresponding author. Fax 55 (31) 3225-0298.

E-mail address: claudia@medicina.ufmg.br

Correspondence address: Departamento de Ginecologia e Obstetrícia, Av Prof Alfredo Balena, 190, 30.310.100 – Belo Horizonte – MG – Brazil

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

woman carries health risks which include an increased incidence of genetic defects, miscarriages, medical disorders, fetal growth retardation and a greater need for operative deliveries.

Surgical female sterilization accounts for 27% of contraception in Brazil [2]. It requires sophisticated equipment and trained personnel. Serious complications are associated with general anesthesia, pneumoperitoneum, cautery and trocar caused trauma in laparoscopic sterilization.

Quinacrine nonsurgical sterilization (QS), developed by Zipper and his colleagues, is safe and inexpensive. It can be done quickly and without the risks of the surgery [4]. Experience has shown that it offers a low risk of serious, immediate side effects [5]. QS is a reasonable option, especially for women who have medical contraindications to a surgical procedure, or have had an earlier surgical sterilization failure. Also, there are numerous women who desire no more children but fear surgery, despite their obvious need for sterilization [6].

While there are several reports on the safety and efficacy of QS, there is no report of ultrasound evaluation in QS. It can be helpful in diagnosing congenital anomalies or tumors of the uterus and may help to avoid technical failure. Transvaginal ultrasound (TUS) is a powerful technique that reveals the endometrial pattern and gives considerable diagnostic information, helping to detect possible pathology of all organs in the pelvis. It can show unexpected adnexal masses, hydrosalpinx, tube-ovarian abscesses, tumors, endometriosis and ectopic pregnancies as well as early intrauterine pregnancies. Transvaginal pelvic ultrasonography can be used for screening of asymptomatic patients. It is an adjunct to the pelvic examination and is especially valuable in examining obese patients. When ultrasound detects an increased endometrial thickness or the presence of air with fluid collections in the intestines, diagnoses of a serious nature can be suspected and will require further detailed study to determine causes. The distension of the endometrial cavity can be due to an obstruction of the normal drainage of the uterus and may be seen with US. It is an invaluable tool for candidates undergoing QS.

Efficacy may be improved with protocol innovations, e.g. multiple insertions, higher doses, use of antibiotics, anti-inflammatory drugs and contraceptives for 3 months after QS [7–9]. The position as well as duration of rest post-insertion might help tubal closures [10,6]. The most important advance in reducing failure rate of QS was the discovery, by Hieu, of the value of placing all pellets at the fundus of the uterus [11,12]. Drugs as an adjunct may help improve results with QS. The pregnancy rate appeared lower in a subgroup that received oral papaverine [13].

2. Materials and methods

A prospective non-randomized study using QS in 128 women requesting sterilization was developed at the Family Planning Clinic, School of Medicine, Federal University of Minas Gerais, in Belo Horizonte, Brazil. After approval of the protocol by the Ethics Committee of the University, this clinical trial was begun in March 1999 and ended March 18, 2003. Patient volunteers received education about QS from printed brochures and from oral communication by doctors. Both the wife and husband signed an informed consent.

Initially, patients requesting sterilization for family planning were selected. Inclusion criteria were as follows:

Age – older than 29 years.

Parity – 2 or more live children; the last child older than 3 months.

In younger women, i.e., less than 30 and/or with fewer than 2 children, medical indications for QS were accepted but only after careful evaluation.

Exclusion criteria were: pregnancy, pathologic pelvic conditions, liver disease, mental health problems, uterine fibroids depending on the size, as well as patients unable to return for a second insertion or for follow-up visits. Choices of other methods of contraception were offered to these women.

The quinacrine used was packaged as 7 pellets in a modified Copper-T IUD inserter (Sipharm, Sisseln, Switzerland). After making a voluntary informed choice of the method, each woman in the reproductive age received the first transcervical insertion of 252 mg of quinacrine, during the proliferative phase of the menstrual cycle. One month later, a second insertion was made. At all times aseptic precautions were taken. Insertions were done making sure that each quinacrine pellet was placed at the very top of the uterine fundus as described by Hieu. To accomplish this with certainty, the inserter loaded with pellets, is advanced to 0.5 cm

from the top of the uterus and then the push rod is advanced until all pellets are in the upper uterine cavity. The patients were advised to lie in a supine position for at least 60 minutes after the procedure.

To study quinacrine pellet breakdown inside the uterus, we did ultrasound (US) scanning during the first 60 minutes after QS. Following that period, the patients were asked to stand up and walk around for 5 minutes. We repeated US scanning at 20, 25 and 30-minute intervals after standing up (80, 85 and 90 minutes elapsed since QS).

Next, standing up for the second time, walking around again for 5 minutes, US scanning was repeated at 10 and 30-minute intervals – i.e., at 100 and 120 minutes after QS.

The women who had had vaginal bleeding greater than 10 ml shortly after the QS, had a third insertion one month after the second.

Sony Video graphic Printer UP 890MD documented all the images; the Ultrasound Scanner was an SA-880 Medison, with the range of frequency of the vaginal probe between 5.5 and 7.5 MHz.

The temporal pattern of failure seen in QS studies shows a preponderance of pregnancies taking place in the first 3 months following the initial insertion. This suggests that use of an additional contraceptive in this period may improve the efficacy of the method [14]. Before the first insertion, 94 women (73.4% of the patients) received 150 mg of Depot medroxyprogesterone acetate (DMPA), for the purpose of controlling the effect on the endometrium thickness; 34 women (26.6%) used some other contraceptive method for 3 months after QS. Since some patients could not tolerate hormones, they utilized barrier methods. Others continued with the same contraceptive as had been used before.

Follow-up visits with transvaginal pelvic US were scheduled after the last dose, at 1, 3, 6 and 12-month intervals. In addition, patients were asked to return once a year, as well as at any time if complications or complaints occurred.

3. Results

The incidence of gross failure pregnancy rate was 3.1% with an efficacy of 96.9% [15]. The intended sample size of 147 patients was based *a priori* on a sample size calculation. The precision was assumed to be 2% (CI 95%). The sample size was 65 patients when type 1 error was assumed to be 3% (CI 95%).

SPSS V.8 for Windows statistical software was used to make the statistical analysis.

The risks are low or non-existent for the main concerns of ectopic pregnancies, birth defects, and cancer [12], as well as inflammatory diseases. Gynecologic problems and ectopic pregnancy rate were similar in women who had received either one or two insertions [16]. In histological studies of sections obtained from cervix, endometrium, myometrium and fallopian tubes after transcervical insertion of quinacrine, no abnormalities were revealed [14]. Lippes, citing the Winthrop bibliography of 1942, observed that numerous toxicologic studies (animal and human observations) predicted the safety of quinacrine, which has been in use for many other indications for over 70 years [17].

Patients' median age was 34 years, ranging from 21 to 46 years.

Parity's median was 3.0, ranging from 1 to 10 live children.

The hysterometer measurements averaged 7.85 (SD 0.59), ranging from 6 to 9.5 cm.

The mean follow-up time was 23.3 months.

Before the first insertion, 94 women (73.4% of the patients) received DMPA (Depo-Provera®). During 3 months after QS, 34 women (26.6%) used some other contraceptive method (Table 1).

When quinacrine pellets are inserted at the uterine fundus, the dissolved pellets can be seen within seconds via ultrasound. This "Lake of Quinacrine" stays at the fundus for up to two hours. When the patient stands up and walks about, some quinacrine flows out through the vagina and the image of the puddle on the screen

Table 1
Contraceptive method used for 3 months after QS, Maternidade Santa Fé, Belo Horizonte ($N = 128$)

Method	Frequency	Percentage
Depo-Provera®	94	73.4
Oral contraceptives	28	21.9
Condom	5	3.9
Abstinence	1	0.8
Total	128	100.00

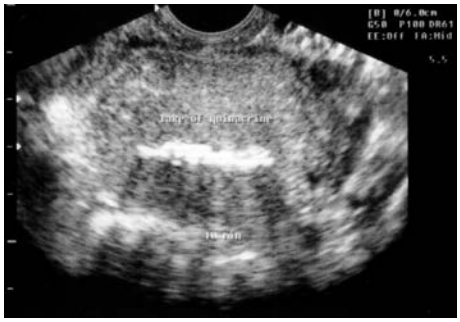


Fig. 1. Transvaginal ultrasound scanning. Coronal plane: "Lake of Quinacrine". Transversal view of the uterus, 10 min after QS.

Table 2
Menstrual pattern one year after QS in Maternidade Santa Fé, Belo Horizonte ($N = 110$)

Menstrual pattern	Frequency	Percentage
Amenorrhea	11	10.0
Small increase	4	3.6
Reduction	14	12.7
No change	81	73.6
Total	110	100.00

becomes a little less opaque. These procedures were repeated with 10 patients, obtaining the same results in each case (Fig. 1).

A total of 129 women participated voluntarily in this QS trial. One of them exhibited such a narrow cervix canal that it was impossible to insinuate the inserter into the uterine cavity without causing bleeding. Since the presence of much blood lowers efficacy [18], we decided to exclude this patient.

The remaining 128 patients demonstrated the following transient side effects: yellow vaginal discharge for 7 to 10 days (all patients); headache (4 cases; 3.1%); mild abdominal pain (11 cases; 8.6%); vaginal pruritus (7 cases; 5.5%) and nausea (1 case, 0.8%). Twenty-one patients (16.4%) had vaginal bleeding after QS which was sufficient to require a third insertion. This was done one month later. No cases of pelvic inflammatory disease have been diagnosed so far. Neither infections nor pregnancy failures were observed before two years elapsed after QS. Two pregnancies were reported, one occurred at 25 months and the other at 37 months after QS. One terminated with a spontaneous abortion and the other is having a normal gestation.

One year after QS, menstrual patterns could be evaluated in 110 cases (Table 2). A reduction in menstrual flow was reported and was acceptable to 14 patients (12.7%). Only 4 women (3.6%) described a small increase in their vaginal bleeding while 81 patients (73.6%) observed no change in their menstrual pattern. Eleven women (10%) still had amenorrhea one year after QS.

3.1. Case report

S.M.A.$^{4–0–0–4}$, 38, was admitted to the first US study in June 2001. After discovering her bicornuate uterus, we recognized that both IUD and QS might fail. Her last delivery was in February 2001; she suffered mastectomy of the left breast during pregnancy and was breast-feeding on the right.

In the previous year, she had not only had breast cancer, but also venous thromboses after delivery. Thus, a new pregnancy and the use of hormones were seriously contraindicated. Even though they were poor and already had 4 living children, her husband did not accept vasectomy. So, in December 2001 we decided to do two quinacrine sequential insertions guided by US scanner – one in each cavity of the uterus. The ultrasound screening showed two "Lakes of Quinacrine" completely separated. The process was repeated one month later. The patient did not complain of any side effects (Fig. 2).

One of the 128 patients had an allergic reaction with abdominal pain and hemorrhagic diarrhea, which started twenty days after the first insertion. Although she received oral analgesics, it was necessary to hospitalize her. She was examined at the Emergency Service in the Hospital of the Federal University of Minas Gerais, and was then submitted to all necessary appropriate exams (including laboratory tests, tomography and endoscopy). No associated pathologies were found. One month later, uncertain about the association between QS and her symptoms, we did the second insertion. Her reaction was the same, however,and after only 24 hours was once again admitted to the hospital. In the past, the patient had not taken either quinacrine nor suffered malaria before the QS. Neither the pain nor the hemorrhagic diarrhea returned, while her anemic state has been cured. Her follow-up by US scanning and pelvic exams were normal.

Only a transient decrease in endometrial thickness was observed during the first 6 months, which cor-

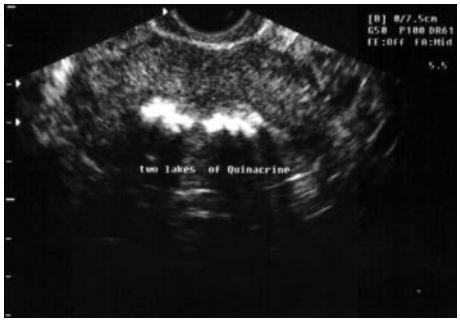


Fig. 2. Transvaginal ultrasound scanning. Transverse view of bicornuate uterus. Two "Lakes of Quinacrine", 30 min after QS. Maternidade Santa Fé, Belo Horizonte (case report S.M.A.).

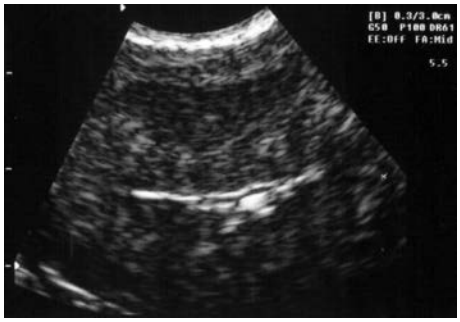


Fig. 3. Transvaginal ultrasound scanning. Endometrial line with high-level echogenicities. Intrauterine adhesions. Coronal plane. Maternidade Santa Fé, Belo Horizonte.

responds to the incidence of oligomenorrhea. Some patients, who had received DMPA, have had a variable period of amenorrhea followed by menstrual irregularities. Therefore US of the endometrium could only be analyzed 3 months after QS. The pregnancy failure rate (Pearl) was 0.805 per 100 women.

In most patients the endometrium could be observed as an echogenic interface in the center of the uterus. After QS, the endometrial line was frequently seen with irregular high-level echoes, or punctuated echogenicities. Those images might be produced by intrauterine adhesions and were much more visible when patients had amenorrhea (Fig. 3).

Frequently, vaginal ultrasonographic transverse views of the uterine cavity when seen as a triangle, showed two plug-like echogenic points, at the level of the cornua (Figs. 4–6). The plugs could be measured and the length of the scars were graded and dually classified by two different sonologists, using a standardized set of objective criteria (Table 3). The scars were easier to see 3 to 6 months after QS (Table 4 and Fig. 7).

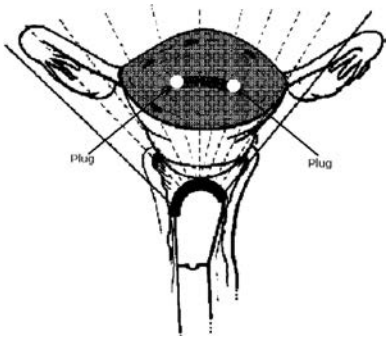


Fig. 4. Diagram of semicoronal plane. Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

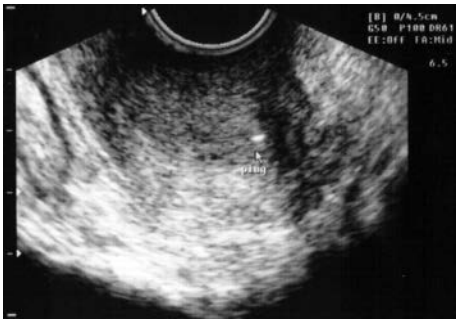


Fig. 5. One echogenic point (right-hand side). Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

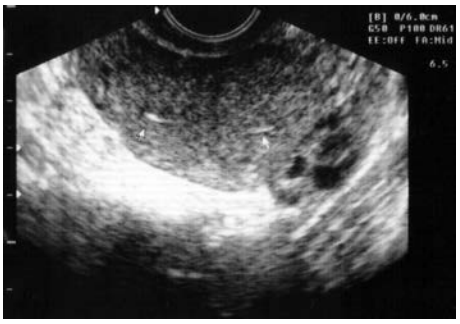


Fig. 6. Two echogenic points. Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

Table 3
Classification of echogenic points, Maternidade Santa Fé, Belo Horizonte

0	Absence of plugs
+	Two plugs <2 mm or presence of plug at only one side
++	Two plugs = 2 mm
+++	Two plugs >2 mm

Table 4
Classification of echogenic points (frequency of plugs in each follow-up visit), Maternidade Santa Fé, Belo Horizonte

Classification of echogenic points	Follow-up visits (months)			
	1	3	6	12
Absence of plugs	56.4%	15.2%	20.8%	25.6%
Two <2 mm plugs or presence at only one side	29.0%	45.7%	49.0%	50.0%
Two 2 mm plugs	12.0%	32.4%	22.9%	20.5%
Two >2 mm plugs	2.6%	6.7%	7.3%	3.9%
Total	100.0%	100.0%	100.0%	100.0%

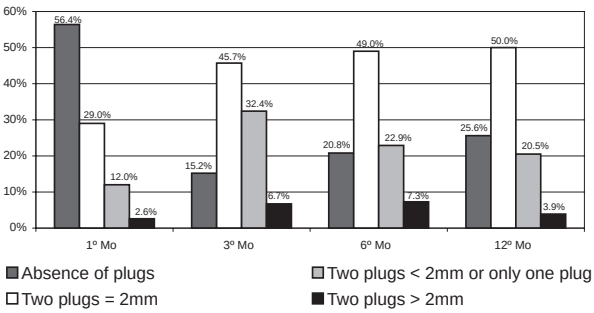


Fig. 7. Frequency of plugs according to elapsed time after QS, Maternidade Santa Fé, Belo Horizonte ($N = 128$).

4. Discussion

The most important factor limiting the sample size (128 patients) was our insistence that all procedures be done by the same physicians. Failure rate was strongly affected by each operator's skill [11]. In order to minimize errors, the first author (CRCF) assisted by Dr. Magalhães has done the sterilizations and examinations. The pregnancy failure rate of 0.805 per 100 women was low, compared to the literature on QS. We believe vaginal ultrasound had prevented some technical failures because it permitted a better approach for exclusion of patients with anatomic abnormalities.

When the quinacrine pellets are inserted at the uterine fundus, the dissolved pellets can be seen within seconds via ultrasound. This "Lake of Quinacrine" stays at the fundus for up to two hours. This observation introduced a protocol innovation. We increased the time patients lie in the supine position after a quinacrine insertion [7].

In a country like Brazil with a high incidence of iron deficiency anemia, vaginal bleeding patterns should be evaluated. With heavy or prolonged bleeding, especially if anemia is noted clinically, Copper-T IUD and operative procedures are not recommended [19]. The levonorgestrel IUD (an expensive choice for Brazilian people) showed 11.2% of patients with reduced bleeding and 5.6% with increased bleeding [20]. As we have noted, QS showed a pleasantly surprising and positive effect by reducing menstrual flow in 12.7% of the patients evaluated one year after QS. Furthermore, 10% developed amenorrhea. A reduction in blood loss is a convenient and beneficial event for our women. These results coincided with the fact that 73.6% had no menstrual changes, which were largely considered desirable by our patients. An increase in blood flow was mentioned by only 3.6% of the women. It was not a real complaint and was always referred to as a "small difference".

After QS, the endometrial line was frequently seen with irregular high-level echoes, or punctuated echogenicities. Those images might be produced by intrauterine adhesions, or perhaps linked to inflammatory processes with scarring. They were much more visible when patients had amenorrhea. The transient decrease in endometrial thickness was observed during the first 6 months and corresponds to the greater incidence of oligomenorrhea in some QS patients. It was observed after QS, both in patients who used DMPA and those who adopted other contraceptive methods. In this period of time it is difficult to affirm whether this effect is due to the use of contraceptives or to the cicatrization process which accompanies QS.

Hysterosalpingography (HSG) and hysteroscopy revealed the same accuracy in the diagnosis of tubal obstruction [22]. However, HSG is not a good choice

to confirm the closure of fallopian tubes because the pressure it creates can dislodge tubal occlusions [23].

Ultrasonography scanning is a non-invasive real-time image method to scan the pelvis. According to the current study, this tool may be helpful to identify the blockage of the cornua of the uterus based on the echogenic points we observed and classified (Table 4). The potential difficulty with the utilization of this approach is the ability to obtain a proper image of the whole length of the "plugs" optimally visualized for measurement. Fig. 4 shows a diagram of a vaginal ultrasonographic transverse view of the uterine cavity seen as a triangle, with two plug-like echogenic points at the level of the cornua. The plugs could be visualized and measured.

The length of the scars were doubly graded and classified by two different sonologists (Ferreira and Magalhães). Each patient was scanned twice, and results compared. Because of the great simplicity of US, classifications were similar. This procedure was designed for greater accuracy, reproducibility and lower interobserver discrepancy of measurements. Our results should be confirmed by additional large randomized studies.

Prehysterectomy studies [16] showed that the inflammatory and fibrotic processes take six or more weeks to complete. This suggests a reasonable possibility that the progress of inflammation to scarring and closure may vary individually in time. The scars were easier to see 3 to 6 months after QS.

Once inside the uterus, quinacrine becomes fluid within seconds, seen as a "Lake of Quinacrine". This lake stays at the fundus for up to two hours. The echogenic points need to be more thoroughly studied in order to affirm whether ultrasonographic scanning may be helpful in identifying the blockage of the uterine cornua. The echogenic points seem to be linked to the scars and inflammatory processes. They are more easily seen 3 to 6 months after QS. Because an early pregnancy failure is probably due to imperfect tubal closure, the use of ultrasound may prevent such a failure. However, pregnancy due to later recanalization cannot be avoided as we have seen this more than 2 years after QS.

QS is safe, effective and acceptable. It should be offered everywhere as an option to women requesting sterilization.

Acknowledgments

The quinacrine pellets were supplied by the Center for Research on Population and Security, Research Triangle Park, North Carolina, USA.

References

[1] Site of the Geography and Statistics Brazilian Institute (Instituto Brasileiro de Geografia e Estatística) www.ibge.gov.br. Accessed March 18th, 2003.
[2] Sites of the Ministry of Health (Ministério da Saúde) of the Brazilian Government www.saude.gov.br and www.datasus.gov.br. Accessed March 17th, 2003.
[3] Seneviratne HR. Reproductive hazards in women over 40 years. *Int J Gynecol Obstet* (Suppl) 1994; S46:22.
[4] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.
[5] Potts M, Benagiano G. Quinacrine sterilization: a middle road. *Contraception* 2001; 64(5):275–276.
[6] Sarin AR. Quinacrine Sterilization: experience among women at high risk for surgery. *Adv Contracept* 1999; 15:175–178.
[7] Thakur PS, Quinacrine sterilization in Tripura, India. *Contraception* 2001; 64(5):277–279.
[8] Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvant to quinacrine nonsurgical female sterilization. *Adv Contracept* 1995; 11:303–308.
[9] Randic L, Haller H, Sojat S. Non-surgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen. *Fertil Steril* 2001; 75:830–831.
[10] Ferreira CRC, Barbosa DR, Hanan MZ, Ferreira DC. Quinacrine sterilization: endometrial assessment by vaginal ultrasonography. *Int J Gynecol Obstet* (Suppl) 2000; S70:73.
[11] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.
[12] Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. *Adv Contracept* 1998; 14:81–90.
[13] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: Interim efficacy analysis. *Fertil Steril* 2000; 74:1084–1091.
[14] Merchant RH, Prabhu SR, Kessel E. Clinicopathologic study of Fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40:47–54.
[15] Site of WHO. Advances in female sterilization research. Progress in Reproductive Health Research, No. 36. Geneva; 1995. www.who.int/reproductive-health/hrp/progress. Accessed March 17th, 2003.
[16] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. op. cit. Part II: Interim safety analysis. *Fertil Steril* 2000; 74:1092–1100.

[17] Lippes, J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2001; 77(6):1106–1109.
[18] Mullick BC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet non-surgical female sterilization. *Adv Contracept* 1995; 11:239–244.
[19] WHO. Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria Initiating and Continuing Use of Contraceptive Methods. Geneva; 1996.
[20] WHO. China to upgrade its IUD technology. Progress in Reproductive Health Research, No. 60. Geneva; 2002.
[21] Kessel E. 100.000 Quinacrine Sterilizations. *Adv Contracept* 1996; 12:69–76.
[22] El-Sahwi S, Kamel M, Haiba N, Osman M. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization. *Adv Contracept Deliv Syst* 1992; 8:151–159.
[23] Soroodi-Moghaddan S. Quinacrine pellet method of nonsurgical female sterilization in Iran: Preliminary report on a clinical trial. *Int Fam Plann Perspect* 1966; 22(3):122–123.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S67–S71

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

The effect of special training for quinacrine sterilization (QS) in Faisalabad, Pakistan: a report on an 1833-women subset of 11,000 cases

A. Bashir*, M. Bashir, S. Afzal

Mother & Child Welfare Association, Faisalabad 38000, Pakistan

Abstract

Objective: To determine the impact of retrained clinicians on the efficacy of transcervical quinacrine sterilization. *Method:* Retraining of clinicians in the accepted insertion technique was conducted in 1996. From 1 January 1997 through 2001, they performed 1089 quinacrine sterilizations in 11 MCH clinics of the Mother & Child Welfare Association at Faisalabad, Pakistan. Of these, 885 women had a recorded follow-up visit (81.4%) by 31 December 2001. *Result:* Reported pregnancy failures declined after retraining from 5.4% (SE 2.3) for one year of use to 1.1% (SE 0.4) for 5 years of use. The rates at 4 years of use showed the expected increase in failures for women 30 years old or younger of 1.5% (SE 0.7) compared to 0.9% (SE 0.4) for those over 30; a lower rate of 0.8% (SE 0.4) for breastfeeding subjects and 2.2% (SE 1.1) for mothers not breastfeeding; but rates were similar for uterine length and post insertion traumatic bleeding. *Conclusion:* Quinacrine sterilization appears safe with acceptable efficacy.

Keywords: quinacrine sterilization, female sterilization, sterilization training

1. Introduction

Quinacrine sterilization (QS) was introduced in Faisalabad, Pakistan, by the late Professor Altaf Bashir in 1990 [1] at the Gulzar Colony MCH Centre of the Mother & Child Welfare Association. The preceding year, a survey of 993 married women in Faisalabad [2] revealed that only 12.1% were using a contraceptive, 3.2% of whom were sterilized. During 1990, a concerted effort was made to popularize family planning methods including the introduction of QS. A repeat survey [3] in January 1991 of 1005 married women showed contraceptive prevalence at 41.7% including 18.1% using female sterilization, the largest increase of any method. Information about contraception was provided mainly by trained traditional birth attendants (TBAs) [4]. During 1990, 2100 QS procedures were performed, of which 79% were for women aged 31–40 years; 68% of these patients had parity of 5 to 8. In this group, 85 pregnancy failures (2.4%) were reported for that year. Popularity of QS was sustained with 1583 cases being performed in 1991, 1550 in 1992 [5], and a total of over 10,000 cases were reached by 1995.

During this early experience, the family planning promotion was integrated into a well-organized MCH effort to reduce maternal morbidity and mortality. It succeeded in bringing maternal mortality in Faisalabad significantly below the national average [6].

* Corresponding author. Tel.: 91-41-711550; Fax: 92-41-535261

E-mail address: macwafsdyahoo.com

Correspondence address: Mother & Child Welfare Association, 18 Gulzar Colony (near Passport Office), Faisalabad 38000, Pakistan

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

QS was carried out in camps and cases were referred to MCH clinics, primarily by TBAs. In our first approach to this nonsurgical method of sterilization, QS procedures involved single transcervical insertions of seven quinacrine pellets each containing 36 mg for a total of 252 mg. These were performed in the proliferative phase of the menstrual cycle. A Copper T IUD inserter was used and we followed the Copper T insertion technique. With this approach under aseptic conditions, the sterile dry inserter was loaded with clean quinacrine pellets and, as with an IUD placement, the loaded inserter was advanced transcervically to the fundus where the inserter sleeve was withdrawn to release all pellets in a line from the fundus. No deaths were reported in this large experience and complications were rare. The safety of QS was well established. Faisalabad had gained the largest single insertion experience with QS.

Because reports suggested that a revised insertion technique [7,8] with multiple insertions [7] might improve efficacy, we then focused our attention on this new technique.

2. Materials and methods

A preliminary study of a convenience sample of 948 QS cases in 11 MCH clinics of the Mother & Child Welfare Association extending from 1990 to 1995 showed a cumulative life-table pregnancy failure rate of 5.4% (SE 2.3) in 1990 which on a continuing basis did rise with time. In 1996, a retraining effort was initiated for all nurse-midwife inserting clinicians with particular attention to using the then recommended technique first described by Hieu [7]. This involved advancing the loaded inserter transcervically to the fundus, then withdrawing it 0.5 cm. Then, while holding the inserter sheath steady, the plunger was advanced to deposit all pellets at the very top of the uterine fundus. Although patients were advised to return for a second insertion in one month as recommended internationally [9], few did so because the single-insertion procedure had been so well established in the community. Following this training, a series of 1089 QS cases were performed by these trainees during the period 1 January 1997 through 2001. Several research questions were explored, including the impact on efficacy of such things as patient's age, breast-feeding, length of uterus and evidence of traumatic bleeding. Each of these items was recorded on a register recommended by the International Federation for Family Health. Efficacy rates are based on use from last insertion to last patient contact. Cases at risk are limited to recorded data for each item evaluated. This may have amounted to less than 885 cases followed.

3. Results

In this series of 1089 QS procedures conducted after retraining in the 11 MCH clinics, 885 (81.4%) women had a recorded follow-up visit, of whom 158 (17.9%) received only a single insertion. There was no statistically significant difference in failure rates between single- and 2-insertion data, so these data were combined for the analysis. Efficacy, combining single- and 2-insertion cases, is shown in Table 1, with a pregnancy failure rate of 1.1% (SE 0.4) at 5 years of use.

The difference in efficacy by age can be seen in Table 2 with a failure rate of 0.9% (SE 0.4) for women older than 30 and 1.5% (SE 0.7) for those 30 or younger at 4 years of use.

The difference in failure rates for breastfeeding is evident in Table 3 with 0.8% (SE 0.4) for breastfeeding subjects and 2.2% (SE 1.1) for non-breastfeeding patients at 4 years of use.

The difference in efficacy by length of uterus is shown in Table 4 where uteri sounding over 6 cm had failure rates of 1.2% (SE 0.4) while those sounding 6 cm or under had 1.9% (SE 1.3). The difference in

Table 1
Cumulative life-table pregnancy failure rate for 885 followed quinacrine sterilization cases by months of use. Faisalabad, Pakistan, 1997–2001 ($N = 1089$)

Month	1 + 2 insertions, $N = 885$		
	At risk	Rate (%)	Standard error (SE)
12	878	0.3	0.2
24	751	1.0	0.3
36	479	1.1	0.4
48	217	1.1	0.4
60	48	1.1	0.4

Table 2
Cumulative life-table pregnancy failure rate by months of use for quinacrine sterilization by subject's age. Faisalabad, Pakistan, 1997–2001 ($N = 885$)

Month	>30 years ($N = 610$)			⩽30 years ($N = 275$)		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
12	605	0.3	0.2	274	0.4	0.4
24	527	0.7	0.3	225	1.5	0.7
36	362	0.9	0.4	115	1.5	0.7
48	172	0.9	0.4	45	1.5	0.7
60	43	0.9	0.4			

Table 3
Cumulative life-table pregnancy failure rate by months of use by subject's breastfeeding status. Faisalabad, Pakistan, 1997–2001 ($N = 640$)

Month	Breastfeeding ($N = 449$)			Non-breastfeeding ($N = 191$)		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
12	447	0.2	0.2	191	0	
24	384	0.5	0.3	187	1.1	0.7
36	291	0.8	0.4	101	2.2	1.1
48	148	0.8	0.4	61	2.2	1.1
60	32	0.8	0.4			

Table 4
Cumulative life-table pregnancy failure rate by months of use for subject's uterine length. Faisalabad, Pakistan, 1997–2001 ($N = 760$)

Month	Uterine length ⩽6 cm ($N = 128$)			Uterine length >6 cm ($N = 632$)		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
12	128	0		627	0.4	0.3
24	116	0.8	0.8	540	1.2	0.4
36	84	1.9	1.3	383	1.2	0.4
48	45	1.9	1.3	165	1.2	0.4
60				48	1.2	0.4

efficacy because of post-insertion bleeding over 1 ml (Table 5) showed a failure rate of 0.7% (SE 0.7) compared to 1.2% (SE 0.5) when there was no post insertion bleeding. Failure rates noted in Tables 4 and 5 were recorded after 4 years of use, and the differences were not statistically significant.

4. Discussion

The retraining effort appeared to be successful as pregnancy failure rates declined from 5.4% (SE 2.3) to 0.3% (SE 0.2) at 12 months of use. This brings into question the need for a second insertion where the low failure rate for a single one may be acceptable in some localities. The higher failure rates reported by Hieu and his colleagues [7] may have been related to menstrual regulation (MR) procedures performed for delayed menstrual periods without a pregnancy test [10] and reported as pregnancy failures. Pregnancy tests were not available to Hieu or to the government at the time of this Vietnamese field trial. Amenorrhea lasting a month or more following insertion of quinacrine pellets affects

Table 5
Cumulative life-table pregnancy failure rate by months of use for quinacrine sterilization by report of post-insertion uterine bleeding. Faisalabad, Pakistan 1997–2001 ($N = 628$)

Month	Post-insertion bleeding ($N = 172$)			No post-insertion bleeding ($N = 456$)		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
12	171	0		453	0.4	0.3
24	134	0.7	0.7	407	0.9	0.4
36	94	0.7	0.7	306	1.2	0.5
48	49	0.7	0.7	167	1.2	0.5
60				44	1.2	0.5

30% of the women. This fact was not widely known by Vietnamese clinicians and therefore their patients were never forewarned. Experiencing amenorrhea, the woman would simply go to her local clinic, report a late period and request an MR without confirmation of pregnancy. She would receive an MR, and a pregnancy failure would be recorded following QS. It is understandable then that a significant proportion of the MR procedures may well have been done simply for a delayed menstrual period [11].

The difference in failure rates by age, while not statistically significant, is in the expected direction for younger women having a greater risk of pregnancy failure. In this case, a pregnancy rate of 0.9% (SE 0.4) was recorded for women over 30 and of 1.5% (SE 0.7) for women under 30 years of age.

Breastfeeding alone offers some protection against pregnancy. As expected, there is a marked difference in failures by breastfeeding status, with 0.8% (SE 0.4) for breastfeeding mothers and 2.2% (SE 1.1) for those who are not doing so.

There is little difference in pregnancy failures by length of uterus, being 1.2% (SE 0.4) for uteri over 6 cm and 1.9% (SE 1.3) for uteri 6 cm or less. This difference is, however, in the same direction as that found by El Kady and his associates [12].

The difference in pregnancy failures may vary because of post-insertion bleeding. When this amounted to over 1 ml the failure rate was 0.7% (SE 0.7) versus 1.2% (SE 0.5) when post-insertion bleeding was absent. While not statistically significant this difference is in the opposite direction of that reported by El Kady [12] whose study involved a smaller number of subjects. It is suggested that additional data from other centers is needed before reconsidering present recommendations [9] to repeat procedures with post-insertion bleeding.

QS is clearly safer than surgical sterilization, particularly in terms of early complications [13]. Long-term follow-up shows no increased risk of cancer [14]. Recent reports [8,15,16], including this paper, confirm that the efficacy with presently recommended insertion techniques approaches that of accepted methods of surgical sterilization [17]. QS is ready for use in service programs, especially in developing countries.

Acknowledgment

The authors are grateful to Mr. Hafeez Javed and Mrs. Razia Sultana for their assistance in this study, and wish to thank the staff of MCWA for their contribution to our program.

References

[1] Bashir A, Cheema MA, Akram S, Naheed R. Quinacrine nonsurgical female sterilization. *The Gynaecologist* 1993; 3:129–136.
[2] Bashir A, Cheema MA, Akram S, Mustansar M. Family planning in Pakistan: results from a survey in Faisalabad City. *The Gynaecologist* 1991; 1(2–3):94–98.
[3] Bashir A, Cheema MA, Mustansar M, Naheed R, Akram S. Family planning practices in Pakistan: a step towards success. *Quarterly Specialist* 1991; 8:31–36.
[4] Bashir A. Refresher courses of Traditional Birth Attendants. *JPMA* 1982; 32(7):168–169.
[5] Bashir A, Mustansar M, Cheema MA, Choudhury MY. Nonsurgical female sterilization: 3 years' experience with quinacrine. *Gynaecol Bimonthly* 1992–3; 3(2,3):129–136.
[6] Khalid S. The Faisalabad mother & child health programme. *Gynaecol Bimonthly* 1992–3; 3(2,3):116–118.

[7] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 871 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.
[8] Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization. *Adv Contracept* 1995; 11:303–308.
[9] Institute for Development Training. Female voluntary non-surgical sterilization: the quinacrine method. Module 12 of Training Course in Women's Health. IDT, Chapel Hill, North Carolina, 1996.
[10] Sokal DC, Weiner DH. What is the future of quinacrine sterilization? (letter) *Fertil Steril* 2001; 75:1244–1245.
[11] Kessel E. Menstrual regulation. In: M Potts, P Bhiwandiwala, editors, Birth Control: An International Assessment. Baltimore: University Park Press, 1979, 187–200.
[12] El Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59:301–304.
[13] Layde PM, Peterson AB, Dicker RC, DeStefano F, Rubin GL, Ory HW. Risk factors for complications of interval tubal sterilization by laparoscopy. *Obstet Gynecol* 1983; 62:180–184.
[14] Sokal DC, Dabancens A, Guzman-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. *Fertil Steril* 2000; 74:169–171.
[15] Soroodi-Maghaddam S. Preliminary report on a clinical trial of the quinacrine pellet method for nonsurgical female sterilization in Iran. *Int Fam Plann Perspect* 1996; 22:122–123, 127.
[16] Sarin AR. Quinacrine sterilization: experience among women at high risk for surgery. *Adv Contracept* 1999; 15:175–178.
[17] Peterson HB, Xia Z, Hughes JM, Wilson LS, Tylar LR, Trussel J. The risk of pregnancy after tubal sterilization: Findings from the U.S. Collaborative Review of Sterilization. *Am J Obstet Gynecol* 1996; 174:1161–1170.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S73–S76

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) among high-risk women: a study of 134 cases

A.R. Sarin[a,*], R.K. Sarin[b]

[a]*Department of Obstetrics & Gynecology, Government Medical College, Patiala, India*
[b]*Aastha Medical Center, Patiala, India*

Abstract

Objective: To determine if quinacrine sterilization (QS) is safe and effective in women at high risk for surgery. *Methods*: A trial was initiated at the Government Medical College in Patiala, India, in December 1993. Patient intake was terminated in July 1999 and the cut-off date for this analysis was March 31, 2003. Using a modified IUD inserter, seven 252 mg quinacrine pellets with 50 mg of diclofenac were transcervically inserted into the uterus. DMPA 150 mg was administered IM at the time of the first insertion as a back-up contraceptive. This same combination was inserted a month later. A total of 134 women underwent QS. Of these, 92 were considered to be at high risk for surgery, 27 were afraid of surgery or voluntarily opted for QS, and 15 had had failed surgical sterilization or surgery was found not to be technically feasible. Follow-up was scheduled for 1, 3, 6 and 12 months, and then annually after the second insertion or whenever side effects or complications were experienced. *Results*: Mean follow-up was 7.2 years. No pregnancies or serious complications were experienced. *Conclusion:* QS is a safe and effective option for women at high risk of surgical complications.

Keywords: quinacrine sterilization, nonsurgical sterilization, high-risk women

1. Introduction

Jaime Zipper discovered the potential of quinacrine [1] as a sclerosing agent that causes fibrosis and occlusion of the fallopian tubes. Dr. Zipper published the first human studies on QS in 1970 [2]. Since 1977, quinacrine pellet sterilization (QS) has been used by tens of thousands of women in many different countries [3].

The logistics of offering any method of fertility regulation is influenced by the medical infrastructure and circumstances. One of us (ARS) till recently was heading a tertiary care facility at a Punjab medical school (Government Medical College, Patiala).

The following aspects of our situation are worth consideration:

- Our government advises against surgical female sterilization for women with hemoglobin less than 7 g/dl, but 57% of women in our area are this anemic [4].
- Since we work at a referral center, we see mothers whose lives would be endangered by another pregnancy, and who are very poor risks for surgery.
- Patients who have experienced sterilization failures are often referred to us, and it is well known that previous pelvic surgery increases the risk of serious complications of a surgical sterilization by a factor of 2.7 [5].
- Finally, we are committed to promote and pro-

* Corresponding author. Tel.: +91-175-2213703, 2215887.
E-mail address: sarinrajashi@yahoo.co.in
Correspondence address: Department of Obstetrics & Gynecology, Aastha Medical Center, 7, Bank Colony, Patiala-147001, India

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

vide choices of contraception among well-informed women.

The general situation of our women and children also prompted us to undertake this trial. Fifty-two percent of women in Punjab are illiterate; the mean number of years of schooling is 2.0. They have an average of 2.9 children. Forty-six percent of children younger than 4 years of age in Punjab are underweight and 40% are stunted [6]. Fewer than half of the women who say that they want no more children are actually protected by sterilization.

Currently, the standard technique for female sterilization requires abdominal surgery. In developing countries, it is often difficult to meet the demand for the operation while still maintaining the necessary quality of surgical services. Also, some women who need sterilization have special problems such as high risk of complications due to concomitant medical conditions. Others who desire sterilization refuse it out of fear of surgery. Again, in some cases, surgical sterilization may not be technically feasible.

Most quinacrine sterilizations have been conducted among healthy women, or at least women of average health in a particular area. There have been no reports of QS trials focused on high-risk women. So to meet their special needs, we initiated a trial of QS. In a developing country such as India, QS seems to be a promising method and from the user's immediate perspective, it is a 'woman friendly' procedure. Before embarking on this clinical trial, we carried out our own studies on hysterectomy specimens following transcervical quinacrine pellet insertion in cases of elective hysterectomies [7]. Also, we reviewed the published reports showing the safety and reasonable efficacy of QS [8–10]. This trial was designed especially for high-risk women. Earlier, we published a brief account of this experience [11]. The present report is an update after a longer follow-up (maximum, 10.3 years).

2. Materials and methods

This research was carried out from December 1993 through July 1999 when the Drug Controller of India banned the use of quinacrine for this purpose as a result of an article in the *Wall Street Journal* [12]. However, we are still monitoring the women who had undergone QS. The cut-off date for this analysis was March 31, 2003.

We studied 134 women of reproductive age who had two transcervical insertions of 7 quinacrine pellets (252 mg; Sipharm, Sisseln, Switzerland) with 2 diclofenac pellets (50 mg) a month apart during the proliferative phase of the menstrual cycle. A modified IUD inserter was used to place the pellets at the fundus following the standard protocol [13]. One 150-mg injection of depot medroxyprogesterone acetate (DMPA) was given with the first insertion as a back-up contraceptive.

Table 1 describes the clinical features of our cases: 92 women were at high risk of surgery; 27 had voluntarily chosen a non-surgical procedure; and 15 included those who had experienced earlier surgical sterilization failure or for whom the operation was not technically feasible. All of these women gave their informed consent to undergo QS.

Follow-up was scheduled for 1, 3, 6 and 12 months, and then annually, after the second insertion or whenever side effects or complications were experienced. Home visits were made when the women did not report to the clinic. Three additional patients were lost to

Table 1
Clinical features of high-risk women undergoing QS in Patiala, India, 1993–1999 ($N = 134$)

Indication	QS cases (N)
High risk for surgery ($N = 92$)	
severe anemia (Hb <7 g/dl)	61
cardiovascular disease	11
bronchial asthma	8
pelvic inflammatory disease	12
Non-feasibility of surgery ($N = 15$)	
previous surgical failure	7
technical problems	8
tubo-ovarian mass, 2	
thickened tubes, 4	
marked obesity, 2	
Voluntary choice	27
Total	134

follow-up and are not included in this analysis. Thus, all 134 women reported on continued to be followed.

3. Results

No pregnancies or serious complications were reported. The mean follow-up to date is 7.2 years (range 3.9 to 10.3 years). Table 2 summarizes the side effects and complications. The main complaint was transient menstrual irregularity, due probably to the DMPA injection. Other side effects included transient lower abdominal pain, oligomenorrhea or amenorrhea and mild post-insertion bleeding.

Table 2
Side effects and complications after QS among 134 high-risk women in Patiala, India, 1993–1999

Events	No.
Immediate	
Transient lower abdominal pain	3
Post-insertion bleeding	3
Vaginal discharge	13
Low backache	4
Menstrual disturbances requiring treatment	
Oligomenorrhea	21
Amenorrhea	6

The conditions and circumstances faced by these patients were many and varied. The following case reports serve as illustrations:

3.1. Case 1: Anemia

B, a daily wage earner, was para 5 and had had 4 abortions by the village traditional birth attendant (TBA). She had tried the CuT-IUD, which had to be removed due to menorrhagia. She was refused surgical sterilization, as her hemoglobin was only 6.5 g/dl. We performed QS in December 1995 with no side effects.

3.2. Case 2: Rheumatic heart disease and mitral stenosis

K, para 3, had rheumatic heart disease (RHD) with mitral stenosis. In the preceding two pregnancies, she went into congestive heart failure (CHF) and had to be hospitalized. Her husband did not agree to vasectomy. Surgical sterilization was not feasible because of RHD and concomitant anemia. She underwent QS in February 1996 and is doing well on medical treatment for RHD.

3.3. Case 3: Hypertension

HK, para 6, had 3 medical termination of pregnancy (MTP). She had intractable uncontrolled hypertension (BP = 180/100 mmHg). She was refused tubectomy. We performed QS in August 1996, and she is doing well on antihypertensive drug therapy.

3.4. Case 4: Bronchial asthma

S, para 4, 2MTPs and had bronchial asthma. She had tried CuT-IUD, which caused menorrhagia, switched to oral contraceptives (OCs), but had to stop due to severe nausea. She was refused tubectomy because of bronchial asthma. We performed QS in September 1994 without problems.

3.5. Case 5: Laparoligation failure

A, para 3, had one MTP. She presented for laparoscopic sterilization. During the procedure, the right fallopian tube was found to be thickened and adherent. The ring could not be applied on it. She refused minilap but readily agreed to QS, which was carried out in November 1996.

3.6. Case 6: Fear of surgery

C, para 3, had displaced a CuT-IUD and had to undergo laparotomy for this. She was too frightened of any further surgery. She opted for QS, which was done in April 1994.

3.7. Case 7: Laparoligation and minilap failure

SK, Para 6, conceived again after a failed laparoscopic sterilization when she was para 4. She went in for minilap just after the fifth full term normal delivery. Unfortunately, this too failed and she ended up with a sixth child. She became frustrated with surgical sterilization and opted for QS, which was performed in September 1995.

3.8. Case 8: Laparoligation failure

D, para 3, had 4 MTPs. She tried oral contraceptives (OCs) and a CuT-IUD but stopped both due to intolerable side effects. She opted for laparoligation. The procedure failed; the trocar did not reach the peritoneal cavity because of her marked obesity (weight 95 kg). She opted for QS, which was performed in May 1996.

4. Discussion

In our clinical practice, we find that a significant proportion of women are poor candidates for surgical sterilization. They need a non-surgical method of contraception. The QS experience in normal women exceeds 100,000 cases [3] and long-term concerns about the risks of ectopic pregnancy, birth defects and cancer appear to be similar to those for surgical sterilization [14]. There have been no failures in this trial of high-risk women, although failures are reported to be about twice those of surgical sterilization [14]. There were no major complications in this trial. However, more experience is needed in providing this option for such women.

We conclude that QS is a reasonable option, especially for women who are at high risk with the surgical procedure and for those where it is not technically feasible. Also, QS is a practical alternative for women who are apprehensive about surgery, but desire a permanent method of contraception. It is clinically efficacious and safe.

Acknowledgment

The International Federation for Family Health provided the quinacrine pellets for this trial.

References

[1] Zipper JA, Medel M, Prager R. Alterations in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. *Am J Obstet Gynecol* 1968; 101:971–978.
[2] Zipper JA, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the Fallopian tube. *Fertil Steril* 1970; 21:582.
[3] Kessel E. 100,000 quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.
[4] Sarin AR. Severe anemia of pregnancy: recent experience. *Int J Gynecol Obstet* 1995; 50(Suppl 2):545–549.
[5] DeStefano F, Greenspan JR, Dicker RC, Paterson HB, Strauss LT, Rubin GL. Complications of interval laparoscopic tubal sterilization. *Obstet Gynecol* 1983; 61:133–138.
[6] Population Research Center, Center for Research in Rural and Industrial Development (PRC, CRRID) and International Institute for population Sciences (IIPS). 1993. National Family Health Survey (MCH and Family Planning) Punjab 1993. Bombay; PRC, CRRID and IIPS.
[7] Sarin AR, Mohindroo A, Chandra P, Gill SS. Histologic changes in fallopian tubes after lower dose of transcervical quinacrine insertion. *Fertil Steril* 1998; 70 (Suppl) 1:S164.
[8] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.
[9] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.
[10] El-Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59:301–304.
[11] Sarin AR. Quinacrine sterilization; experience among women at high risk for surgery. *Adv Contracept* 1999; 15:175–178.
[12] Freedman A. Two Americans Export Chemical Sterilization to the Third World. *Wall Street Journal*. June 18, 1998:1.
[13] Institute for Development Training. Female voluntary non-surgical sterilization: the quinacrine method. Module 12 of Training Course in Women's Health. IDT, Chapel Hill, North Carolina, 1996.
[14] Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. *Adv Contracept* 1998; 14:81–90.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S77–S85

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

The acceptability, efficacy and safety of quinacrine non-surgical sterilization (QS), tubectomy and vasectomy in 5 provinces in the Red River Delta, Vietnam: a follow-up of 15,190 cases

D.T. Hieu[a,*], T.T. Luong[b], P.T. Anh[b], D.H. Ngoc[b], L.Q. Duong[b]

[a]*Director (retired), Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi, Vietnam*
[b]*Department of Maternal and Child Health/Family Planning, Ministry of Health, Hanoi, Vietnam*

Abstract

Objectives: To compare the safety, efficacy and acceptability of quinacrine sterilization (QS), tubectomy and vasectomy in Vietnam. *Methods:* This study was initiated in January 1998 and completed in February 2000. A sample of 9 districts in 5 provinces, where the prevalence of QS was known to be high, was selected. Every person sterilized in these 9 districts between January 1, 1988 and March 31, 1998 was identified and systematically interviewed by family planning clinicians who had received special training for this project. *Results:* A total of 15,982 sterilization users were identified and 15,190 were interviewed and examined, including a gynecologic exam, if needed: a follow-up rate of 95%. Of those interviewed, 9,753 used tubectomy, 3,734 used QS and 1,703 used vasectomy. All three methods were found to be safe, although morbidity associated with tubectomy was more serious than with QS or vasectomy. No deaths were reported. After more than 5 years of follow-up, tubectomy had the lowest failure rate: 1.0%, followed by 4.1% with vasectomy. A pregnancy rate of 13.2% was reported with quinacrine, although only a small fraction of these failures were confirmed. A strong preference for QS was found. *Conclusion:* QS has an important role to play in sterilization services in Vietnam.

Keywords: surgical sterilization, quinacrine sterilization, female sterilization, vasectomy

1. Introduction

The use of contraception increased substantially in Vietnam during the decade of the 1990s, especially in the provinces of the Red River Delta (Table 1). This is a reflection of both the desires of couples for smaller families and the effort made by the government to make family planning services available. The crude birth rate (CBR) and the proportion of couples with more than 3 children fell precipitously during this decade (Table 2). By 1998, the total fertility rate (TFR) had fallen to 2.48 nationally and to 1.91 in the province of Thai Binh (Table 3).

Until the late 1980s, family planning in Vietnam relied chiefly on IUD use with abortion or menstrual regulation (MR) as a back up. Until 1990, tubectomy was rarely performed and then only in association with cesarean section or surgical treatment in the abdomen or pelvis. Interval sterilization was rarely seen in Vietnam before 1990. This method accounted for less than 1% of the method mix. In 1989, quinacrine sterilization (QS) was introduced to the family planning program by the Ministry of Health. It was widely accepted until 1993 when the program was halted for re-evaluation following a letter from the World Health Organization claiming that quinacrine probably

* Corresponding author. Tel./Fax: 84-4-943-3207.
E-mail address: ngaquan2000@yahoo.com
Correspondence address: 41 Tran Quoc Toan, Hanoi, Vietnam

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Table 1
Contraceptive prevalence rate (CPR) in Vietnam and in the 5 study provinces during the 1990s[a,b]

Area	1992		1996		1998	
	All methods CPR	modern methods	All methods CPR	modern methods	All methods CPR	modern methods
Vietnam	53.8	41.3	68.3	52.9	71.9	57.9
Hai Duong	66.3	62.7	79.1	71.0	80.6	71.2
Hung Yen					78.9	72.4
Thai Binh	73.3	67.1	80.9	71.1	79.1	69.6
Nam Dinh	63.6	57.5	74.1	65.1	72.8	67.6
Ha Nam					77.4	72.8

[a] Data from the Vietnam Government Statistical Office.
[b] Note: In late 1986, Hai Hung Province was divided into Hai Duong and Hung Yen Provinces. At the same time, Nam Ha Province was divided into Nam Dinh and Ha Nam Provinces. The data in the table for 1992 and 1996 are for the original larger provinces before subdivision.

Table 2
Population and crude birth rate (CBR) of Vietnam and the 5 study provinces during the 1990s[a]

Area	Population (per 1000)			CBR (per 1000)			Over 3 children	
	1992	1996	1999	1992	1996	1999	1992	1996
Vietnam	68,361	74,310	76,325	30.0	22.8	19.9	37.1	32.7
Hai Duong	2,614	2,780	1,650	24.5	18.2	18.8	21.3	18.5
Hung Yen			1,069			19.8		
Thai Binh	1,741	1,831	1,786	21.7	19.2	15.5	18.1	11.4
Nam Dinh	2,538	2,721	1,888	26.6	20.9	18.5	33.8	28.9
Ha Nam			792			18.2		

[a] Vietnam Government Statistical Office surveys 1992, 1996, and 1999.

causes cancer [1]. The program has not resumed. In 1990, the no-scalpel vasectomy was actively introduced to Vietnam by the Ministry of Health. In 1992 and 1993, the Ministry undertook a major effort to promote the use of tubectomy and vasectomy. The number of sterilization procedures in Vietnam grew rapidly from 1990 to 1994. A part of this growth was due to QS, especially in the provinces of the Red River Delta. However, the bulk of the growth was due to surgical sterilization. The rapid growth in surgical sterilization can be attributed to the national government's incentive policies for three groups: providers, promoters and especially for users. In 1995, the number of surgical procedures declined rapidly (Table 4), including in the Red River Delta, and this decline continues.

Table 3
Population, crude birth rate (CBR) and total fertility rate (TFR) in Vietnam and in the 5 study provinces in 1998[a]

Area	Population	CBR (1998 census)	TFR (1998 census)
Vietnam	76,324,753	19.89	2.48
Hai Duong	5,037,155	18.77	2.28
Hung Yen	1,047,040	19.77	2.42
Thai Binh	1,173,820	15.49	1.91
Nam Dinh	716,427	18.52	2.32
Ha Nam	965,240	18.15	2.30

[a] Source: Vietnam 1998 population census, 1999.

One difficulty in evaluating QS has been the assessment of failure of this procedure. During the period QS was offered in Vietnam, pregnancy tests were unavailable. The price of a pregnancy test was US$6

Table 4
Sterilization distribution by year in Vietnam and in the 5 study provinces during the 1990s.[a]

Area	Number of users							
	1991	1992	1993	1994	1995	1996	1997	1998
Vietnam	21,092	48,703	120,503	143,104	129,645	121,043	99,391	94,356
Hai Duong		4,085	8,076	7,000	4,408	3,824	1,600	1,298
Hung Yen							1,025	861
Thai Binh	1,383	3,354	3,786	4,488	3,500	1,961	1,223	837
Nam Dinh	3,405	4,503	5,692	4,217	2,888	2,669	1,740	1,317
Ha Nam							577	466

[a] Data from the Vietnam Government Statistical Office.

which the government could not afford. In comparison, the cost of a QS procedure was under US$1. Thus, if a woman was late for her menstrual period and believed she was pregnant, she simply reported to the commune health clinic and requested a menstrual regulation (MR) procedure. There was never any confirmation of pregnancy. Pregnancy was assumed.

It was decided that the best approach to evaluate QS, given that no pregnancy tests were available, would be to determine the worst-case scenario. The worst case would be that every woman reporting to the clinic with a late period following QS was in fact pregnant. In other words, any woman who missed her period and obtained an MR was reported as a pregnancy failure of QS. This was the only approach available to us at the time and represented at best a crude estimate of the failure rate. Unfortunately, amenorrhea is a frequent side effect of QS compelling us to estimate a higher pregnancy rate. In a carefully conducted study of menstrual pattern changes following QS in Indonesia, Agoestina reported that among women who had regular cycles in the beginning, 26% had amenorrhea after the second insertion and 21% after the third [2]. She does not report on amenorrhea after the first insertion. In Chile, Guzman-Serani reported that 35.7% of his patients experienced amenorrhea after at least one of the three insertions [3]. In our paper on 31,781 cases of QS, we found amenorrhea in only 0.3% of the women following insertion of quinacrine [4]. Nearly all of these women, instead of reporting amenorrhea, said that they were pregnant and asked for and received an MR. Thus, the QS failure rates cited in previous publications [4,5] undoubtedly overstate the true pregnancy rate, which will never be known. Further study is needed to refine previous estimates.

Sterilization is an important part of the contraceptive mix and is critical in reducing the need for abortion. The purpose of this study is to compare sterilization methods used in Vietnam and to determine why the practice declined so sharply in the 1990s. Such knowledge will enable us to plan a superior strategy to increase the use of sterilization.

2. Methods

This retrospective study included both an interview and a clinical examination. The study sample was chosen in the following manner:

Five provinces where QS, tubectomy and vasectomy were known to have been performed in significant numbers were selected. In each province, 2 districts were chosen except in Thai Binh where only one district was selected. Each had to meet the following criteria: All commune health centers must be accessible by car. The district leadership must express a readiness to participate and to agree to the need for such a study. This phase was initiated during the first quarter of 1998.

The name of the districts involved in this study were: Bink Luc and Ly Nhan in Ha Nam Province; Xuan Truong and Giao Thuy in Nam Dinh Province; Dong Hung in Thai Binh Province; Yen Mo and Nho Quan in Ninh Binh Province; and Chau Giang and Tien Lu in Hung Yen Province. Thus, there was a total of 9 districts involved.

Investigators were chosen from among health workers at provincial Maternal and Child Health/Family Planning (MCH/FP) centers of the study provinces (2 physicians from each) and from district health centers (1 physician from each). A district team consisted of 2 physicians (1 provincial and 1 district) and 1 or 2 midwives/nurses. The team leader was the doctor from the provincial MCH/FP center. A 5-day training course was organized for the 10 doctors from the provincial MCH/FP centers. They, in turn, organized courses for their district colleagues. All training was conducted in the second quarter of 1998.

A list of users sterilized between January 1, 1988 and March 31, 1998, was completed by the local investigators in cooperation with health authorities. Then each user was invited to the commune health center (CHC) to be interviewed individually and have a clinical pelvic examination if needed. Interviewing was initiated in July 1998 and completed in March 1999.

In cases of illness or discomfort, the team leader provided the patient with appropriate management and treatment. She was monitored by the district investigator. Each woman who participated in the study was offered a small gift by the study team. Data collection was completed in March, 1999.

3. Results

Table 5 presents the number of sterilization users and the number of interviewees by method. The total number of users was 15,982 and the total number of interviewees was 15,190. The percent of follow-up ranged from 92.8% to 96.2%, exceedingly high given the numbers of years that had passed since sterilization.

Table 6 shows that the number of both female and male sterilizations procedures peaked in 1993, the year the QS program was halted and the second year of the implementation of incentive policies for surgical sterilization. The number then decreased rapidly from 4,274 in 1993 to 861 in 1997. The experience in the study districts thus paralleled that of the country as a whole as shown in Table 4. Nearly all (99.3%) of the 13,487 women were farmers. Their mean age at the time of sterilization was 34.7 years and they had completed a mean of 6.6 years of school. When asked if they had experienced any pressure to undergo sterilization, either QS or tubectomy, 13,405 (99.4%) said no while 82 (0.6%) said yes. The latter had pressure from their husbands because their husbands did not want another child. 91.6% of the women had the approval of their husband to obtain the sterilization procedure while 8.4% did not.

Table 5
Number of users and interviewees by method who were sterilized between 1989 and 1998 in the 9 sample districts, Vietnam

Method	No. users	No. interviewees	Interview rate
Tubectomy	10,139	9,753	96.2
QS	4,008	3,734	93.2
Vasectomy	1,835	1,703	92.8
Total	15,982	15,190	95.0

All women who had opted for tubectomy had received a cash incentive of 150,000 VND (approximately US$25) from the authorities according to the regulations of the National Committee for Population and Family Planning. Among the QS users, 18.2% had received a small gift from local authorities. The incentives policies applied only to surgical methods of family planning and did not include QS.

During the three-year period, 1990 to 1992, most female sterilization procedures were QS (see Table 6). The national government never promoted QS and never funded any incentives for QS. Use of the method was halted by the government in December 1993 when a letter arrived from the World Health Organization (WHO) claiming that quinacrine probably causes cancer. However, the number of QS procedures performed had plummeted from 1,910 in 1992 to 244 in 1993 even before WHO intervention. Because the demand was so strong, a handful of QS cases were carried out after the program was officially halted. In 1992 the government began offering incentives for tubectomy and vasectomy and their number increased rapidly, peaking the next year, but then they declined rapidly.

Table 7 presents the outcomes of all pregnancies of all women interviewed prior to their sterilization procedures. Child loss was remarkably low. While the mean number of childbirths was 3.4, the mean number of living children was 3.3. The women had had an average of just over 1 induced abortion or menstrual regulation.

Table 8 is most telling. Women who had a single

Table 6
Number of sterilization users followed-up in sample districts by method and year, Vietnam

Year	Tubectomy		QS		Vasectomy		Total	
	N	%	*N*	%	*N*	%	*N*	%
Before 1989	323	93.3	23	6.7	–	–	346	100.0
1990	112	21.9	399	78.1	–	–	511	100.0
1991	118	9.3	1,141	90.0	8[a]	0.7	1,267	100.0
1992	235	10.3	1,910	83.8	134	5.9	2,279	100.0
1993	3,118	73.0	244	5.7	912	21.3	4,274	100.0
1994	2,229	89.3	10	0.4	256	10.3	2,495	100.0
1995	1,467	88.5	5	0.3	185	11.2	1,657	100.0
1996	1,156	89.1	1	0.1	140	10.8	1,297	100.0
1997	811	94.2	1	0.1	49	5.7	861	100.0
1998 Jan–Mar	184	90.6	0	0.0	19	9.4	203	100.0
Total	9,753	64.2	3,734	24.6	1,703	11.2	15,190	100.0

[a] Before 1992.

Table 7
Fertility status of female sterilization (QS and tubectomy) users, Vietnam, from January 1, 1988 to March 31, 1998

Parameter	Mean	Standard deviation (SD)
Pregnancies	4.6	1.82
Childbirth	3.4	1.22
Induced abortion	0.56	1.00
Spontaneous abortion	0.15	0.46
Menstrual regulation (MR)	0.51	1.17
Living children before sterilization	3.3	1.02
Current living children	3.3	1.02
Living sons	1.9	0.86
Living daughters	1.4	1.05

Table 8
Failure rate for QS according to protocol used, Vietnam, 1989–1993

Protocol	No. QS users	No. pregnancy failures	Failure rate (%)
One insertion	472	127	26.9
Two insertions	3,068	360	11.7
Three insertions	81	1	1.2
One insertion & DMPA[a]	113	5	4.4
Total	3,734	493	

[a] DMPA, depot medroxyprogesterone acetate.

Table 9
Tubectomy failure rates by year of tubectomy, Vietnam

Tubectomy year	Tubectomies (*N*)	Pregnancies (*N*)	Failure rate (%)
Before 1990	323	7	2.2
1990	112	0	0.0
1991	118	2	1.7
1992	235	3	1.3
1993	3,118	36	1.2
1994	2,229	29	1.3
1995	1,467	11	0.7
1996	1,156	10	0.9
1997	811	3	0.4
1998	184	0	0.0
Total	9,753	101	1.0

insertion for QS reported a pregnancy 26.9% of the time. Women who had a depot medroxyprogesterone acetate (DMPA) injection with a single insertion reported a pregnancy 4.4% of the time. Two insertions led to women reporting pregnancy 11.7% and 3 insertions resulted in pregnancy 1.2% of the time. The women who had third insertions all had MRs after their second insertions because of a late period. We will return to these findings in the discussion.

Failure of tubectomy was very low throughout the decade of the 1990s (see Table 9). This is a reflection

Table 10
Side effects/complications after QS, Vietnam, ($N = 3,740$). From 1989 to 1993

Side effect/complication	*N*	%
Yellow vaginal discharge	373	10
Mild pain lower abdomen	451	12.1
Others	289	7.7
Total	1,113	29.8

Table 11
Side effects/complications following tubectomy ($N = 9,753$), Vietnam. From January 1, 1988 to March 31, 1998

Side effect/complication	*N*	%
Bleeding at the incision	57	0.58
Hematoma at the abdominal wall	20	0.20
Fever (>38ºC)	179	1.83
Suppuration at the incision	210	2.15
Pain at the surgical site	508	5.20
Others	182	1.86
Total	1,156	11.9

Table 12
Side effects/complications following 1,703 vasectomies, Vietnam. From 1991 to 1998

Side effect/complication	*N*	%
Bleeding at scrotum	7	0.4
Hematomae	19	1.1
Infection	20	1.2
Fever	23	1.4
Pain	171	10.0
Others	55	3.2
Total	295	17.3

Table 13
Reasons for choosing vasectomy, Vietnam. From 1991 to 1998

Reason	*N*	%
Simple procedure, no major surgery	666	39.2
Want to terminate childbearing	1,409	82.9
Wife cannot be sterilized	207	12.2
Incentives will be given	91	5.4
Others	75	4.2
Total	1,703	143.8

of good training and good program implementation, including monitoring. The failure rate at the time of the interview period was 1.0%. A lower rate is rarely reported.

Side effects and complications reported by QS users were mild and non-threatening. They are reported in Table 10. None required hospitalization. All were temporary, lasting from a few hours to a few days. Yellow vaginal discharge needed only genital washing, and pain was relieved by papaverine or paracetamol in one or two days. On the other hand, side effects and complications of tubectomy were more serious (Table 11) but not life-threatening, and none were severe. All tubectomy patients were hospitalized for a week or more and antibiotics were prescribed for them. Some required additional hospitalization for treatment of complications, which, in general, were more serious and more expensive to manage than those seen with QS.

Vasectomy was rare before 1992 as can be seen in Table 6. In the districts studied, the number quickly peaked at 912 in 1993 and then the number fell precipitously to only 49 in 1997. All districts had a similar experience. As with female sterilization, most couples were relying on the IUD just prior to the vasectomy (83%). Interestingly, in 5% of the couples, the wife was currently using tubectomy. Vasectomy was accepted at an older age (a mean of 42.7 years) compared to QS and tubectomy but the number of years of school completed was identical (mean of 6.6 years). Table 12 lists the complications and side effects of vasectomy though none are major. They affected 17.3% of the men. Table 13 shows the reasons for choosing vasectomy. A full 83% said the finality of the procedure made it attractive. Its simplicity and that it was not major surgery appealed to 39%.

A total of 69 of 1,703 men who obtained a vasectomy experienced a failure of the method resulting in a pregnancy for a rate of 4.1%. The outcomes of these 71 pregnancies were as follows: childbirth 37.7%, induced abortion 53.6%, spontaneous abortion 7.3%, and ectopic pregnancy 1.4%.

4. Discussion

There were many important findings in this study. We can now discuss QS, tubectomy and vasectomy in Vietnam authoritatively and we can compare these methods to each other. Several reasons for the startling decline in the use of sterilization in Vietnam became apparent. Unfounded rumors regarding all methods abound. For example, many of the women believed vasectomy would impair sexual function and discouraged their husbands. QS declined rapidly in 1993 before the WHO letter claiming that quinacrine probably causes cancer [1]. This was mainly due to the large incentives paid to patients, promoters and clinicians for surgical sterilization which were never paid for QS. As a consequence of these promotions, many individuals sought sterilization before they were ready, and they eventually became very unhappy with their decision. These dissatisfied men and women are very poor ambassadors for sterilization and no doubt undermined the credibility of the program.

This study also established that we did a poor job of introducing QS, largely because of a serious shortfall in resources. It also confirmed that we did well technically with the introduction of surgical sterilization. The failure rate with tubectomy was a low 1% with an average follow-up of more than 4 years, an acceptable rate. The failure rate with vasectomy was 4% after a similar follow-up period. Part of this rate can be attributed to the learning curve and this rate is likely to fall with more experience. No life-threatening complications were reported in this study with any of the three methods.

However, QS had a clear advantage with regard to cost-effectiveness. QS costs only US$1, while tubectomy costs US$100 or more. By policy, 3–5 days' hospitalization were usually required with tubectomy, and after discharge, paid sick leave was always 7–10 days. Complications of surgical sterilization, though not life-threatening, were more serious than with QS. They needed to be managed at health facilities and some of these patients had to be hospitalized. No deaths were reported in the provinces studied. However, one death from tubectomy was reported in a Central Highlands province. On the other hand, QS complications only needed to be treated at home with simple or no medications. Investment costs for surgical sterilization are much greater than for QS, involving expenses for personnel, training and facilities.

This study found that there was a strong preference for QS and many women interviewed and others encountered during the course of the study expressed their desire that QS be offered once more. During the course of this study, many representatives of local Women's Unions, speaking for their constituents, strongly urged the investigators to do everything possible to make QS available again.

Our research demonstrates that the stage is set for extensive use of sterilization in Vietnam as the method of choice among couples who want no more children. The rate of child loss among those who sought sterilization was found to be very low – an average of 0.1 children per couple. This is reflected nationally in the contraceptive prevalence data which reveal that couples in Vietnam strongly desire to limit the size of their families. Couples have realistic expectations that their children will survive. The high contraceptive prevalence level also indicates a strong commitment by the government to make good contraceptive methods available to everyone.

In the United States, nearly 80% of couples are sterilized before the wife reaches the end of her reproductive years. They are confident that their children will survive. This condition is now met in Vietnam, making sterilization more desirable. It is rightfully seen as the safest and most use-effective method. Because of its quantum leap in use-effectiveness, sterilization offers the opportunity to a family planning program to make a parallel transition in effectiveness. Family planning programs that offer only temporary methods reach a plateau where program effectiveness levels off well below the desired point. Both sterilization and abortion then create new potential plateaus. Abortion is currently easily accessible everywhere in Vietnam, but some couples choose not to use this service for religious or other reasons, and do not succeed in limiting their family size to the desired number of children. Sterilization can also sharply reduce the demand for abortion, making the family planning program more cost effective. For these reasons, accessibility to good sterilization services is an important goal for all reasonable family planning programs.

In this retrospective study, we have documented the failure of our attempt in the 1990s to make good sterilization services available in Vietnam. Our purpose was to shed light on the reasons for this failure and to identify the manner in which to achieve

program success. Two separate and very different initiatives were undertaken in the 1990s to make safe and effective sterilization services available. We began with QS. The first study was undertaken in Nam Ha Province in 1989 (Nam Ha was later subdivided into Ha Nam and Nam Dinh Provinces) and results were very promising. Our second investigation was undertaken in 1990, again with good results. Then demand quickly soared. Before long, commune clinics were reporting that more than 100 women would line up in front of the building for QS on days it was offered. There were no government promotions or campaigns for QS. Unfortunately, there was no budget for training clinicians or other clinic staff, or for community information and education programs or educating counselors. Individuals only knew that they wanted their childbearing terminated and that QS would accomplish this safely. This demand for QS services was spontaneous and from the grass roots. It was apparent to them that QS did not harm women and that it usually worked. It was not clear early on that these critical program shortcomings could have serious negative effects on the program. It was clear that women found the QS method very attractive. For example, in one province, women were counseled both on QS and tubectomy and then given the choice of the two methods. For every woman choosing tubectomy, 11 chose QS. But by late 1992, it appeared that the failure rate with QS was much higher than expected. More and more pregnancies were being reported and this no doubt affected the credibility of QS with both clinicians and women. The reputation of the procedure became tainted. By then we recognized that perhaps there were serious shortcomings in the introduction of QS into our family planning program.

What was strongly discouraged was the use of a single insertion protocol for QS, as this usually reflected poor training and monitoring of clinicians. There was one exception. It was believed for a time that the addition of a single injection of DMPA at the time of the insertion may improve the efficacy of QS [6]. This was later disproved [7]. However, one trial of a single insertion plus DMPA was conducted in these provinces and some of these women appear in Table 8. This table also shows that a significant proportion of women received a single insertion without DMPA, documenting that our training and program monitoring were deficient. The 113 women who had 3 insertions returned to the clinic for a third insertion following an MR that was probably unnecessary.

The data reported in Table 8 offer new evidence on what was responsible for the high QS failure rate seen in our program. It now appears that women who missed a menstrual period returned to the clinic and reported that they were pregnant. They then requested an MR which they received. A failure of QS was then recorded in their record. Given that this method was so new and there was no education about QS offered by the government, women understandably were not confident in its results. Most of these women were rather desperate to avoid another child. The surest treatment was an MR. As previously mentioned, no pregnancy test was available.

The data in Table 8 support this explanation. The reported failure rate for women having only one insertion is 26.9%. However, in a smaller series undertaken to evaluate a possible potentiating effect of DMPA, the failure rate was only 4.4% after more than 6 years. Women were made aware that DMPA caused amenorrhea and were not concerned that it might be a sign of pregnancy and apparently usually ignored this condition. The rate of 4.4% is close to that reported for single insertion in some other countries, but is a small fraction of 26.9%. The DMPA was shown in other studies not to have a potentiating effect and has been abandoned for this purpose [7]. Also, Table 8 reports on the results of a three-insertion protocol. These 81 women had received a third insertion after they had undergone an MR following 2 insertions of quinacrine pellets. Their failure rate of 1.2% after more than 6 years is in line with experiences with this three-insertion protocol in other countries.

This is compelling evidence that the numbers cited by Sokal and his colleagues in 2000 [5] grossly overstate the true failure rate of QS. The true rates of pregnancy in our program are likely much closer to those seen in other countries than the rates of 12.9% at 5 years after two insertions and 27.3% after one insertion that he reported. We believe that the training preparation for QS was inadequate and that the QS program was permitted to grow much too quickly, allowing our monitoring of the program to be overwhelmed. There was too little evaluation and what was undertaken was done too slowly. We also recognize that there should have been community information and education (I&E) programs developed and implemented.

There should have been much more attention given to counseling, with an emphasis on the side effects of QS, including amenorrhea.

For obvious reasons, QS is viewed in Vietnam among providers, patients and the public in general, as failing far more often than it actually does. There are tens of thousands of Vietnamese women who are very happy with their QS who will be supportive of the reintroduction of the method. But before doing so, the practice of QS must be improved by retraining our family planning staff. Much has been learned both from our program and from others and should be incorporated into our retraining efforts. There were serious negative consequences of payment of incentives for surgical sterilization. Too often individuals elected sterilization for the wrong reasons and were unhappy with their decision or treatment. They expressed their discontentment in ways that served to undermine the sterilization program. The payment of incentives has been counter-productive in the long run and should be discouraged.

Given the findings of this research, a survey is needed to determine current perceptions of QS, tubectomy and vasectomy. Misperceptions must be addressed in any I&E program and in subsequent counseling. All methods should be made available and every couple counseled on all three so that they can then make an informed choice with which they will be happy. We have learned that satisfied users of a service are the most effective promoters.

References

[1] The Editors. Death of a study: WHO, what, and why. Lancet 1994; 343:987–988.

[2] Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–151.

[3] Guzman-Serani R, Bernales A, Cole LP. Clinical report: quinacrine-fused pellets. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, editors, Female Transcervical Sterilization. Philadelphia: Harper & Row. 1983: 100–104.

[4] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh, DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[5] Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis. *Fertil Steril* 2000; 74:1084–1091.

[6] Mullick BC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet non-surgical female sterilization. *Adv Contracept* 1995; 11:239–244.

[7] Randic L, Haller H, Sojat S. Non-surgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen. *Fertil Steril* 2001; 75:830–831.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S87–S91

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

A 22-year experience with quinacrine sterilization in a rural private clinic in Midnapore, India: a report on 5 protocols and 1838 cases

A. Roy

Family Practitioner, Maligram, Midnapore, West Bengal, India

Abstract

Objectives: Evaluate the safety and effectiveness of quinacrine for non-surgical female sterilization in five different protocols. *Methods*: The 5 trials were conducted sequentially. The first and largest, with 985 cases, tested the use of a curved inserter to place a 50 mg dose of quinacrine near each tubal ostia. The next 3 trials were carried out to determine the effect of adjunct procedures on the efficacy of the standard recommended protocol. The three adjuncts were 75 mg of intrauterine diclofenac, 10 mg medroxyprogesterone IM and either 10 mg of atropine IM or 20 mg of hyoscine butylbromide IM. The final trial focused on the currently recommended protocol. *Results*: The 100 mg dose placed at the tubal ostia with the curved inserter resulted in a failure rate of 9.0% at 20 years. Diclofenac or medroxyprogesterone did not improve efficacy over quinacrine alone. Atropine or hyoscine butylbromide substantially diminished the effectiveness of the quinacrine. The failure rate with the standard protocol in our series of 122 cases was 0.8% at 3.5 years. Side effects were minor. There were no deaths nor serious complications with any of these protocols. *Discussion*: All 5 protocols appeared to be safe and the standard one was the most effective.

Keywords: quinacrine sterilization, non-surgical female sterilization, female sterilization, sterilization

1. Introduction

After graduating from a homoeopathic medical college, I set up my office in 1980 in a mud hut at Maligram in the Midnapore District of West Bengal, India. My office was the only medical practice in the area which was not electrified until 1985. Government primary health centers were located at distances of 6 and 7 kilometers and a district hospital was 60 kilometers away. I was able to obtain additional training through courses provided by the Indian Rural Medical Association (IRMA), including the use of some allopathic drugs recommended by the World Health Organization for primary health care [1]. My practice grew rapidly and my clinic facilities improved into a brick building by 1990. It is housed presently in a 3 storied 10 bed hospital, also used by some visiting qualified surgeons.

In 1981, I was selected by IRMA to participate in clinical trials of quinacrine sterilization. I was trained in the method by a qualified obstetrician/gynecologist at their headquarters in Kolkata (Calcutta). From May 1981 until March 1999, I participated in 5 clinical trials. IRMA designed the protocols and provided supplies. All trials were approved by the ethics committee of IRMA, known as the Executive Committee.

2. Methods and materials

The 5 studies are summarized in Table 1. I performed

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Table 1
Summary of five quinacrine sterilization (QS) protocols conducted at Balichak, Midnapore, West Bengal, India, 31 May 1981 to March 1999 ($N = 1838$)

Protocol		Trials			
Name	Medications (mg)	pellets (N)	dose (mg)	insertions (N)	cases (N)
Curved inserter	Q 25	4	100	3	985
Diclofenac (D)	Q 36	6	216	2	325
	with D 25	3	75	2	
Medroxyprogesterone (M)	Q 36 with M 10 IM	6	216	2	313
Atropine (A)	Q 36 with A 10 IM	7	252	1	46
Buscopan (B) (hyoscine butylbromide)	Q 36 with B 20 mg IM	7	252	1	47
Standard	Q 36	7	252	2	122

all insertions. They were carried out in a uniform manner except for the curved inserter study. Using aseptic precautions as with an IUD insertion, a bimanual examination was made, a speculum introduced, a tenaculum applied and uterine depth measured. Clean pellets were loaded in a sterile, dry inserter and the inserter was gently passed through the cervical canal until it touched the uterine fundus. The device was then withdrawn 0.5 cm and its plunger slowly advanced to deposit all pellets at the very top of the fundus. The inserter and other instruments were then removed. The woman rested for 30 minutes in a supine trendelenburg position before discharge. All cases were prescribed 3 cycles of oral contraceptives at the time of the first insertion. Data were recorded on a register recommended by the International Federation for Family Health.

Materials received from IRMA were of foreign manufacture, except for the curved inserter trial for which quinacrine pellets were made to order by a pharmacist in Kolkata. The diclofenac pellets were produced in India. Life table rates were based on months of use from last insertion to most recent follow-up visit.

2.1. Curved inserter

The rationale for using the curved inserter was to place pellets as close to the ostia as possible. Half of the dose of 100 mg was loaded and inserted to one cornual angle, the device withdrawn, and the remaining pellets inserted to the other cornual angle. The 3 insertion protocol followed the procedure of Zipper's original pellet study [2]. The protocol for this research was given up when a prehysterectomy study with comparative data showed no benefit of insertions at the cornual angles compared to the mid-fundus [3]. The study was initiated on 31 May 1981 and completed on 3 June 1991.

2.2. Diclofenac

The idea that diclofenac might both relieve pain associated with quinacrine insertions and possibly improve efficacy by relaxation of the tubal ostia was first suggested by Zipper and his colleagues [4]. This protocol included 2 insertions one month apart of 216 mg of quinacrine and 75 mg of diclofenac. After additional studies showed high efficacy without the addition of diclofenac or ibuprofen, they were deleted [5]. This trial was initiated 30 April 1991 and completed on 21 March 1994.

2.3. Medroxyprogesterone

Medroxyprogesterone is known to relieve uterine contraction. We thought it might also relieve spasm of the tubal ostia and thereby possibly improve the efficacy of QS by allowing more quinacrine to flow into the tubal lumens. Following earlier experience in the use of a method calling for quinacrine 216 mg to be inserted at 2 visits [4], we reasoned that medroxyprogesterone 10 mg IM be added to this protocol. The trial began on 28 February 1994 and was completed on 19 October 1996.

2.4. Atropine/Buscopan

Further thought on relaxation of smooth muscles to prevent spasm of the tubal ostia led to this comparative study (every other case assignment) of 2 smooth muscle relaxants, atropine 10 mg IM and Buscopan (hyoscine butylbromide, C.H. Boeringer Sohn, Ingelheim Am Rhein, Germany) 20 mg IM with 2 insertions of quinacrine 252 mg. This study began on 15 October 1996 and was completed on 29 October 1997.

2.5. Standard

When 2 insertions of 252 mg quinacrine were accepted as standard protocol [6], I adopted this procedure. Admissions began on 22 November 1997 and were halted on 9 March 1999, because the government banned the method following publication of an article in the *Wall Street Journal* attacking QS [7].

3. Results

Only minor complications and side effects were reported in the five studies. None required hospitalization and there were no deaths.

3.1. Curved inserter

Of 985 cases admitted, 39 were lost to follow-up. The life table cumulative failure rate was 7.4 per hundred women after 5 years and at 10 years it was 8.4. It increased accumulatively and only slightly to 9.0 at 20 years (Table 2).

Table 2
Cumulative life-table pregnancy failure rates for 3 insertions of 50 mg quinacrine to each cornual area using a curved inserter. Midnapore, West Bengal, India 1981–1991 ($N = 946$)

Month	At risk	Rate (%)	Standard error (SE)
12	922	3.0	0.5
24	891	5.1	0.8
36	884	6.6	0.8
48	880	7.0	0.8
60	876	7.4	0.9
120	862	8.4	0.9
180	418	8.6	0.9
240	53	9.0	1.0

3.2. Diclofenac study

Of 325 cases admitted 11 were lost to follow-up. The life table failure rate at 10 years was 2.2 (Table 3). Diclofenac has been dismissed as an adjunct. The success in this series is owed to the quinacrine which was given twice in a dose of 216 mg.

Table 3
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (216 mg) and diclofenac (75 mg) at Midnapore, West Bengal, India. 30 April 1991 to 1 March 1994 ($N = 314$)

Month	At risk	Rate (%)	Standard error (SE)
12	313	0.3	0.3
24	313	0.3	0.3
36	311	1.0	0.6
48	309	1.6	0.7
60	309	1.9	0.8
120	76	2.2	0.8

3.3. Medroxyprogesterone

Of the 313 cases admitted, 5 were lost to follow-up. The life table failure rate with this protocol was 2.9 after 7 years (Table 4). There were no failures after the third year.

Table 4
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine 216 mg and intramuscular injection of medroxyprogesterone (10 mg) at Midnapore, West Bengal, India, 28 February 1994 to 19 October 1996 ($N = 308$)

Month	At risk	Rate (%)	Standard error (SE)
12	304	1.6	0.7
24	300	2.6	0.9
36	299	2.9	1.0
48	299	2.9	1.0
60	299	2.9	1.0
72	238	2.9	1.0
84	121	2.9	1.0

3.4. Atropine/Buscopan

In this small comparative study 93 women were admitted, 46 for atropine and 47 for hyoscine butylbromide,

Table 5
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (252 mg) for sterilization when atropine or hyoscine butylbromide is administered IM at each insertion. Midnapore, West Bengal, India. 15 October 1996 to 29 October 1997 ($N = 92$)

Month	Atropine 10 mg			Hyoscine butylbromide 20 mg		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
6	45	6.5	3.6	45	2.2	2.2
12	40	13.0	5.0	37	19.6	5.9
18	37	19.6	5.9	37	19.6	5.9
24	35	23.9	6.3	36	21.7	6.1

of which one was lost to follow-up. The 2-year life table failure rate among the women receiving atropine was 23.9% and among those receiving hyoscine butylbromide, the rate was 21.7%, both exceedingly high (Table 5).

3.5. Standard

In this trial of 122 women, the life table failure rate at 42 months was 0.8% (Table 6).

Table 6
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (252 mg) for sterilization. Midnapore, West Bengal, India. 22 November 1997 to 9 March 1999 ($N = 122$)

Month	At risk	Rate (%)	Standard error (SE)
6	122	0	
12	121	0	
18	121	0.8	0.8
24	121	0.8	0.8
30	121	0.8	0.8
36	118	0.8	0.8
42	57	0.8	0.8

4. Discussion

Because patients are not mobile, there is an advantage of a quinacrine trial in a remote private setting and that is the high rate of follow-up. All subjects were known to me as I have been their family physician for years. Also, conducting such investigations in remote rural areas offers a more realistic assessment of QS clinical trials in these environments where this method can make the greatest difference to women's reproductive health care.

Perhaps the most important finding of our 22 years of experience with this method has been its excellent safety record. Women observe the outcomes of this procedure among their relatives, friends and neighbors. They discuss the results, often for years. Therefore there is no need to recruit women for QS. They learn about it from satisfied users and seek it on their own initiative. After 22 years, the women in my practice all know others who have undergone this procedure and they continue to come, in ever-increasing numbers asking for it. With their own observations in their own community, they have concluded that this method offers them the best alternative.

The only curved inserter prehysterectomy study [3] involved small numbers. Considering the efficacy of this trial with such a low dose, a randomized comparative trial with pregnancy as an end point is still needed with a dose closer to an accepted standard. This might best be done initially with ultrasound control [8]. However, the increased skill needed for clinicians and the pain experienced by the patients might deter use of this protocol if improved efficacy is marginal over the present standard.

The failure rate in the diclofenac trial using 216 mg quinacrine for 2 insertions is most acceptable at 2.2% at 10 years. However, it is not significantly different from the standard protocol at 3 years (1.0% vs. 0.8%, respectively). This is also true of the medroxyprogesterone trial, where a failure rate of 2.9% after 7 years is excellent. However, comparing the two protocols, medroxyprogesterone vs. standard at 3 years, the difference (2.9 vs. 0.8) is statistically only

marginally significant; the rate of the standard protocol leans to be more favorable.

The failure rates of the two smooth muscle relaxants atropine and hyoscine butylbromide came as a surprise (23.9% vs. 21.7% at 2 years, respectively). Fortunately, this poor efficacy became evident early and this study was terminated. We can only speculate why these two drugs interfered with the action of quinacrine. The unexpected result may relate to the need for uterine contractions to advance dissolved quinacrine towards the ostia.

Use of the standard protocol of 252 mg quinacrine in our experience confirms the high efficacy and excellent safety of this method.

5. Conclusion

These trials have demonstrated that quinacrine sterilization can be safely and effectively delivered in a private rural setting in India. They have also shown that this method is very acceptable to women in remote areas. They continue to come in increasing numbers requesting this procedure despite the government's ban on using quinacrine for sterilization. The standard protocol like any protocol can be improved and we must continue to try new modalities to accomplish this. However, at this point QS remains the best and probably the only option on the horizon for many women and should be available to them now. I hope the findings cited here will assist my government in making the decision to reverse the ban in India so that my patients can once again take advantage of this excellent alternative to surgical intervention.

References

[1] World Health Organization. Essential Drugs for Primary Health Care: A Manual for Health Workers in South-East Asia. New Delhi: Regional Office for South-East Asia, 1992.

[2] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[3] Merchant NR, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40(1):47–54.

[4] Trujillo V, Zipper J, Viel B, Rivera M. Stérilisation féminine, non-chirurgicale avec l'emploi de quinacrine: efficacité de deux insertions de pastilles de quinacrine. *Rev Fr Gynécol Obstet* 1993; 88:147–150.

[5] Soroodi-Maghaddam S. Preliminary report on nonsurgical female sterilization in Iran. *Fam Plann Perspect* 1996; 22:122–123, 127.

[6] Institute for Development Training. Female voluntary non-surgical sterilization: The quinacrine method. Module 12 of Training Course in Women's Health. Chapel Hill: IDT, 1996.

[7] Freedman A. Two Americans Export Chemical Sterilization to the Third World. *Wall Street Journal*. June 18, 1998: 1.

[8] Ferreira CRC, Magalhaes DRB, Hanan MZ, Ferreira DC. Quinacrine sterilization: endometrial assessment by vaginal ultrasonography. *Int J Gynecol Obstet;* Suppl Sept. 6, 2000 (abstract RT 3.01.05):73.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S93–S96

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) in Iran and the use of HSG as a measure of success

S. Soroodi-Moghaddam

Private Family Planning Practice, Tehran, Iran

Abstract

Objectives: To establish the safety, effectiveness and acceptability of quinacrine sterilization (QS) in Iran. To determine whether the hysterosalpingogram (HSG) performed under low pressure can be used to demonstrate success of the QS procedure rather than waiting for a pregnancy to occur in order to demonstrate failure. *Methods*: This study was initiated in September 1990 in a private family planning clinic in Tehran, Iran. Patient intake for this analysis was completed 31 December 1998 and the cut-off date for follow-up data to be included in this analysis was 30 July 2002. During this period, 268 women received QS. From inception until April 1994, 160 women entered the study. The first 62 women received 3 insertions and the remainder received 2. Short-term side effects were closely followed in these 160 women. From 18 February 1994 until the patient intake cut-off date, 131 women entered the study and 46 of them received an HSG. *Results*: With 4 to 12 years of follow-up there have been 7 pregnancies for a gross pregnancy rate of 2.6%. However, the use of the HSG tripled the risk of pregnancy for women who underwent the procedure. Furthermore, HSG, even when performed under minimal pressure, indicated failure of the QS procedure about 6% of the time when in fact both tubes would have closed had there been no intervention. Side effects were minor when compared to the complications of surgical sterilization. *Conclusions*: QS was found to be safe, effective and preferred over surgical sterilization by Iranian women. HSG understated the number of patients with bilateral tubal closure, or with tubes that would have closed given a little more time.

Keywords: quinacrine sterilization, nonsurgical female sterilization, hysterosalpingogram

1. Introduction

In 1986, the population growth rate in Iran was 3.8%, one of the highest in the world [1]. In 1994, in response to social and economic pressures, the government became very concerned with this situation. As a consequence, the Ministry of Health has taken various steps to promote family planning. Encouraging messages to limit the size of families are evident everywhere and modern contraceptives, including surgical sterilization and vasectomy, are available throughout the country [2].

There is undoubtedly a great demand for tubal occlusion. But the risks associated with surgical sterilization, its inaccessibility to a large proportion of the population, the fear of surgery generally and the fact that many women are poor candidates for any surgery prevent us from meeting the demand. The pressing need for the development of a non-surgical procedure has been apparent for some time. In 1990, the only method ready for clinical trials was one using quinacrine pellets (QS), the creation of Dr. Jaime Zipper and his colleagues [3]. In response to our own requirements, a clinical trial of QS was initiated in my private family planning practice in Tehran.

As one explains QS to patients and other clinicians,

* Tel: 641-8897;
Correspondence address: 3/115 St. Karger Avenue Amin Street, Tehran 14179, Iran

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

the method appears remarkably simple. The response to its description has all too often been, "What sounds too good to be true usually is." By 1994, this reaction was proving to be a great hindrance to the acceptance of this method in Iran. In a preliminary report on the early experience with QS, anecdotal evidence supporting this position is cited [4]. A test for an endpoint other than pregnancy had to be found. In this way we would be able to document the success of the procedure before exposure to the risk of pregnancy became apparent. Because abortion is illegal in Iran, such a test would be important to the acceptance of QS by both physicians and patients.

In 1993, El Kady and his colleagues in Egypt published their results on the use of the hysterosalpingogram (HSG) as such an endpoint in 159 women [5]. He reported that HSG showed open tubes in 27% of them after 2 insertions and 6% after 3. These findings were inconsistent with the failure rates seen in Tehran, but the idea of using the HSG as an endpoint was very attractive. In some women, the pressure it creates in the tubes could have dislodged the plug of scar tissue and reopened a tube. Perhaps El Kady was using a pressure during the HSG that was higher than needed. El Kady had observed that no failures were reported during the 2 years of follow-up after the HSG showed closure.

In 1994, Alpizar reported on 694 cases in Costa Rica. He had performed HSG on 129 of these women but bilateral obstruction was found in only 89% of them. Again these results were inconsistent with pregnancy rates in Tehran. Alpizar also noted that this rate was increased in women receiving HSG (4.3% as compared to Tehran 2.0%) [6]. Alpizar found fewer than half as many open tubes compared to El Kady (11% vs. 27%). Differences in pressure could account for the difference in rates. In both cases, just how much pressure was used and whether it was consistent was unknown.

The use of HSG in QS had considerable potential value in Iran and elsewhere. The decision was made to undertake a trial to test HSG as an endpoint using a minimal amount of pressure.

2. Methods

Only women who could continue follow-up for a long period were selected for this study. A total of 268 QS procedures were performed. To ensure informed consent, all prospective acceptors and their husbands were counseled prior to the procedure. This preparation included a detailed description of the method and its administration, possible complications and side effects and the risk of failure. The permanent and irreversible nature of the procedure was explained. Both members of the couple signed an informed consent form.

The International Federation for Family Health (IFFH) QS protocol [7] based on the work of Zipper and his colleagues, was applied throughout the study. Originally, Zipper had recommended that quinacrine be administered in three doses of 252 mg (seven pellets of 36 mg each) at one-month intervals [7]. But after the first 62 procedures a second regimen was followed. Zipper had changed his recommendation to two monthly doses plus 50 mg of an antiprostaglandin to lessen spasm and thereby reduce the failure rate and pain. These changes were adopted for the last 98 procedures of that study, using 55.5 mg of ibuprofen in the form of three 18.5 mg pellets. Use of this protocol continued until the patient intake cut-off date for this report. Side effects were carefully recorded in these 160 women.

On February 18, 1994, a third protocol was adopted. Many women were requesting HSG because they or their family physicians wanted reassurance that the procedure was successful in closing the tubes before they terminated other contraceptive methods. Patients who requested an HSG were offered this service. However, they were referred to a single radiologist, a colleague sympathetic to QS who agreed to use minimal pressure. No attempt was made to assign patients to the two groups. It depended entirely on the woman's preference. This protocol was continued until December 31, 1998, the case intake cut-off date for this report. Follow-up of all cases continued until 31 December 2002.

In our investigations, a modified Copper-T IUD inserter was used to administer the quinacrine pellets, as follows: after preparing the cervix and sounding the uterus, the clinician set the flange on the inserter sleeve, and advanced the inserter to the fundus. She then withdrew the inserter 0.5 cm, fixed the inserter sleeve and slowly advanced the plunger to expel all pellets at the fundus. The inserter was then withdrawn. Fundal placement was used from the very beginning in 1990, although it was not described in the literature

until 1993 [8]. After each insertion, the woman was given a five-day course of antibiotics.

Women returned to the clinic for follow-up one, two and 15 days after each insertion; one, two, three and six months after the last insertion; and then annually. There was no charge for these visits. A cycle of oral contraceptives was provided at the time of the last insertion and at the one- and two-month follow-up visits. Every woman was followed until the cut-off date for this report. There is considerable confidence that every pregnancy and serious complication would have been reported (Table 1).

Table 1
Additional follow-up of the 160 patients in the series reported in *International Family Planning Perspectives* [Ref. 4], after 5.9 years of follow-up (case intake from September 1990 to April 1994), Tehran, Iran

Number of cases	Pregnancies	
	N	%
First 62 (3 insertions)	2	3.2
Last 98 (2 insertions)	1	1.0
Total 160	3	1.9

3. Results

A total of 46 women had an HSG, while 85 QS patients undergoing the procedure during the same time period did not.

Complications and side effects following QS for the first 160 patients have been documented elsewhere [9]. These are summarized in Table 2 in addition to the prescribed treatment. The type and frequency of these adverse events (AE) did not change during the remainder of this series. All have been minor and easily treated. There have been no allergic reactions except possibly for local pruritis.

Failures from the first two protocols are reported in Table 3. These patients have been followed for 8 to 12 years each. Pregnancies experienced with the third protocol are shown in Table 3. Follow-up has ranged from 4 to 9 years for this group. Pregnancy among women receiving an HSG was twice as high as it was among non-HSG patients (4.3% vs. 2.4%). There were 7 pregnancies in this series of 268 cases for a gross rate of 2.6% with 4 to 12 years of follow-up. The seventh pregnancy was a blighted ovum occurring 12 months after QS and resulted in a spontaneous abortion after 2 months. This patient had not had an HSG. There have been no ectopic pregnancies.

Table 4 reveals that HSG grossly overstates failure of

Table 2
Complications and side effects reported following nonsurgical female sterilization with quinacrine pellets, and prescribed treatment, Tehran, Iran 1990–1994 ($N = 160$)

Complication	*N*	Treatment
Lower abdominal pain	18	analgesic
Itching (local)	16	cortisone cream
Fever $\geqslant$5 days	14	antibiotic (4 days)
Backache	8	analgesic (2–3 days)
Vaginal discharge	8	anti-fungal, antibiotic vaginal suppository (6 days)
Spotting	8	none
Decreased menses	7	none
Cervical adhesion	1	surgical correction
Bleeding	1	vasoconstrictor

Table 3
Pregnancy following QS during period (February 18, 1994 to December 31, 1998) when 46 of 131 patients requested HSG 2–4 months post second insertion, with 6 months to 5 years follow-up, Tehran, Iran

HSG	Cases (*N*)	Pregnancy	
		N	%
Performed	46	2	4.3
Not performed	85	2	2.4
Total	131	4	3.1

Table 4
HSG vs. pregnancy as an endpoint among QS patients, September 1990 to December 1998, Tehran, Iran ($N = 268$)

	Endpoint	
	HSG (*N*)	Pregnancy (*N*)
Cases (*N*)	46	222
Positive (*N*)	4	5
Failure (%)	8.7	2.3

tubal closure. This experience with HSG suggests that 8.7% of women did not have tubal closure. But among patients who did not have an HSG, only 2.3% went on to become pregnant.

4. Discussion

HSG is probably not very useful even if the technique did not cause pregnancies. The failure or pregnancy rate using HSG as the endpoint was 3.8 times higher than that for pregnancy (8.7% vs. 2.3%). This was an improvement over the findings of El Kady and Alpizar, perhaps due to the use of a lower pressure. Nevertheless, this rate, in our opinion, is not acceptable.

In the four cases where the HSG was positive for an open tube (Table 4), the two-insertion QS procedure was repeated without difficulty. In three cases, the HSG was repeated after the second procedure. In the other case, the clinician declined to repeat the HSG. Because of false positives, and because HSG may blow out a plug of scar tissue with resulting pregnancies, we would not recommend HSG as an endpoint for QS.

QS was found to be both safe and effective in Iranian women. This experience is consistent with the assumptions of researchers everywhere. After 12 years of performing this procedure and an enormous amount of feedback from patients, this investigator highly recommends this method. In Iran, the greatest obstacle to its widespread adoption is simply the lack of awareness among our physicians of the extensive scientific evidence already documented internationally confirming QS to be safe, effective and acceptable to women.

References

[1] Aghajanian A. Population change in Iran, 1966–86: a stalled demographic transition? *Population and Development Review* 1991; 17:703–15.

[2] United Nations Population Fund. Family Planning in the Islamic Republic of Iran. Tehran, 1994.

[3] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[4] Soroodi-Moghaddam S. Quinacrine pellet method of nonsurgical female sterilization in Iran: preliminary report on a clinical trial. *Int Fam Plann Perspect* 1996; 22:122–123.

[5] El Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59:301–304.

[6] Alpizar F. Quinacrine pellet sterilization in Costa Rica. *QS Newsletter* 1997; 2:3.

[7] International Federation for Family Health (IFFH). Protocol for straight and comparative studies of nonsurgical female sterilization by quinacrine pellets and quinacrine pellets plus adjuvants. Otis, Oregon, USA. 1992.

[8] Hieu DT, Tan TT, Tan DN, Nuguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S97–S100

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization of 1997 women in Daharpur, Midnapore, West Bengal, India: a comparison of 3 protocols

S.K. Pal

Family practitioner, Daharpur, Midnapore, West Bengal, India

Abstract

Objectives: Determine the efficacy of two different dosage regimens of quinacrine placed at each cornual angle, employing a curved inserter, and for fundal placement of doses from 252 mg to 360 mg of quinacrine, depending on the age of the woman. *Methods*: 1. The first trial involved 3 double insertions, a month apart, of 50 mg of quinacrine at each cornual angle. This trial was initiated on 14 August 1979 and completed on 26 June 1984 with 418 subjects admitted. 2. The second was a single double insertion of 100 mg at each cornual angle. This trial, initiated on 30 November 1984, was completed on 11 June 1985 with 100 subjects admitted. 3. The third trial began 2 January 1995, was completed 26 January 1998 and included 1479 subjects. There were 2 insertions, a month apart, with fundal placement of all pellets. The dose depended on the woman's age and ranged from 252 mg in the oldest to 360 mg in the youngest. The cut-off date for this trial was 23 January 2003. *Results*: Only relatively minor side effects or complications were seen. None required hospitalization. Failure rates with multiple low dose or single dose cornual placement of pellets were unacceptably high. When higher doses of fundal placement of quinacrine were used at two visits, one month apart, no failures occurred. *Conclusions*: The third protocol shows great promise.

Keywords: quinacrine sterilization, sterilization, female sterilization, non-surgical female sterilization

1. Introduction

After receiving my degree from a homeopathic medical school in 1978, I opened a practice at Daharpur, a rural area of West Bengal, India. In 1979, I was chosen for training in quinacrine sterilization (QS) at the headquarters clinic of the Indian Rural Medical Association (IRMA) in Kolkata (Calcutta). Following this initial experience with QS, I participated in 2 clinical trials, the protocols of which were approved by the ethics committee of IRMA, also known as the Executive Committee. All supplies were provided by IRMA and I served as family physician to all volunteers of the trials. Following IRMA approval of the standard QS protocol for service programs, a third QS trial was conducted where I modified the standard procedure in an attempt to further reduce the failure rate with the method.

2. Materials and methods

QS involves transcervical insertion of quinacrine in the proliferative phase of the menstrual cycle. The method was developed by Zipper, first using a liquid slurry [1] and then pellets [2]. He found that quinacrine produces a sterile inflammation leading to an occlusive scar in the uterine horn of the rat [3]. This was applied in human patients and it was confirmed that scars developed in the human fallopian tube [4].

* Tel: 03228268344/9528268344;
Correspondence address: Tamluk Hospital More, Tamluk, Midnapur, West Bengal, India

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Quinacrine pellets became available in India initially as 25 mg pellets prepared at a pharmacy in Kolkata and used in the 2 curved inserter trials now described. Later drugs of foreign manufacture became available as 36 mg pellets (Sipharm, Sisseln, Switzerland), which were used in the third experience.

An early hypothesis concerning QS was that inserting pellets in the cornual angle near the tubal ostia would improve efficacy. Such trials were proposed by the Indian Fertility Research Programme in which IRMA participated.

The initial curved inserter trial involved 3 double insertions a month apart with 2 25 mg pellets (50 mg) being placed at each cornual angle. "*Double insertions*" is defined as two insertions of quinacrine accomplished at the same sitting wherein the operator places quinacrine pellets at the two cornual angles of the uterus. Double insertions are accomplished by placing 2 pellets in the inserter, advancing it to the cornual angle on one side, releasing 2 pellets, removing the inserter, reloading the inserter with 2 additional pellets, then reintroducing the inserter to the cornual angle on the other side and releasing the 2 additional pellets. The need for 3 insertions followed the experience of Zipper [2]. The lower dose was an estimate which was expected to be justified at follow-up. This trial was initiated on 14 August 1979 and completed on 26 June 1984 with 418 subjects admitted and 68 lost to follow-up. For the curved inserter studies, cumulative life-table rates were calculated based on use from third insertion to last patient contact.

The second curved inserter study was part of an effort to find an acceptable single insertion dose. In this trial the dose of quinacrine was doubled to 4 pellets at each cornual angle (100 mg) but as one double insertion. The trial was initiated on 30 November 1984 and completed on 11 June 1985 with 100 subjects.

The third experience involved a straight inserter and pellets were carefully deposited at the fundus. Following the standard recommended protocol [5], 2 insertions a month apart were provided. In an effort to improve efficacy of the standard protocol, several changes were introduced as follows:

(1) Insertions were strictly limited to days 11, 12 and 13 of the menstrual cycle.
(2) Cervical erosion was treated and insertions delayed until healing was evident.
(3) When trichomonas was diagnosed, oral treatment was prescribed for both partners.
(4) The number of pellets used was adjusted by age in years of subjects as listed. The rationale of this was that younger women are more fertile and more likely to experience a pregnancy failure.

Age <25	10 pellets or 360 mg
Age 25–32	9 pellets or 324 mg
Age 33–40	8 pellets or 288 mg
Age >40	7 pellets or 252 mg

(5) In an effort to increase rapid absorption of quinacrine by the tubal epithelium to incite inflammation and a scar, all pellets less one were placed in a sterile, dry inserter and immersed in sterile water up to the level of the pellets in order to moisten them for faster dissolution. Then the last dry pellet was put in the inserter and all pellets were installed at the very top of the uterine fundus.
(6) After each insertion, patients with normal uteri were left in a horizontal supine position for 30 minutes. Patients with anteverted uteri were placed in a supine trendelenburg position and those with retroverted uteri in a prone trendelenburg position for 30 minutes.

This clinical experience was initiated on 2 January 1995 and completed on 26 January 1998. 1479 subjects were recruited. The number of patients at risk per month was calculated with a cut-off date of 23 January 2003.

3. Results

Insertions in all 3 studies were well tolerated and no serious complications were reported. Table 1 shows efficacy of the 2 curved inserter trials. The placement of 50 mg of quinacrine at each cornual angle was inadequate with a 4-year failure rate of 12.2%. When the dose was doubled to 100 mg at each cornual angle, it quickly became clear that this did not help. At 6 months the failure rate was 25.9% and this technique was abandoned. All pregnancy failures were terminated within 10 weeks' gestation.

In comparison, the results of the 2-insertion protocol, basing the dose on the age of the woman, were unambiguous. There were no reported pregnancy failures in

Table 1
Cumulative life-table pregnancy failure rates for 2 curved inserter quinacrine sterilization trials at Daharpur, West Bengal, India

Month	Three insertions 100 mg (*N* = 418) 1979–1984			Single insertion 200 mg (*N* = 100) 1984–1985		
	At risk	Rate (%)	SE[a]	At risk	Rate (%)	SE[a]
6	314	1.6	0.7	27	25.9	6.4
12	268	6.3	1.3			
18	219	7.8	1.6			
24	179	8.8	1.7			
30	148	9.9	1.9			
42	78	10.8	2.0			
48	48	12.2	2.5			

[a] SE = Standard Error.

Table 2
Women at risk by age for quinacrine sterilization with age-dependent dose transcervical insertions at Daharpur, West Bengal, India (1995–1998)

Month	At risk				
	<25 yr (*N* = 174) 360 mg	25–32 yr (*N* = 1081) 324 mg	33–40 yr (*N* = 217) 288 mg	>40 yr (*N* = 7) 252 mg	Total (*N* = 1479)
12	174	1081	217	7	1479
24	174	1081	216		1478
36	174	1081	216		1478
48	174	1081	216		1478
60	170	1056	214		1448
72	147	831	174		1154
84	73	490	108		674

this group. Table 2 shows the number of women at risk in each age category.

4. Discussion

These two curved inserter trials demonstrated that these devices alone would not permit the use of lower doses of quinacrine without a loss of efficacy. Curved inserter trials were discontinued after a prehysterectomy comparative study by Merchant and her coworkers [6] revealed no apparent benefit. However, a randomized trial of curved inserters using the standard dose of 252 mg and multiple insertions has not been done.

The end result of my modifications of the standard recommended protocol was a series of 1479 women who did not report a single failure or serious complication. Unfortunately, it is not possible from this experience to isolate the relative importance of each protocol change. Collectively, efficacy improved with higher doses of quinacrine.

Merchant [6] believes even a single insertion of 9 pellets or 360 mg may be adequate for near perfect efficacy. Only 7 women in this series of 1479 were over age 40 and thus received the standard dose of 7 pellets or 252 mg twice. This age group of women is known to have lower natural fertility. All others had a dose of 288 to 360 mg. The higher dose may have improved efficacy.

On the other hand, immersion of the quinacrine

pellets in sterile water, which caused more rapid absorption may have been a factor in our gratifying results. A comparative trial between the standard 30-minute and 100-minute dissolution times showed higher failures for the prolonged time [B. Mullick, personal communication], suggesting that rapid release may improve efficacy. A 7-day slow release study in pigs gave no evidence of tubal damage [7], also suggesting that rapid absorption was needed for this purpose. However, with my immersion of the pellets in sterile water, the risk of cortical excitation as seen with the quinacrine slurry [1] must be considered, although no such case was seen in my experience.

On 26 January 1998, because of the complete absence of pregnancy failures and serious complications in this trial of 1479 women, I adopted this protocol for my practice. I no longer considered this approach experimental. Between 26 January 1998 and learning of the ban imposed by my government on the use of quinacrine for female sterilization, I performed an additional 1500 cases without a single pregnancy or serious complication reported. The Indian government has not yet rescinded its ban.

5. Conclusion

The standard protocol of 2 monthly insertions of 252 mg quinacrine is considered best. QS is preferred especially where surgical sterilization is not easily and safely available [8]. Improvements in quinacrine sterilization may be expected once it is in the hands of many clinicians. I hope my experience will provide thought for further enhancing the efficacy of this important advance in women's reproductive health care.

References

[1] Zipper JA, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil Steril* 1970; 21:581–589.

[2] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[3] Zipper JA, Prager R, Medel M. Biologic changes induced by unilateral intrauterine instillation of quinacrine in the rat and their reversal by either estradiol or progesterone. *Fertil Steril* 1983; 24:48–53.

[4] Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM. Quinacrine-induced pathologic changes in the fallopian tube. *Fertil Steril* 1980; 33:666.

[5] Institute for Development Training. Female voluntary non-surgical sterilization: The quinacrine method. Module 12 of Training Course in Women's Health. Chapel Hill: IDT. 1996.

[6] Merchant NR, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40(1):47–54.

[7] Zaneveld LJD, Goldsmith A. Evaluation of slow-release quinacrine pellets in the pig. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, editors. Female Transcervical Sterilization. Philadelphia: Harper and Row. 1983:122–127.

[8] Potts M, Benagiano G. Quinacrine sterilization: a middle road. *Contraception* 2001; 64:275–276.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S101–S106

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization: results in 180 women

S. El Sahwi*, M. Kamel, M. El Faham, I. El Makhzangy

Department of Obstetrics & Gynecology, Shatby Maternity Hospital, Alexandria, Egypt

Abstract

Objectives: Document the effects on the tube and uterus of one, two and three doses of 252 mg of quinacrine. *Method*: The study included 180 fertile women seeking permanent contraception at the Shatby Family Planning Clinic in Alexandria, Egypt, in 1988. All cases received three applications of seven 36 mg quinacrine hydrochloride pellets during the proliferative phase of three consecutive menstrual cycles. The patients were randomly divided into groups A, B and C. Hysterosalpingography (HSG) was performed on the 6th day of menstruation and hysteroscopy on the 10th day of the same cycle after the first application in group A, the second, in group B and the third, in group C. The study was concluded in 1999. *Results*: HSG showed 52 cases of bilateral obstruction, four of bilateral patency, and four of unilateral patency in group A. All in groups B and C elicited bilateral tubal obstruction. Cornual obstruction was seen in 33%, 65% and 85% in group A, B and C, respectively. Intramural obstruction was found in 50%, 33% and 10% in the three groups. Isthmic tubal obstruction was detected in 8%, 2.5% and 5% in groups A, B and C, respectively. Four types of ostial appearances could be recognized hysteroscopically. Type 0 (patent tubes), Type I (distal tubal blockage), Type II (intramural obstruction) and Type III (cornual obstruction). In group A, Type 0 was evident in 10%, Type I in 8%, Type II in 50% and Type III in 33% of cases. The respective figures in group B were 0%, 2.5%, 33% and 65%, while in group C, they were 0%, 5%, 10% and 85%. Hysteroscopy showed no abnormal endometrial findings in group A, but 35% and 85% of cases in group B and C showed some changes. *Conclusions*: Two applications of quinacrine were 100% effective. The side effects of quinacrine pellet applications were minimal and well tolerated by all the users. The possibility of reversal of the procedure is outlined.

Keywords: quinacrine non-surgical sterilization, hysteroscopy, hysterosalpingography

1. Introduction

The need for female sterilization far exceeds the ability of most countries to provide services. A simple, non-surgical procedure is needed to fulfill the unmet contraceptive demand. Quinacrine was originally introduced in 1931 to prevent and cure malaria. Today it continues to be prescribed for giardiasis and lupus erythematosus. This drug has sclerosing properties for some tissues and has been used for the management of recurrent pleural effusion. Zipper and his colleagues performed blind transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization [1]. Various doses, concentrations and solvents, as well as different instillation schedules were evaluated. Three instillations proved to be the most effective schedule of quinacrine delivery but there were still pregnancy rates of almost 10%. Zipper's research led to the development of quinacrine hydrochloride pellets and a delivery system designed to bring the chemical

* Corresponding author.
E-mail address: samirelsahwi8hotmail.com (S. El Sahwi)

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

into prolonged contact with the tubal ostia. The results were encouraging. At one year after three insertions of 252 mg quinacrine pellets (7 pellets each containing 36 mg), the gross life-table pregnancy rate was 3.1 per 100 women [2]. It was suggested that high placement of pellets near the ostia resulted in more intense inflammation and presumably fibrosis [3]. Histopathological studies after transcervical insertion of quinacrine pellets in prehysterectomy volunteers indicated that tubal occlusion occurs by a process that starts with inflammation, leads to fibrosis, which is limited to the cornual area and the intramural portion of fallopian tubes [4,5].

The endometrial lining of the uterine cavity appears to recover from any inflammatory response. This was attributed to the protective action of zinc which is at high levels in the endometrium but is low in the fallopian tubes [6]. Toxicology studies for intrauterine use of quinacrine were completed at Johns Hopkins University in the early 1980s leading to approval of prehysterectomy trials by the United States Food and Drug Administration (USFDA) [7]. Recently, controversy concerning its use for sterilization has been reviewed by Benagiano [8].

The objective of this research was to evaluate the optimal number of quinacrine hydrochloride applications that allows the highest efficacy in tubal occlusion. Moreover, the intrauterine cavity and the condition of the endometrium were studied by both hysterosalpingography (HSG) and hysteroscopy after each of the three applications. The side effects of quinacrine instillation were also assessed.

2. Material and methods

A limited clinical trial of quinacrine sterilization was started in 1988. Initial promising data [9] led to a second longer trial involving 180 women who requested sterilization and volunteered for this method at the Shatby Family Planning Clinic of the University Hospital in Alexandria, Egypt. Before admission to the study the risks and benefits of the method and details of the procedure were carefully explained to them. Additional contraceptives were prescribed for 3 months after quinacrine insertion. Patients with pelvic inflammatory disease (PID), psychiatric problems, and severe liver infections were excluded. Those selected were randomly divided into three groups: A, B and C, each consisting of 60 cases.

Using a copper T-IUD applicator, seven quinacrine hydrochloride pellets 36 mg each, were deposited in the upper part of the uterine cavity [10]. Each woman received three applications on three consecutive cycles during the proliferative phase of the menstrual cycle.

HSG was performed on the sixth day and hysteroscopy on the tenth day of the menstrual cycle that followed the first application in group A, the second in group B and the third in group C. Hysteroscopy was performed under paracervical block using the 4 mm Storz panoramic instrument. The uterine cavity was distended with CO_2 gas. Systemic exploration of the anterior, posterior and lateral walls of the uterine cavity as well as exploration of the tubal ostia were done. The study was concluded in 1999.

3. Results

3.1. Demographic characteristic of the cohort (Table 1)

The women ranged in age from 32 to 45, with a mean age of 36.5 years in group A, 37.5 years in B and 36.4 years in C (Table 1). The parity ranged from 3 to 14 with mean parity 6.2 in group A, 7 in B and 7.5 in C. The number of living children ranged from 3 to 11 with a mean of 5.4 in group A, 6.5 in B, and 6.2 in C. There were no significant differences among the three groups.

Table 1
Age, parity, and number of living children in the three groups at Shatby Family Planning Clinic, Alexandria, 1988–1999

Group	Age (yr)		Parity (*N*)		Living children (*N*)	
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
A	32–45	36.5±3.3	3–12	6.2±2.3	3–10	5.4±1.7
B	32–45	37.5±4.1	4–12	7.0±2.0	4–9	6.5±1.6
C	32–42	36.4±3.2	3–14	7.6±2.9	3–11	6.2±2.5
Total	32–45	36.8±3.5	3–14	6.9±2.9	3–11	6.0±2.0

3.2. Hysterosalpingographic (HSG) findings (Table 2)

In group A, 52 cases of bilateral tubal occlusion were

Table 2
Distribution of cases according to the level of obstruction as seen by hysterosalpingography at Shatby Family Planning Clinic, Alexandria, 1988–1999

Condition of the fallopian tubes	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Patent	12	10	0	0	0	0
Obstruction						
Isthmic	9	8	3	2.5	6	5
Intramural	60	50	39	33	12	10
Cornual	39	33	78	65	102	85
Total	120	100	120	100	120	100

N, number of both fallopian tubes in 60 cases.
Significant ($p \leqslant 0.05$).

Table 3
Distribution of cases according to the type of obstruction as diagnosed by the hysteroscope at Shatby Family Planning Clinic, Alexandria, 1988–1999

Condition of the fallopian tubes	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Type 0[a]	12	10	0	0	0	0
Type I	9	8	3	2.5	6	5
Type II[a]	60	50	39	33	12	10
Type III[a]	39	33	78	65	102	85
Total	120	100	120	100	120	100

N, number of both fallopian tubes in 60 cases.
[a]Significant ($p \leqslant 0.05$).

seen, 4 showed bilateral tubal patency, and 4 unilateral tubal patency. While in group B and C bilateral tubal occlusion occurred in all the cases. Three types of tubal obstruction could be elicited on the HSG films (cornual, intramural and isthmic).

Cornual: The percentages of fallopian tubes with cornual obstruction were 33 for A, 65 for B, and 85 for C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

Intramural: Intramural obstruction was elicited in 50%, 33% and 10% of the fallopian tubes in groups A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

Isthmic: The proportions of isthmic obstruction in the fallopian tubes were 8%, 2.5% and 5% in groups A, B and C, respectively. The differences among the three groups were not significant.

3.3. Hysteroscopic findings (Table 3)

According to hysteroscopic appearances of the tubal ostia there were 4 patterns of changes: Type 0, 1, 2 and 3.

- *Type 0 (patent tubes):* No obstruction could be seen by the hysteroscope or noticed on the monitored CO_2 hysteroinsufflator system. In group A, 3 cases showed bilateral, and 6 unilateral tubal patency. Type 0 was not detected in groups B and C, which was significant ($p \leqslant 0.01$).
- *Type I (distal tubal blockage):* An obstruction could not be seen through the hysteroscope, but was noticed on the monitored CO_2 hysteroinsufflator. Type I obstruction was detected in 8%, 2.5% and 5% of the fallopian tubes in groups A, B and C, respectively. The differences among the three groups were not significant.
- *Type II (intramural obstruction):* An occlusion of the intramural portion was seen through the cornual orifices of the fallopian tube. Type II obstruction was detected in 50%, 33% and 10% in group A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).
- *Type III (cornual obstruction):* An obstruction was denoted by absence of the cornual orifices of the fallopian tube which is replaced by reactive fibrosis restricted to the expected site of the cornua. In some cases the reaction was extensive and seen in the form of a rough raised dome-shaped elevation in the tubal horn. We considered this intense cornual obstruction. The proportion of fallopian tubes that showed type III obstruction were 33%, 65% and 85% in groups A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

3.4. Abnormal endometrial findings seen by the hysteroscope (Table 4)

In group A no abnormal findings were detected, while 21 cases (35%) in B and 51 (85%) in C showed abnormal endometrial changes. The differences among the three groups are statistically significant ($p \leqslant 0.05$). Various types of abnormal endometrial changes were noted by hysteroscopy. Atrophic/polypoid reactions were significantly higher in group C.

Table 4
Type of abnormal hysteroscopic endometrial findings (60 cases in each of the three groups) at Shatby Family Planning Clinic, Alexandria, 1988–1999

Type of abnormal endometrial changes	Group A		Group A		Group A	
	N	%	*N*	%	*N*	%
Bullous reaction	0	0	0	0	3	5
Ulcerative reaction	0	0	0	0	3	5
Atrophic reaction	0	0	12	20	18	30[a]
Hyperemic reaction	0	0	0	0	3	5
Polypoid reaction	0	0	6	10	15	25[a]
Fine adhesions	0	0	3	5	9	15

[a] χ^2 Significant.

Table 5
Side effects of the application of quinacrine pellets (60 cases in each of the three groups) at Shatby Family Planning Clinic, Alexandria, 1988–1999

Side effect	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Transient yellow discharge	60	100	60	100	60	100
Menstrual changes	6	3.3	48	27	93	52
Colicky pain	6	3.3	24	8	30	17
Vaginal spotting	6	3.3	30	10	42	23

3.5. Side effects of quinacrine pellet application (Table 5)

- All patients had noticed a yellowish discharge that lasted for a few days after each application. The discharge was odorless and non pruritic.
- Some women complained of delay and diminished menstrual flow in the cycles that followed QS. These changes were observed in 3.3%, 27% and 52% of the patients after first, second and third applications, respectively.
- Colicky pain was observed immediately after pellets had been inserted and lasted for a few hours in 3.3%, 8% and 17% of the patients after first, second and third applications, respectively.
- Vaginal spotting was a temporary complaint that followed the procedures and lasted for few days. It was observed in 3.3%, 10% and 23% of the women after the first, second and third applications, respectively.

4. Discussion

In many parts of the world, sterilization has become the leading method of fertility control [11]. The need to make this procedure simple, safe, inexpensive and thereby more acceptable, even in countries with limited surgical facilities is well recognized. Use of quinacrine pellets has become the most widely adopted method of non-surgical female sterilization [12].

This present study supports previous research indicating that transcervical insertion of quinacrine pellets is free from serious side effects [13,14]. There were no deaths in the present series and no death has been reported for this method anywhere in the world [12]. Long-term follow-up of quinacrine sterilization acceptors in Chile found no increased risk of cancer [15]. All the side effects were transient and of short duration, as documented by others [10,16]. Those reported in the present study were temporary pain, vaginal discharge, hypomenorrhea and oligomenorrhea. Some patients complained of mild vaginal spotting which was easily tolerated in all cases. Randic and her colleagues [17] found that most women had an unpleasant yellowish vaginal discharge of which the duration varied, but only a few experienced mild pruritis of the vulval area. In the present study a yellow discharge was seen in all the patients but was transient, mild, non-pruritic and well tolerated by users.

Reports concerning the optimal number of transcervical insertions of quinacrine pellets are remarkably varied. A single intrauterine application of a low dose of quinacrine even when observed over a prolonged period of time is insufficient to cause tubal occlusion in a patient. All the tubes were patent with no histological changes in the tubal cavities [18]. Guzman-Serani and his colleagues recommended three insertions of quinacrine pellets, each one month apart and they reported 95% effectiveness after 3 years [19]. Other investigators have observed that 2 or 3 insertions have given similar results [20].

Merchant and her coworkers [5] considered the presumed need of three insertions at monthly intervals as an important drawback to the quinacrine pellet method of female non-surgical sterilization. The results

of their studies suggested that the second and third insertions do not contribute significantly to the efficacy of the method. They concluded that a single insertion of 324 mg quinacrine will be highly effective in bringing about occlusion of the tubes provided the insertion is carried out during the proliferative phase of the cycle in women with no endometrial abnormality.

This controversy indicates that there is a need for further clinical studies to determine the optimal number of transcervical insertions of quinacrine hydrochloride pellets for the occlusion of the fallopian tubes, as well as to detect any abnormal findings in the endometrium that may be related to quinacrine application.

Comparing the results of the two modalities used in this study, HSG and hysteroscopy showed that there was complete conformity of observations between the two methods. Hysteroscopic diagnosis of tubal patency, intramural and cornual obstruction was the same as the HSG diagnosis in the three groups. In distal obstructions, HSG has the advantage of precisely localizing the site of occlusion.

Tubal obstruction was elicited in only 90% of cases after one application, while it rose to 100% after both the second and third placements. This indicates that at least two insertions of quinacrine are required to achieve complete effectiveness of the method. Isthmic obstruction of the fallopian tube was insignificantly higher after one application compared to after two and three applications.

In general, the isthmus was the anatomical part to be least affected and least occluded by quinacrine, regardless of the frequency of insertions: 8%, 2.5% and 5% in groups A, B and C, respectively. Intramural occlusion was the most common after one application (50%), while cornual obstruction was significantly higher after the second and third insertions, 65% and 85%, respectively. This finding suggests that the proportion of cornual obstruction of the tubes is higher with more frequent quinacrine insertions. This has an important bearing when considering reversal of the method. The success rate of reversal in cases of intramural or isthmic obstruction is expected to be better than cases with cornual obstruction.In addition to its accuracy in the diagnosis of tubal obstruction, hysteroscopy has the advantage of determining the extent of the fibrosis at the cornual site and detecting any endometrial changes that might occur after quinacrine insertion. Abnormal endometrial findings in the form of bullous reaction, atrophic reaction, fine adhesions, hyperemic reaction and polypoid formations were hysteroscopically detected in women who received two or three applications, while they were not apparent after one application. Randic reported 2 cases of hematometra resulting from quinacrine sterilization when ibuprofen (3 pellets each containing 18.5 mg) was added in a second group. Hematometra were successfully treated with the introduction of a uterine sound through the cervical canal [17].

The differences among the three groups as regards the types of abnormal endometrial findings were significant among atrophic and polypoid reactions. Therefore, with more applications there may be a higher incidence of certain endometrial changes. These results need more prospective studies to detect whether these endometrial findings are temporary or permanent. Also the clinical implications of such changes have to be properly assessed, by subjecting these cases to a longer period of follow-up.

N.B.: Elsewhere in this issue: Soroodi questions the use of HSG as an endpoint rather than pregnancy. She has found that this procedure, even when performed with minimal pressure, opens closed tubes in a small proportion of women. The end result in her series was a pregnancy rate three times as high among women who received HSG as compared to others who did not.

References

[1] Zipper J, Medel M, Proger R. Alteration in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. *Am J Obstet Gynecol* 1968; 101:971.

[2] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: Preliminary data on a non-surgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[3] Parmley TH, Dubin NH, Strandberg J, Laufe LE. Histologic changes following intrauterine administration of Quinacrine Hydrochloride in female transcervical sterilization. Proceeding of International Workshop on Non-surgical Methods of Female Occlusion. Chicago, Illinois, June 24, 1982, pp. 89–93.

[4] Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM. Quinacrine induced pathologic changes in the Fallopian tube. *Fertil Steril* 1980; 33:666.

[5] Merchant RN, Doctor VM, Shaku SS, Kessel E, Mumford SD. Clinicopathological study of fallopian tubes after transcervical insertion of Quinacrine hydrochloride pellets. *Adv Contracept* 1986; 2:79–80.

[6] Zipper J, Insunza S. Pharmacological agents that potentiate or exhibit the occlusive action of Quinacrine in the rabbit and

rat uterus. In: Duncan G, Falb RD, Speidel JJ, editors, Female Sterilization. New York: Academic Press. 1972:131–137.
[7] Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. *Contraception* 1996; 54:181–186.
[8] Benagiano G. Non-surgical female sterilization with quinacrine: an update. *Contraception* 2001; 63:239–245.
[9] El Sahwi S, Moustafa M, Mamdouh M, El Makhzangy I. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of Quinacrine pellets for non-surgical sterilization. *Adv Contracept Deliv Syst* 1992; 8:151–159.
[10] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31.781 cases of non-surgical female sterilization with Quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–227.
[11] Church A, Geller JS. Voluntary female sterilization: number one and growing. *Popul Rep C* 1990; 10:3–15.
[12] Kessel E. 100.000 Quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.
[13] Merchant RN, Prabhue SR, Chougale A. Utero-tubal junction, morphology and clinical aspects. *Int J Fertil* 1983; 28:199–205.
[14] Zipper J, Edelman D, Cole L, Rivera M. Overview of clinical trials with Quinacrine. In: Female Transcervical Sterilization. Philadelphia: Harper & Row. 1983:94.
[15] Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1988–1991. *Fertil Steril* 1995; 64:324–334.
[16] Agoestina T, Kusuma I. Clinical evaluation of Quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–51.
[17] Randic L, Haller H, Sojat S. Non-surgical female sterilization: comparison of intrauterine application of Quinacrine alone or in combination with ibuprofen. *Fertil Steril* 2001; 75(4):830–831.
[18] Laurens JD, Zaneveld DVM, Goldsmith AMD. Lack of tubal occlusion by intrauterine Quinacrine and tetracycline in the primate. *Contraception* 1984; 30(2):161–167.
[19] Guzman-Serani R, Bernales A, Cole LP. Quinacrine hydrochloride and pellets: Three year follow-up on non-surgical method of female sterilization. *Contracept Deliv Syst* 1983; 5:131.
[20] Suhadi A, Anwer M, Soejoenoes A. Four-year clinical evaluation of Quinacrine pellets for non-surgical female sterilization. *Adv Contracept* 1998; 14:69–77.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S107–S111

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Female sterilization with quinacrine using hysterosalpingography (HSG) as an endpoint after a single-insertion protocol in Caracas, Venezuela

A. Giugni Chalbaud*, G. Plaza Mora

Concepción Palacios Maternity Hospital, Caracas, Venezuela

Abstract

Objective: To evaluate the intrauterine insertion of quinacrine as an alternative nonsurgical female sterilization method by confirming bilateral occlusion of the fallopian tubes using HSG in a group of women who desire permanent sterilization. *Methods:* After doing hysterosalpingography to confirm patency of both fallopian tubes, 324 mg of quinacrine were introduced with a modified IUD inserter in 30 patients who came to Concepción Palacios Maternity Hospital seeking permanent sterilization, between June 2000 and September 2001. Follow-up with HSG was done 3 months later to verify occlusion of the fallopian tubes. *Results:* 26 of 30 patients (86%) had bilateral tubal occlusion as determined by HSG. There were minor side effects such as: pain (66.7%), yellow discharge (100%) and menstrual abnormalities (13.3%). One woman became pregnant after HSG showed bilateral occlusion. HSG may interfere with the action of the quinacrine. *Conclusion:* QS is a simple and safe alternative to surgical sterilization with few side effects.

Keywords: quinacrine, transcervical intrauterine insertion, sterilization, hysterosalpingography

1. Introduction

The world population in the year 2000 was 6,000 million inhabitants. The increase in population mainly affects less developed countries, where the average annual growth is 2%, equivalent to a doubling of the population in 35 years. In contrast, the population of industrialized nations will double in 115 years, representing an annual growth rate of 0.6% [1]. Obviously, there is a worldwide need to find better birth control methods.

Female surgical sterilization is currently the most prevalent permanent contraceptive method worldwide, and is in ever growing demand in developing countries [1]. In the United States, surgical sterilization has become the contraceptive method of choice for married couples, with an increase of 16% to 36% between 1973 and 1988 [1,2]. Yet several studies have reported failure rates of 3 to 4 per 1,000 surgical procedures within the first 2 years of surgery [2,3]. Surgical sterilization also involves large expenses for infrastructure and implementation, creating a heavy burden on the community, especially in countries with limited resources. In view of the burgeoning need for birth control in less developed regions, new methods for nonsurgical sterilization, applicable to large populations, are being investigated. In addition, a nonsurgical method could help to eliminate the concerns of women who fear surgery, or who cannot get transportation or child care during surgery and recovery, especially in rural settings [1].

* Corresponding author. Tel.: 058-02-753-7617, 014-307-2932 (Cell)
E-mail address: aldoyu@hotmail.com
Correspondence address: Urb. Colinas de Bello Monte, Calle Suapure, Res. Los Roques, PB. Apto 1, Caracas, Venezuela

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Among the new nonsurgical sterilization methods, several drugs, such as quinacrine, elemental iodine and other substances that cause sclerosis of the fallopian tubes have become available [2,4]. Quinacrine, a 9-aminoacridine[6-chloro-9(L-methyl-4-diethylamino)butyl-2-methoxy-acridine], is an antimalarial drug which, until the introduction of chloroquine in 1945, was the main synthetic agent for antimalarial prophylaxis, since it can effectively suppress the four types of human malaria. Although it is no longer used for this indication, it is prescribed as a therapeutic alternative for giardiasis and recurrent malignant pleural effusions [5,6]. Quinacrine's few side effects occur with the systemic administration of high doses for prolonged periods. Adverse events, such as dizziness, headaches, vomiting and diarrhea are infrequent. Stimulation of the central nervous system manifested as restlessness, confusion, anxiety, euphoria or changes in behavior, and its deposit in skin, characterized by yellow pigmentation, are even less frequent. Another effect attributed to quinacrine is its mutagenic potential [5,7], but it is recognized that administration by mouth is not carcinogenic [5,7,8]. Sokal et al. [9] in a follow-up involving 13,444 person-years concluded that the rate of cancer among women exposed to intrauterine quinacrine was not significantly different from the expected rates in the general population. Its use is contraindicated in people with psoriasis, exfoliative dermatitis and glucose-6-phosphate dehydrogenase deficiency (G6PD) [6].

In the quinacrine sterilization (QS) method, pellets are placed in the fundus of the uterus through the cervix, with a modified intrauterine device (IUD) inserter [7] during the proliferative phase of the menstrual cycle. Its effect is topical at low doses and for short periods of time. This precipitates a selective inflammatory process in the interstitial portion of the fallopian tubes, with eventual fibrosis and occlusion in a period of approximately 6 weeks [5,7,10]. Merchant and Prabhu [11] state that the tubal occlusion is directly related to the dose of quinacrine applied. The concentration of quinacrine in the uterus after the transcervical insertion is higher than that achieved after the administration by mouth, but only for a few hours [5,7,8]. Two basic insertion regimens have been described: in one of them, 252 mg of quinacrine are applied once a month for 2 or 3 months, and in the other, a single dose of 324 mg is used [8,11]. These treatment plans may or may not be combined with the transcervical, parenteral or oral administration of nonsteroidal drugs, such as ibuprofen or diclofenac, which decrease the local inflammatory response and the side effects [5,12,13].

Very few side effects associated with the transcervical insertion of quinacrine have been reported [12,14,15]. These adverse events (AE) are minor and transient compared with those caused by surgical sterilization; among them are: mild hyperthermia, mild vaginal discharge and menstrual abnormalities. Trujillo and his coworkers [16] report that the complications and side effects are similar to those that occur during the insertion of an IUD. In 1996 Laufe and Sokal [17] reported minor transient side effects such as: colicky abdominal and pelvic pain, headache and dizziness, in the 24 hours after insertion. No deaths have been reported with the use of QS [8,9]. The risk of birth defects from QS has been reported to be the same as one would expect from surgical sterilization [7].

From the decade of the 1970s to the present time, several studies have been completed [10,15,18] to evaluate the efficacy and safety of quinacrine as an alternative method for female sterilization. Currently, efficacy is estimated as 3 pregnancies per 100 women in one year [8]. Many authors agree that the failure rate is caused by an incorrect insertion technique [7,8,10,13].

The transcervical intrauterine insertion of quinacrine tablets has been shown to be a safe, acceptable and effective nonsurgical method of female sterilization [9,10]. The main advantage of the method is its capacity to increase contraceptive prevalence, and QS will thereby avoid maternal morbidity and mortality. This is especially true in rural and urban areas of the Third World [8].

We decided to undertake a study of the efficacy of QS in our hospital in Caracas, Venezuela. We would attempt to confirm the occlusion of the fallopian tubes by HSG three months after the procedure.

2. Materials and methods

A prospective, descriptive and experimental clinical study of QS was carried out in a population of patients who came to the Gynecology, Family Planning and Delivery Room Services of the Concepción Palacios Maternity Hospital in Caracas, Venezuela, and expressed

their desire to have permanent sterilization. The sample was a group of 30 women who fulfilled the following inclusion criteria: older than 25 years, having satisfied their personal reproductive expectations and who, after an explanation of the method to be used, and its risks and benefits, gave their consent in writing for inclusion in the study. We excluded those with a history of allergy to iodine, extensive ablative surgical procedures of the cervix, cervical pathology, tubal surgery, prior unilateral or bilateral occlusion of the fallopian tubes, fibroids and patients with associated medical problems, such as psoriasis and exfoliative dermatitis.

To inform the couples about the risks and benefits of the technique, they were invited to view a video explaining the technique. Then the staff discussed the QS procedure with them and answered all questions raised. To qualify for admission, the women were given a gynecological examination. Their medical history was entered on a clinical record and they were enrolled in the study.

HSG was done between days 7 and 10 of the menstrual cycle before the insertion of quinacrine, to evaluate for tubal patency. During the proliferative phase of the menstrual cycle after doing the HSG, 324 mg of quinacrine was introduced into the fundus of the uterus, through the cervix, with a modified IUD inserter; 400 mg of ibuprofen by mouth every 8 hours was prescribed for pain, for 3 days. It was recommended that patients use contraceptive barrier methods in the first three months after the insertion.

Follow-up was carried out to verify how well the patient tolerated the QS, the patency of the fallopian tubes, and the presence of side effects. Tolerability was evaluated by interviewing each patient 48 hours after the quinacrine insertion. The first interview was scheduled to discover the absence or presence of pain. We did not use a scale for it. We also asked about the use of ibuprofen, finding that some patients did not need to take the medication. The women were interviewed again before the second HSG, 3 months after the insertion. At that time, we asked about events affecting the menstrual cycle, bleeding and yellow spotting. The patency of the fallopian tubes was examined by HSG 3 months after the insertion. The time of follow-up was approximately 8 months after the second HSG. We telephoned all the patients to be sure they were satisfied with the method and had no pregnancies.

The data obtained were collected in a clinical record. They were presented in tabular form and analyzed by a statistician, using descriptive and inferential statistical methods.

The project was carried out with the collaboration of the medical and paramedical staff of the Gynecology, Family Planning and Delivery Room Services of the Concepción Palacios Maternity Hospital, and with the technical and medical staff of the radiology service of that institution. The medication and the inserters, the video explaining the technique, as well as some financial support were donated by The Center for Research on Population and Security. The cannulae for performing the HSG were provided by the research group. The costs for the implementation of the project were covered by several sources that included supplies from the Concepción Palacios Maternity Hospital, and contributions from the research staff.

3. Results

The average age of the sample of women was 33.8±4.05 years; 19 (63.3%) were between 28 and 35 years of age, as shown in Table 1.

After undergoing the QS procedure, 20 patients (66.7%) were in pain, and 11 of these (55%) needed an oral analgesic; 7 patients (23.3%) experienced bleeding; and the yellow discharge lasted less than 11 days in 23 patients (76.7%). In the following months, 4 patients (13.3%) had menstrual problems, 2 (6.7%) had oligomenorrhea, and 2 (6.7%) had polymenorrhea (Table 2). Twenty-six patients (86.7%) had bilateral tubal occlusion. Three women (10%) had unilateral tubal occlusion, and one (3.3%) bilateral tubal patency (Table 3); these 4 women were prescribed another contraceptive method.

Table 1
Distribution of patients according to age, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Age (years)	Frequency	Percentage
28–31	10	33.3
32–35	9	30
36–39	8	26.7
⩾40	3	10
Total	30	100

33.8±4.05 years.

Table 2
Distribution of patients according to complaints and treatment after QS, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Complaint	Frequency	Percentage
Pain		
without	10	33.3
with	20	66.7
Analgesic for pain ($N = 20$)		
used	9	45.0
not used	11	55.0
Menstrual abnormalities		
none	26	86.7
oligomenorrhea	2	6.7
polymenorrhea	2	6.7
Yellow discharge spotting (days)		
1–10	23	76.7
11–20	4	13.3
21–30	3	10.0
Bleeding		
without	23	76.7
with	7	23.3

Table 3
Distribution of 30 patients according to results of follow-up hysterosalpingography (HSG) after QS, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Results of HSG	Frequency	Percentage
Tubal exclusion		
bilateral	26	86.7
unilateral	3	10.0
Tubal patency	1	3.3

4. Discussion

The average age of our patients was 33.8 years, similar to the 35 years reported by Sokal and his colleagues [19]. This is explained by the fact that, at this age, most women have fulfilled their fertility expectations. It has also been demonstrated that the effectiveness of the method is greater in patients older than 35 because they are less fertile [19,20].

The percentage of patients with bilateral tubal occlusion demonstrated by HSG after the transcervical insertion of quinacrine in this series was 86.7% (26 of 30 women). While there is research [21] that used HSG as a method to evaluate tubal occlusion, those studies are not comparable to the present one, since the doses and insertion protocols were different. El Kady and his coworkers [22] reported bilateral tubal occlusion in 73% of subjects after two doses of 252 mg. Generally, the efficacy of the method is determined by calculating the cumulative rate of pregnancy [7,8,14,19] and by anatomic/pathologic studies of sections of hysterectomy in patients with a history of QS [11]. We performed an HSG because we believed it to be an objective way to evaluate short-term tubal occlusion, since calculating the rate of pregnancy requires follow-up of patients for periods longer than 1 year, time which was not available to us. Failure of the QS was determined in a total of 5 patients: 4 women had either unilateral tubal occlusion or bilateral tubal patency, and a fifth woman became pregnant after HSG indicated bilateral tubal closure.

It is difficult to explain what occurred during and following HSG. There may be false interpretations of occlusion of the tubes due to: tubal spasm during the procedure; insufficient injection of contrast medium; or interruption of the procedure before tubal opacification [22–24]. On the other hand, the pressure of the HSG medium could have opened a tube in the woman who became pregnant following the HSG that had indicated bilateral closure. If this is true, then the HSG could just as easily have opened closed tubes during the performance of the test. The HSG may not be good following QS and needs further evaluation. Two patients, one with bilateral and the other with unilateral tubal occlusion, had a pregnancy after two months. Failure of the method occurred in a total of 5 patients which, according to the literature, is attributable to errors in the insertion technique [10].

After QS, 20 patients (66.6%) had pelvic pain, which differs from the reports by Mumford et al. [25] and Hieu et al. [10], who found pain in between 9% and 25% of patients. The rationale is that the dose generally used is 252 mg per application, different from the 324 mg applied in this study; higher doses may cause more tissue destruction and, consequently, more pain. Of the patients who had pain, 11 (55%) said they had taken an analgesic; data in the literature indicates that the administration of non-steroidal anti-inflammatory drugs does not modify the efficacy of the method [12,13].

The main menstrual abnormalities due to QS reported in the literature are oligomenorrhea or amenorrhea, with a frequency of 1% to 20%. These are caused by inflammation and desquamation of the endometrium as an effect of the medication. These abnormalities last several months while the endometrium regenerates [25]. In this series, 2 patients presented with oligomenorrhea and 2 with polymenorrhea, for a total of 13.32% with menstrual irregularities.

The yellow discharge caused by spillage of quinacrine into the vagina was present in 100% of cases, which contrasts with the 23% noted elsewhere [25]. We attributed this to the higher dose of the medication used, which increases the likelihood of spillage. There were none of the complications found by other investigators, such as pelvic infections, uterine perforation or synechia and hematometra, and there have been no ectopic pregnancies [10,25,26].

We can conclude from the results of this study that female sterilization with quinacrine is a simple and safe method that has few side effects, and that it is an alternative to surgical sterilization. We recommend consideration of the possibility of widespread application of QS so that populations with limited resources have access to the method.

References

[1] Pati S, Carignan C, Amy P. What's new with female sterilization: an update. Contemp OB/GYN 1998; 38:91–117.

[2] Wilson EW. Sterilization. *Bull Clin Obstet Gynaecol* 1996; 10(1):103–119.

[3] Peterson HB, Pollack AE, Warshaw J. Tubal sterilization. In: Rock JA, Thomson S, editors. Te Lindes Operative Gynecology. 8th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:135–138.

[4] Wilson EW. The development of new technologies for female sterilization: conclusions and recommendations for research. *Int J Obstet Gynecol* 1995; 51(Suppl 1):S71–S74.

[5] Zipper J, Dabancens A, Guerrero A, Trujillo V. Quinacrine: sclerosing agent of the utero-tubal junction in women, with anticarcinogenic actions in transplanted tumors in mice. *Int J Obstet Gynecol* 1995; 51(Suppl 1):S47–S55.

[6] Goldsmith RS. Fármacos antiprotozoarios. En: Katzung B, Farmacología Básica y Clínica. México; Editorial El Manual Moderno, S.A. de C. V. 1991:650–669

[7] Kessel E. Quinacrine sterilization: an assessment of risk for ectopic pregnancy, birth defects and cancer. Adv Contracept 1998; 14:81–90.

[8] Kessel E. 100,000 quinacrine sterilizations. *Adv Contracept* 1996; 12:69–76.

[9] Sokal D, Dabancens A, Guzmán-Serani R, Zipper J. Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996. *Fertil Steril* 2000; 74:169–171

[10] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of nonsurgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[11] Merchant RN, Prabhu SR. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil Stud* 1995; 40:47–54.

[12] Suhadi A, Anwar M, Soejoenoes A. Four-year clinical evaluation of quinacrine pellets for nonsurgical female sterilization. *Adv Contracept* 1998; 14:69–77.

[13] Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization. *Adv Contracept* 1995; 11:303–308.

[14] Suhadi A, Soejoenoes A. Quinacrine pellets nonsurgical female sterilization in Wonosobo, Indonesia. *Fertil Steril* 1997; 67:966–968.

[15] Mullick BC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet nonsurgical female sterilization. *Adv Contracept* 1995; 11:239–244.

[16] Trujillo V, Zipper J, Viel B, Rivera M. Nonsurgical female sterilization using quinacrine: efficacy of two insertions of quinacrine pellets. *Rev Fr Gynécol Obstet* 1993; 88:147–150.

[17] Laufe LE, Sokal DC. Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets. *Contraception* 1996; 54:181–186.

[18] El Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59:301–304.

[19] Sokal DC, Hieu T, Weiner D, Vinh D, Vach T, Hanenberg R. Long-term follow-up after quinacrine sterilization in Vietnam. Part I: Interim efficacy analysis. *Fertil Steril* 2000; 74:1084–1091.

[20] Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. *Int J Obstet Gynecol* 1995; 51(Suppl1):557–569.

[21] Gardner B. Esterilización Femenina con Quinacrina. Caracas: Universidad Central de Venezuela. 1993.

[22] Zighelboim I. Errores y defectos de la histerosalpingografía. *Rev Obstet Gynecol Venez* 1983; 43:87–91.

[23] Santimone M. Atlas de histerosalpingografía. Servicio de Ginecología y Reproducción Humana del Hospital "Carlos J Bello" de la Cruz Roja Venezolana. Caracas: 1997.

[24] Hunt R, Siegler A. Hysterosalpingography: techniques and interpretation. USA: Year Book Medical Publishers Inc, 1990:105–119.

[25] Mumford SD, Bhiwandiwala P, Kessel E. Esterilización voluntaria no quirúrgica de la mujer: el método de la quinacrina. Chapel Hill, North Carolina: Institute for Development Training, 1997.

[26] Sokal DC, Hieu DT, Weiner D, Vinh D, Vah T, Hanenberg R. Long term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis. *Fertil Steril* 2000; 74:1092–1101.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S113–S115

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization in Libya: 200 cases

M.S. El Mahaishi*, A.M. Azzidani

Department of Gynecology & Obstetrics, Misurata Central Hospital, Lamis Clinic, Misurata, Libya

Abstract

Objective: Document the safety, effectiveness and acceptability of quinacrine sterilization (QS) as an alternative to surgical sterilization in Libyan women. *Methods*: This study was initiated 1 October 1998 at the Misurata Central Hospital and Lamis Clinic. Patient intake was completed 30 September 2002. The cut-off date for this analysis was 31 December 2002. A total of 200 women were given 2 doses, each consisting of 252 mg of quinacrine hydrochloride in the form of 7 pellets inserted one month apart. They were placed at the uterine fundus during the proliferative phase of the menstrual cycle using a modified IUD inserter. Women were asked to report any unusual observations or side effects and instructed to use a barrier method or safe period for one month from the time of the first insertion. Follow-up was scheduled at 3, 6 and 12 months after the date of the second insertion and every 6 months thereafter. *Results*: Sixty-six women have been monitored for up to 3 years and follow-up of all patients continues. There has been no loss to follow-up. No side effects of any consequence have been reported. Thus far, no pregnancies have been reported for this protocol. *Conclusions*: Findings in this study are consistent with those seen in other countries. QS has been shown to be safe, effective and acceptable among Libyan women.

Keywords: quinacrine sterilization, female sterilization, nonsurgical female sterilization

1. Introduction

Family planning is essential to families all over the world, and female sterilization is the leading method of contraception among women who have decided not to have any more children. Although they remain fertile into their late 40s or early 50s, many have already had all the children they want during their 20s or 30s. Since the early 18th century, sterilization has been performed surgically. But in 1977, a nonsurgical method of sterilization using the drug quinacrine was developed by Zipper in Chile [1].

Quinacrine, also known as Atabrine or Mepacrine, is a drug that was originally introduced in 1931 to prevent and cure malaria, and has subsequently been used by more than 100 million people. This included men, and even women who were pregnant as well as children. Today it continues to be prescribed for giardiasis, lupus, rheumatoid arthritis and tapeworm. After 70 years of use, its safety record remains unquestioned [2].

The QS method involves the transcervical intrauterine administration of quinacrine hydrochloride to nonpregnant women during the proliferative phase of the menstrual cycle (days 9–12). In the most commonly studied regimen, seven pellets, each containing 36 mg of quinacrine hydrochloride, are introduced into the uterus with a modified Cu–T IUD inserter. A second insertion is done one month later [2].

The local action of quinacrine is a partial necrosis of the endometrial lining of the uterus and the mucosal lining in the intramural segment of the fallopian tubes. Although the endometrium regenerates itself over a period of one or more menstrual cycles, inflammation

* Corresponding author. Tel.: 218-51-61-6626; Fax: 218-51-61-6411.

E-mail address: lamis01@hotmail.com (M.S. El Mahaishi)

Correspondence address: P.O. Box 65, Misurata Hospital, Misurata, Libya

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

of the tubes progresses into the inner muscular coat with sclerosis, preventing regeneration of tubal mucosa. Over the next 6–12 weeks, a small fibrous mass forms, joining the walls of the intramural tube and occluding or filling the lumen. After inflammation of the fallopian tubes subsides a plug of scar tissue remains [3].

Since 1977, clinical trials in numerous countries have found the method to be safe and effective. This includes research carried out in: Chile (Zipper et al., 1980 [1]), India (Bhatt and Wasak, 1985 [4]), Indonesia (Agoestina and Kusuma, 1992 [5]), Vietnam (Hieu et al., 1993 [6]), Pakistan (Bashir, 1993 [7]) and Iran (Soroodi-Maghaddam, 1996 [8]).

Quinacrine sterilization (QS) has the potential of being an inexpensive, safe and well-accepted procedure that would benefit women in both industrialized and developing countries.

2. Materials and methods

This 200-case clinical trial was initiated 1 October 1998 and patient enrollment was completed on 30 September 2002. Women seeking sterilization were recruited for the study. Anyone with a history of psychosis, psoriasis or hepatic disease was excluded. Postpartum women were required to wait until they had menstruated at least once before entering the study.

All patients were given two doses, each consisting of 252 mg of quinacrine hydrochloride in the form of pellets, one month apart. The pellets were placed at the very top of the uterine fundus during the proliferative phase of the menstrual cycle (between days 9 and 11 from the first day of menstruation) with a modified Cu-T IUD inserter. The authors performed all procedures. Patients were asked to use either a barrier method or the safe period between the two insertions and to report any unusual observation or side effect. Follow-up was scheduled at 3, 6 and 12 months after the second insertion and every 6 months thereafter. The cut-off date for data collection for this report was 31 December 2002.

3. Results

A total of 201 patients were recruited. One woman became pregnant between the first and second insertions. This pregnancy was discovered by vaginal ultrasound during a routine examination just before the second insertion. Upon review of her medical history, it was learned that the patient was only 5–6 weeks postpartum and had not had a menses when she received her first dose of quinacrine. Since the research protocol had not been adhered to, she was excluded from the study. The woman went on to have a normal vaginal delivery of a male child. There were no signs of any congenital abnormalities.

The age of the women ranged from 34 to 45 years and the mean was 38 years. The number of children ranged from 5 to 13. The only side effect was a yellow discharge, which persisted for no more than 3 days from the time of the insertion. No other complications or side effects have been reported.

Follow–up has been 100% and we continue to monitor all patients. As of the cut-off date, of the 200 patients, 66 had completed their 3-year follow-up, 80 their 2-year follow-up and 54 the 1-year follow-up. There have been no pregnancy failures.

4. Discussion

Every patient was counseled that they might experience adverse events (AE) like headache, dizziness, backache, feeling hot, yellow vaginal discharge, itching, oligomenorrhea, amenorrhea, endometritis and possibly ectopic pregnancy. However, only yellow vaginal discharge was reported. Perhaps women did not report these other effects after having been forewarned that they are normal outcomes of this procedure. There were no uterine perforations, pelvic inflammatory disease or hematometra. Side effects simply were not a problem for our patients in this study.

Surgical sterilization is an invasive method that carries a significant risk of morbidity and a small risk of mortality. In a small percentage, reversal of sterilization is possible with the surgical methods. It is not known whether reversal of the quinacrine method can be done. Nevertheless, quinacrine is an acceptable alternative to surgical sterilization. Women preferred quinacrine over surgical methods. The demand for the procedure increased throughout our trial.

From this study and other research in different countries, we conclude that sterilization can be achieved safely and with high efficacy using QS.

References

[1] Zipper J, Cole LP, Goldsmith A, et al. Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. *Int J Gyn Obstet* 1980; 18:275–279.

[2] Lippes J. Quinacrine sterilization: the imperative need for American clinical trials. *Fertil Steril* 2002; 77:1106–1109.

[3] Merchant NR, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40(1):47–54.

[4] Bhatt R, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.

[5] Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–151.

[6] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–227.

[7] Bashir A. Quinacrine: nonsurgical female sterilization. *Adv Contracept Deliv Syst* 1993; 9:37–42.

[8] Soroodi-Maghaddam S. Preliminary report on a clinical trial of quinacrine pellet method for nonsurgical female sterilization in Iran. *Int Fam Plann Perspect* 1996; 22:122–123.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S117–S120

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) in a private practice in Daytona Beach, Florida: a preliminary report

R.B. Whitney

Medical Director, Family Planning, Inc., USA

Abstract

Objectives: To affirm that QS can be performed safely and effectively in a U.S. private office practice. *Methods*: The U.S. FDA Modernization Act of 1997 Pharmacy Compounding Provisions made it possible for American physicians to begin offering QS to their patients. These provisions became effective November 21, 1998. This series was initiated in October 2000. The standard protocol recommended by the International Federation for Family Health (IFFH) is followed. Information on patients is recorded on forms suggested by IFFH to accomplish good post-marketing surveillance. The potential role of uterine septae in QS failures is of particular interest to this investigator. *Results*: Seven cases have been completed. There have been no failures. Side effects have been minor. Women have been exceptionally happy with this method. The Florida Agency for Health Care Administration has examined QS and found it to be an acceptable off-label use of quinacrine. *Conclusion*: Preliminary results have been similar to those reported by QS researchers around the world.

Keywords: nonsurgical female sterilization, quinacrine sterilization, private practice

1. Introduction

In the past 25 years, more than 140,000 women in 34 countries have undergone the quinacrine pellet intrauterine sterilization procedure (QS). This technique, with its unquestionable safety, simplicity, good efficacy and low cost, has primarily been offered in Third World countries. Both the International Federation For Family Health (IFFH) and Family Health International (FHI) have endorsed research into this method. Nevertheless, fierce opposition from certain quarters has led several countries to suspend their programs. It is only within the last five years that three American advocates, Doctors Kessel, Mumford and Lippes, all internationally respected scientists, began to focus efforts to bring the method into the mainstream of reproductive control choices in the United States.

In 2000, the United States Food and Drug Administration (FDA) approved an investigational new drug (IND) trial application to clinically evaluate QS in American women. Some detractors still insist on expensive and time-consuming animal research before using women as subjects. Other investigators, among them Malcolm Potts and Giuseppe Benagiano, have stated that these animal studies "cannot prove human safety." In a recent article, they also observed that such animal tests can produce results "qualitatively different from those subsequently found in humans, as occurred with Depo-Provera." [1] For many years, the World Health Organization (WHO), under the direction of Dr. Benagiano, opposed the practice of QS. Later, Dr. Benagiano joined Dr. Potts in noting a cumulative low risk of serious, immediate side effects, but insufficient data to answer questions about

* Tel: 386-253-1933 (o); 386-767-7787 (h); Fax: 386-254-8227;
E-mail address: rwhitney3@cfl.rr.com (R.B. Whitney)
Correspondence address: 580 Mulberry Street, Daytona Beach, FL 32114, USA.

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

potentially-critical, long-term side effects. The authors are pleased that FDA trials are underway. And they admit that confirmation of the procedure's safety lies in "a very large scale of controlled use." They cautiously advise offering QS only to women who ask for sterilization and "for whom existing methods are not available or present unacceptable risks." This is indeed a conservative and limiting "middle road."

Dr. Jack Lippes, inventor of the famed Lippes Loop intra-uterine device (IUD) and now a principal investigator of QS with the FDA, has recently completed a Phase I trial with 10 women.

The U.S. FDA Modernization Act of 1997 Pharmacy Compounding Provisions became effective Nov. 21, 1998. This enabled American physicians to offer QS to their private patients with individual prescriptions filled by compounding pharmacists.

Quinacrine hydrochloride is an antibiotic manufactured in powder form for medical usage. It has been available since the 1920s and was used extensively in oral tablet form as an anti-malarial prophylactic and treatment for service men and women in the United States armed forces during World War II: as much as 36,500 to 52,000 mg per year per person. Considerable research on its oral usage has shown it to be safe in doses under 3000 mg per month. Millions of American and foreign children have taken the drug for the intestinal parasite, giardia, and it remains the only FDA-approved drug for this purpose. Physicians worldwide continue to use it for these and other medical conditions, such as lupus and tapeworm. Unfortunately, the drug's manufacture in the United States was discontinued in the mid 1990s, and our FDA has refused to allow the importation from a Swiss manufacturer of inexpensive, previously prepared quinacrine pellets for the sterilization procedure. Thus, at present, the powder must be imported and compounding pharmacies are then able to laboriously make much more expensive pellets for the IUD-like insertion process. The Center for Research on Population and Security is the supplier of the pellets for international trials.

2. Methods

The QS method was developed in Chile in the late 1970s by Dr. Jaime Zipper, the inventor of the Copper-T IUD. After some trial and error, the optimal dose for trans-cervical insertion of the pellets was found to be 252 mg in 7 pellets ejected from the modified copper IUD inserter high in the uterus about 0.5 to 1 cm from the fundus with the sheath held steady at that depth. This must be done twice: in consecutive months, and in the week following a menses. If the woman is using the depot medroxyprogesterone (Depo-MPA) method of contraception, which may enhance the success of the technique, there may be no menses to guide one. It is important to the success or efficacy that there be no bleeding during or immediately after quinacrine insertion. Somehow this interferes with the action of the quinacrine. Concentrations of quinacrine in the uterus after insertion are higher than for oral administration for only a matter of a few hours, but they are adequate to cause a significant chemical endometritis from which the thick endometrium always recovers. However, with proper flow into the proximal tubes where the mucosal lining is only a single cell thick, recovery is unlikely and scar tissue "plugs" develop to obstruct any future access of sperm to ovum.

Regarding my practice, I wish to make a few brief points:

- Sedation before insertion is unnecessary, but one might wish to do an anterior cervical lip anesthetic injection for the tenaculum (I use a sharp-toothed one), or an atraumatic instrument;
- Be certain of the position of the uterus in the body in the initial bimanual pelvic exam. When sounding to the fundus, try a gentle rotation or side-to-side motion of the sound to see if there might be a septum;
- Immediately after insertion, the woman should lie on a couch or bed so as to maximize the uterine fundal position downward. We are experimenting with a long foam wedge to facilitate this and hopefully make more of the quinacrine available to the cornuae;
- After 30 minutes, one can see through a reasonably full bladder with ultrasound whether there is quinacrine flowing to the cornuae;
- With the second insertion, one may encounter some immediate cervical bleeding on sounding, probably a residual effect of the first quinacrine insertion. I do not consider this inflammatory effect a contraindication to continuing with the second insertion.

I suspect that some of our failures may be due to uterine anomalies, the most likely of which is some degree of intrauterine septum. Various authors have estimated the incidence of anomalies as high as 10% [2,3], but from my 35 years of gynecologic experience with IUDs and abortion, I believe some septum to be present about 5% of the time. Now we have 3-D vaginal ultrasound to more accurately differentiate between a significant septum and a bicornuate or arcuate uterus, and also to better define the QS cornual scar tissue [4,5]. Patients who have had significant pregnancy wastage or premature labor and delivery may be good candidates for both pelvic and abdominal 3-D sonography, for many studies have often shown ipsi-lateral agenesis of a kidney with uterine body malformations [6]. Any QS failure should have an ultrasound study. It might be very beneficial if all first insertions had access to at least a reasonably good resolution machine to check for symmetry of quinacrine flow toward the cornuae. I also suspect there are a majority of fundal septae which are insignificantly shallow, or less than 2 cm deep and would probably not cause pregnancy wastage. They might, however, deflect the pellets to one side with high insertion. Therefore, I have modified my insertion depth to 1–2 cm back from the fundus for a more central ejection.

My fee is $500 and my cost for the package of two sets of pellets and inserters is about $150, which I require in advance. I also offer a payment plan. I use the IFFH Sterilization Register and Follow-up to record my cases, and have developed my own office protocol for information calls, laboratory tests, history and physical exam forms. My informed consent is extensive and only slightly modified from that developed by Dr. Mumford and others. I have Spanish translations of everything, including a training manual for providers.

3. Results

In my practice I have sterilized 7 women with quinacrine. They have ranged in ages from their late 20s to their early 40s, and have tolerated the two insertions very well, with minimal side effects, mainly low back and/or abdominal ache. None have required pain medications, had fever or headache, or missed any daily activities, such as work, afterwards. Six are Caucasian and one is Hispanic: all without insurance coverage. They have been extremely pleased with the method. I will continue to follow them at 6-month intervals. Questions asked of them recently have produced negative responses about: 1) adverse menstrual changes, such as a missed period followed by a heavy/crampy one (which could be an early miscarriage); 2) sexual discomfort; 3) any changes or abnormal feelings in the abdomen.

4. Discussion

Follow-up of patients 10 or more years post-sterilization will yield valuable information about reservations of many of the method's detractors. They express concern about increased likelihood for cancer, ectopic pregnancy and birth defects in any subsequent pregnancies. We know there are none of these risks with oral consumption of the drug – at much higher doses than used in the sterilization process – and pathology studies suggest that if the quinacrine reaches the fallopian tubes, it closes them completely [7]. The risk of ectopic pregnancy following failure of surgical sterilization in the United States is higher than for QS, using newer insertion techniques. Every year in my country there are about a dozen deaths and about a thousand hospitalizations from complications of surgical sterilization. There has never been a death recorded with the QS pellet method – a remarkable safety record. This includes the rare case of uterine perforation with the inserter and depositing the pellets in the peritoneal cavity. Although painful, once the quinacrine is absorbed, pain diminishes and there are no other sequelae [8].

Antagonists make much of the fact that quinacrine is a mutagen (so is tetracycline) and would have others believe such drugs can cause cancer because of this factor. Direct evidence of quinacrine carcinogenicity in humans or animals has never been established. Finally, the drug does not appear to be teratogenic. In a 31,781 case Vietnamese trial, "there were two cases of quinacrine insertion during early pregnancy. One was a case of ectopic pregnancy, and the other woman gave birth after the study cut-off date. The infant was normal." [9] There are some animal data for both monkeys and rats showing that exposure of the fetus at the time of embryogenesis leads to resorption

or abortion, especially in early gestation, but there was no evidence for treatment-related malformations [7].

The level of need for contraception in the world is rising rapidly. To satisfy the United Nations' median variant population projection of 12 billion people at the end of the 21st century, we must achieve by 2035 a replacement fertility rate of 2.1 children per woman. The United Nations Fund for Population Activities (UNFPA) estimates that this will require 200 million sterilizations in the 10 years ending in 2005, or two years from now. About 85% of these were projected to be female, the rest vasectomies. Given this situation, it is obvious that there is an urgent need for a safe, effective, inexpensive method of sterilization that can be delivered by paramedical personnel in rural areas [10]. QS may be the answer, and a wide, controlled clinical study with good patient information and informed consent, combined with a parallel, retrospective study of previous patients mentioned above, should be implemented immediately. In the United States our society's litigious nature will be a severe restraint unless or until the FDA gives its seal of approval to this remarkable method.

In early 2002, 4 women (mostly radical feminists and sociologists from a New England college) brought a complaint against my medical licensure in relation to my advertising and practice of QS. There was absolutely no scientific merit to their accusation whatsoever, and the complaint was investigated by the Agency for Health Care Administration and the Florida Department of Health. On 17 October 2002, a letter was written to my attorney stating: "Please be advised that the complaint in the matter referenced above has been investigated and reviewed by the probable cause panel of the Board Of Medicine. Pursuant to Section 456.073(9)(c), Florida Statutes, the panel found that there was insufficient evidence to support prosecution and directed the case be dismissed." These same women had also opposed our FDA authorizing research into the validity and safety of QS by Dr. Lippes. Meanwhile, Dr. Mumford and others have been informing clinicians about QS at their professional meetings. The response has been gratifying, but we need more American physicians actively involved with office patients.

It is time for QS to be made available to women everywhere. I hope that other American physicians will join us in offering this method to women in the United States.

References

[1] Potts M, Benagiano G. Quinacrine sterilization: a middle road. *Contraception* 2001; 64:275–276.
[2] Dacosta V, Wynter S, Frederick J, Wynter H, Williams M. Successful pregnancy after hysteroscopic metroplasty. *W Ind Med J* 2002; 51:260–262.
[3] Zabak K, Bonifla JL, Uzan S. Septate uterus and reproduction disorders: current results of hysteroscopic septoplasty. *Gynecol Obstet Fertil* 2001; 11:829–840.
[4] Wu MH, Hsu CC, Huang KC. Detection of congenital mullerian duct anomalies using three-dimensional ultrasound. *J Clin Ultrasound* 1997; 9:487–492.
[5] Sheth SS, Sonkawde R. Uterine septum misdiagnosed on hysterosalpingogram. *Int J Gynecol Obstet* 2000; 69:261–263.
[6] Fried AM, Oliff M, Wilson EA, Whisnant J. Uterine anomalies associated with renal agenesis: role of gray scale ultrasonography. *Am J Roentgenol* 1978; 131:973–975.
[7] Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. *Adv Contracept* 1998; 14:81–90.
[8] Lippes J. Quinacrine sterilization safety and efficacy. American Public Health Association Annual Meeting, Chicago, Nov. 8, 1999.
[9] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.
[10] Black T. The quinacrine imperative. Marie Stopes International, London 1995. Unpublished report, www.quinacrine.com/archive/blac95.pdf.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S121–S123

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) experience in The Philippines: a preliminary report

L.A. Alfonso*, H.A. Albano

Department of Obstetrics and Gynecology, College of Medicine, Southwestern University, Cebu City, Cebu, Philippines

Abstract

Objective: The first clinical trial of Quinacrine Sterilization (QS) in the Philippines was undertaken in Cebu City on January 10, 2000, to evaluate the acceptability, safety, effectiveness and side effects of this technology. We intend to recruit 500 patients to utilize this technique for limiting family size. For the purposes of this report, our cut-off date is April 11, 2003. *Methods*: Over more than two years, QS was performed on 36 volunteer patients. After careful explanation of the procedure and given the opportunity to ask questions, they had signed an informed consent. The trial involved transcervical insertion of 252 mg quinacrine in the form of pellets, and placed at the tip of the uterine fundus on two occasions, a month apart. Condoms were routinely provided to all patients except those on oral contraceptive pills and DMPA after the first insertion to be used for six weeks after the second one. As the numbers are small, no statistical evaluation was called for. *Results*: The accumulated experience was 515 woman-months. There were no pregnancies, neither ectopic nor intrauterine. Adverse events (AE) were mild. Some patients complained of a yellow discharge and itching. Fifty percent experienced mild abdominal discomfort which was easily managed with mefenamic acid. *Conclusions*: Although this is a small study, we believe that QS is both safe and effective and we are strongly encouraged to continue to offer this nonsurgical sterilization method to our patients.

Keywords: female sterilization, quinacrine sterilization, nonsurgical sterilization

1. Introduction

The invention and development of quinacrine sterilization (QS) by Dr. Jaime Zipper opened a new epoch for women to control their reproductive function [1]. QS involves the insertion of quinacrine pellets transcervically into the uterine cavity causing scars to develop and block the fallopian tubes (oviducts). The drug itself has a 70-year history of safety. QS is a procedure that has been the subject of extensive research for over 30 years. The technique was introduced to the Philippines in Cebu City at the Southwestern University Medical School, where a program was started on January 10, 2000. This paper describes our experience with this method of sterilization for more than two years, that is, until April 11, 2003.

2. Materials and methods

Before undertaking this trial of QS, the researchers familiarized themselves with the established world literature describing how to protect human subjects volunteering for clinical research. This included reading and applying such measures as are found in the Helsinki and International Accord Conventions. All of our subjects were volunteers, who received instruction in reproductive physiology.

* Corresponding author. Tel: 63-032-254-7929;
E-mail address: lalfonsoswu.edu.ph (L. Alfonso)
Correspondence address: Sacred Heart Hospital, Southwestern University, Urgello St., Cebu City 6000, Philippines

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Quinacrine sterilization was carefully explained and patients observed a video describing the technique. They were instructed on alternative methods of birth control such as condom, diaphragms, birth control pills, etc. to assure that their free choice was an informed one. They were given opportunities to ask questions and the researchers responded with satisfactory answers in detail. Patients chose QS voluntarily as their best option. Each woman signed an informed consent.

Our intention was to enroll 500 patient volunteers who desired sterilization and to offer them transcervical chemical sterilization with quinacrine. Thirty-six patients have undergone QS. The profile of our patients reveals that their ages ranged from 26 to 43, with parity from 3 to 11. They had had at least three years of high school education. All were married women who felt they had completed their families with their desired number of children. The majority were Roman Catholic. Upon admission, a complete medical history was obtained and a thorough physical examination was performed. No patients were refused because of serious negative findings in the medical history or physical examination.

The quinacrine sterilization trial involved the transcervical insertion of 252 mg divided in seven pellets which were loaded into a modified Cu-T IUD inserter. QS was carried out in each case three to five days after menses ended. The seven pellets were carefully placed at the very top of the uterine fundus as described by Hieu [2]. Occasionally, a client was given mefenamic acid, 250 mg, one to two hours prior to the procedure. Afterwards, she was advised to lie flat on the examination table for at least 30 minutes before leaving for home. A second insertion was repeated four weeks later. Condoms were routinely given to all patients at the time of the first insertion of quinacrine and to continue to be used for six weeks after the second insertion. Our cut-off date for the purposes of this report was April 11, 2003.

Because this trial is small, statistical analysis is simple.

3. Results

There were no major adverse events (AE) reported. An immediate side effect was the loss of about 2 cc of blood following insertion. This was largely due to the cervical injury sustained once the tenaculum applied to the anterior lip of the cervix was detached. One woman complained of fever for one or two days after her first insertion. However, follow-up on this patient revealed that she had an upper respiratory infection acquired that day which probably caused her fever.

The most commonly reported AE was a yellow discharge noticed for a few days after quinacrine insertion. The condition was explained to these women as something to be expected and was transient. They were all reassured. All patients were instructed that if the discharge persisted for several days, especially if it became purulent, they should return to the clinic and would be examined for a possible cervicitis or pelvic inflammatory disease. No such serious AE was reported. About 50% of the group experienced mild abdominal discomfort. Mefenamic acid was prescribed to be taken every four hours if needed.

The 36 patients accumulated 515 woman-months or 42.9 woman years of exposure. No pregnancies of any type, neither intrauterine nor ectopic occurred.

4. Discussion

In the past, sterilization has not been popular in our community for a variety of reasons: cost of the procedure; lack of ready availability; fear of complications; lack of information and knowledge about QS; myths and rumors about sterilization in general; questions about safety and efficacy of any type of sterilization; and religious and moral convictions.

The Reproductive Health (RH) Clinic of the Sacred Heart Hospital, the teaching facility of the College of Medicine of Southwestern University in Cebu City, Philippines, has served all reproductive health needs of the greater population in this area. These services include: reproductive health counseling; family planning; maternal and child nutrition and care; pre- and postnatal care, treatment of reproductive tract infections; male reproductive health care; and campus screening programs. Family planning services include a wide variety of options for natural and artificial methods of contraception, including the permanent methods.

QS has many advantages never heretofore seen with other methods of sterilization, especially surgical techniques, e.g., simplicity, no need for an anesthetic, no incision, few side effects and low cost.

QS was new to our institution. It provided us with the opportunity to introduce an innovative and unique technology to our community. It has been received enthusiastically and will be, and already is, a celebration of women's rights. This clinical trial constituted an introduction to the staff and patients of this method of limiting family size. Admittedly, this series was small. Yet with no pregnancies and only minor AEs noted, QS is gaining acceptance in our area. More clinical trials of QS are warranted. Our research indicates that QS will deservedly continue to be offered in the Philippines.

References

[1] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[2] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S125–S127

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Marie Stopes Society, Pakistan: 1000 cases of quinacrine sterilization (QS)

M. Bilgrami[a], L. Shah[b]

[a]*Managing Director, Marie Stopes Society, Karachi, Pakistan*
[b]*Technical Advisor, Marie Stopes Society, Karachi, Pakistan*

Abstract

Objectives: To evaluate the safety, efficacy and acceptability of QS in Karachi, Pakistan. *Methods:* 1000 women who had chosen sterilization during the 4-year period 1994 to 1997 inclusive were offered QS at both stationary clinics and in a mobile van at 23 sites in the outskirts of Karachi. The protocol involved transcervical insertion to the uterine fundus of 252 mg quinacrine in 7 pellets and 55 mg of ibuprofen in 3 pellets through an IUD inserter, during the proliferative phase of the menstrual cycle. Two doses were administered one month apart. A temporary method of contraception was provided for 3 cycles, usually DMPA. Follow-up was scheduled: monthly for 3 months, quarterly for 1 year and then every 6 months for 4 years. *Results:* The crude pregnancy rate after 4 years was 2.0%. Minor complications and complaints were reported by 59% of the patients. There was one ectopic pregnancy and no major complications. *Conclusions:* QS was found to be safe and effective and has become the most popular method of sterilization in our area of Pakistan.

Keywords: nonsurgical sterilization, quinacrine sterilization, female sterilization

1. Introduction

For some time surgical sterilization has been needed outside cities in Pakistan, but it is not an available option. In July 1993, *The Lancet* published an article by Dr. Do Trong Hieu and his colleagues on a 31,781 case series of quinacrine nonsurgical female sterilizations (QS) in Vietnam [1]. The commentary appearing in that issue of the journal was most supportive of the study [2]. Under development since 1977, QS uses the long-established antibiotic and antimalarial drug quinacrine to initiate inflammation in a short segment of the fallopian tubes [3]. This reaction leads to the formation of 2 plugs of scar tissue that block the tubes, preventing the passage of eggs and sperm through them. According to Hieu there had been no deaths in this series and the rate of serious complications was only 1/50 of that seen with surgical sterilization. They found that the failure rate was higher than with surgical sterilization but acceptable. The cost of the procedure in Vietnam was less than US$1. Vietnamese women showed a strong preference for QS over surgical sterilization. In 1993, in an effort to offer sterilization in areas in Pakistan where it is currently unavailable, the Marie Stopes Society, Pakistan, decided to undertake a clinical trial of 1,000 cases to evaluate QS for possible inclusion in our service program.

2. Materials and methods

QS involves the transcervical insertion of 252 mg of quinacrine in the form of 7 pellets (Sipharm, Sisseln, Switzerland). In 1993, there was evidence that the antiprostaglandin, ibuprofen, served to relax the tubal ostia, thus allowing the quinacrine to enter the tube, and enhancing the successful outcomes of the

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

method. A recommended dose of 55 mg of ibuprofen in the form of 3 pellets was inserted along with the quinacrine pellets. The procedure was performed during the proliferative phase of the menstrual cycle, using a modified CuT IUD inserter. Two doses were administered one month apart. A temporary method of contraception was provided for three menstrual cycles. Most of the clients chose depot medroxyprogesterone acetate (DMPA) as a back-up method. The follow-up visit schedule was: monthly for three months, quarterly for one year and six-monthly for four years. From 1994 to 1997, 1000 women were enrolled in this study. Early in the first year, hysterosalpingography was performed on 14 patients 100 days after insertion, on 10 after a single insertion and on 4 after two insertions of quinacrine. Initially QS was performed at stationary clinics. Later it was offered in the outskirts of Karachi in a mobile van equipped for that purpose. Service was provided at the doorstep of the women. Knowing where they lived obviously helped in their follow-up. These 1000 cases were performed at 23 sites.

3. Results

Among the 10 women who had a single insertion of quinacrine followed by a hysterosalpingogram 100 days later, there were 9 who had bilateral tubal occlusion and one with unilateral tubal occlusion, while all 4 patients who had 2 insertions had bilateral occlusion.

Table 1 shows the number of QS cases performed during each of the 4 years. All the women had 4 years of follow-up. The gross failure rate for each of the 4 cohorts of women is also shown in Table 1. Among the 1000 women there were 20 pregnancies, for a gross pregnancy rate of 2.0% at 4 years. The failure rate fell with each new cohort from 4.2% in 1994 to 0.3% in 1997. One was an ectopic pregnancy.

Table 1
Quinacrine sterilization (QS) procedures performed annually 1994–1997 and the failure rate for each of the four cohorts with 4-year follow-up, Karachi, Pakistan

Year	Cases (*N*)	Pregnancies (*N*)	Gross failure rate (%)
1994	174	7	4.2
1995	231	9	3.9
1996	246	3	1.2
1997	349	1	0.2
Total	1000	20	2.0

Minor side effects were experienced by 59% of the patients. These included yellow discharge and itching, pain in the lower abdomen, backache, amenorrhea, fever, allergy (local and generalized), loss of weight (approximately 1–2% of patients), and post-insertion infection. There were no major complications or deaths.

4. Discussion

We found QS to have many advantages over surgical sterilization. It does not involve invasive surgery and yet it is permanent; low cost makes it affordable to clients; it does not require a physician; it is quickly carried out and easy to deliver. Serious complications are rare and the risk of death extremely small. It is much more cost effective than surgical sterilization.

The greatest deterrent to offering QS is that this use of quinacrine is not authorized by the United States Food and Drug Administration (FDA) and not registered by the Government of Pakistan. Because the method is unapproved, it is more difficult to market. Women were often not confident in accepting QS since it was not a registered product. Another disadvantage is that long-term side effects are unknown. In our experience, follow-up was expensive and time consuming.

In this study the major referral source was the general practitioner. However, some of these doctors were reluctant to refer the cases for lack of FDA approval and Pakistani registration. This caused a major obstacle in the marketing of the method, as well as its utilization. Consequently, the majority of QS cases were generated in camps organized for the purpose of sterilization in general. After women were informed and counseled on both surgical sterilization and QS, many of them chose QS.

Since this method has the potential to replace surgical female sterilization, the following measures are suggested for improving a QS program:

- There should be an initiative creating awareness of this method. An effective marketing program needs to be developed.
- A comprehensive training program for staff should be implemented.

- Most important, there should be training workshops for private practitioners.
- A proper kit for QS should be provided with pre-loaded inserters in order to reduce the chances of infection and re-use of the inserters.
- Sterile packs should be made available.

In our series, the failure rate fell with each new cohort. This diminuation may have been due to the increasing experience of the clinicians and the staff. We found QS to be safe, effective and acceptable in Karachi. Indeed, QS is the most popular method of sterilization in our area of Pakistan, which has a large unmet need for this service.

References

[1] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[2] Feuerstein MT. Family Planning in Vietnam. *Lancet* 1993; 342:188.

[3] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera . Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S129–S131

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

8-Year follow-up in a randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization in Indonesia

T. Agoestina

Department of Obstetrics and Gynecology, Dr. Hasan Sadikin Hospital/Medical School, Padjadaran University, Bandung, Indonesia

Abstract

Objective: To evaluate the efficacy of one vs two insertions of quinacrine and the long-term safety of quinacrine sterilization (QS) 8 years after the procedure in Indonesia. *Methods:* Between March 1993 and September 1995, a randomized trial was conducted in 6 academic centers in Indonesia. In February 2003, a follow-up study was undertaken in Bandung, one of those centers. This survey required a home visit of each woman. A questionnaire was designed to elicit information regarding current general health status, method failure, pregnancy outcomes and other contraceptive methods now used by women who experienced failures. Among the 70 patients receiving a single insertion of quinacrine pellets, 14.3% had become pregnant. There were no pregnancies among the 30 who received 2 insertions. All the women were found to be in good health. No long-term side effects or complications were identified. *Conclusion:* The two-insertion protocol is unmistakably superior to the single insertion. This study provides further evidence that QS is a safe contraceptive method.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

The Indonesian government's formal efforts at family planning began in 1970, and by 1994 the prevalence of modern methods of contraception had exceeded 50%. Despite this success, there are shortcomings in the country's health status in general and in its family planning program in particular. In 1994, maternal mortality was reported to be 326 per 100,000 live births. Yet, in the contraceptive mix in Indonesia, female surgical sterilization accounted for only 2.9% of users. Research in both Indonesia [1,2] and elsewhere [3–5] had shown quinacrine sterilization (QS) to be both safe and reasonably effective. Delivery of quinacrine pellets is remarkably similar to IUD insertion. In Indonesia, we have a great resource in that we have a large cadre of well-trained paramedics who are experienced in IUD placement. These personnel are strategically located throughout the country. With minimal additional training, they can safely and effectively perform QS.

The potential for QS to increase the prevalence of female sterilization led the National Family Planning Coordinating Board (NFPCB), with the approval of its ethics committee, to conduct a trial of this method in 6 academic centers located throughout the country. We viewed the requirement for 2 insertions as disadvantageous. A single insertion would be preferable in our circumstances. For this reason, the Board decided to evaluate the differences in one- and two-insertion protocols in a randomized trial. The financial cost of this evaluation was an important consideration, as

* Fax: 622-225-04642.
E-mail address: dragias@bdg.centrin.net.id (T. Agoestina)
Correspondence address: RS. Ibu & Ank Sukajadi Bandung, JI. Sukajadi No. 149, Bandung 401162, Indonesia

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

it would be for any developing country. However, we recognized from the outset that to definitively demonstrate that the one- and two-insertion protocols were comparable in safety and efficacy was beyond our means.

Of particular interest to us were the single-insertion protocol and center variation in efficacy. We chose a study design using 6 centers, with 100 subjects each, divided into a group of 70 for single insertion and another of 30 to receive two. The original plan called for an expanded trial based on results of this initial research. A single venue with clinical trial experience was chosen from Bandung, Denpasar, Jakarta, Semarang, Surabaya and Yogyakarta. Since I had undertaken a clinical trial of QS in the 1980s, I was appointed principal investigator, to be responsible for the training program. All insertions were performed by obstetricians. The specifics of the study design, as well as the results of this trial, are described in an article on the first-year follow-up [6]. All women entered this 6-center clinical trial between April 1993 and September 1995. There were 2 pregnancies at one year among the 180 receiving 2 insertions (1.1%) but 31 failures after one year among the 420 women with only one (7.4%). Both two-insertion pregnancies and 11 of the 31 among single-insertion cases occurred at the clinic in Denpasar.

The current report is based on the results of an 8-year follow-up of the 100 women who elected QS in Bandung only. At one year, this clinic had a single-insertion failure rate of 2.8% but no two-insertion pregnancies.

2. Materials and methods

For the purpose of conducting an 8-year follow-up of the 100 women electing QS in Bandung, a questionnaire was designed to elicit information regarding their current health status, pregnancy, including pregnancy outcomes and the method of contraception chosen by the women who experienced a failure with QS. Home visits, where the questionnaire was administered, were conducted in February 2003.

3. Results

In the group of 70 patients who had a single insertion of quinacrine, 9 were lost to follow-up. We were unable to locate one of the 30 women who had 2 insertions. In all cases, those lost to follow-up had changed addresses in the 6 years since the 1-year monitoring. Thus 90 of the 100 women were interviewed for a follow-up rate of 90%.

The ages of the women at the time of the home visit ranged from 41 to 50 years. All of them were found to be healthy. None of the 29 who had had 2 insertions became pregnant. Ten of those with only a single insertion had become pregnant, for a crude failure rate of 14.3%. The distribution of these pregnancies over time is shown in Table 1.

Table 1
Time interval of pregnancies following a single insertion of 252 mg of quinacrine, Bandung, Indonesia, March 1993 to September 1995 ($N = 10$)

Years	Pregnancies (No.)
<1	2
1 to 2	3
2 to 3	2
3 to 4	0
4 to 5	1
5 to 6	1
6 to 7	1
Total	10

The outcomes of the 10 pregnancies were as follows: 4 women decided on menstrual regulation followed by surgical sterilization; 6 chose to continue their pregnancies to term and had normal deliveries. Two of these 6 patients requested surgical sterilization after delivery, while 3 selected the IUD and one selected OCs for their method of contraception.

4. Discussion

The distribution of pregnancies as shown in Table 1 suggests that the body continues indefinitely to try to repair the injury to the one-cell thick lining of the fallopian tube caused by only a few hours of exposure to the antibiotic, quinacrine. Sometimes, it succeeds. In most, if not all of the 10 cases, the tubes were blocked and then, with the passage of time, they became unblocked. Somehow, the second insertion reinforces the first in the formation of the

scar. This is an important research question for the future. If the mechanism for this reinforcement could be determined, then perhaps an adjuvant could be developed to be administered at the time of the first insertion, thus eliminating the need for a second one. But this experience clearly demonstrates that two insertions of quinacrine are more effective than one.

That 6 of the 10 women decided to seek surgical sterilization after their QS procedure failed suggests that permanent contraception is highly desirable. Yet, sterilization accounts for only 2.9% of the contraceptive mix of Indonesia. There may be considerable frustrated demand for sterilization services in our country. During home visits for this follow-up study, we encountered many other women who knew about QS and wanted this procedure for themselves.

As noted earlier, the NFPCB had planned to undertake another clinical trial of 600 women that would involve paramedics. But it never took place. With a letter from the World Health Organization to the NFPCB, dated 27 January 1994, containing the statement, "WHO experts and FDA officials have said that they would be surprised if quinacrine did not turn out to be carcinogenic", began a period of international pressure to halt research on this promising new method. After the 600-case clinical trial was completed and the data analyzed, the NFPCB decided in 1997 to ignore the external opinions and proceed with the planned 600-case trial at the health center level with paramedics. After all, the claim that quinacrine might be carcinogenic at the dose required for QS was not credible. Quinacrine had been used clinically for treatment and prophylaxis, even in Indonesia, for 60 years at doses of 36,000 mg per year without any hint that it might cause cancer.

I was invited to present the findings of this study at the 2000 FIGO meeting in Washington, DC and authorized to inform the gathering that we had been given verbal approval to proceed with the second trial of 600 cases. As a part of my presentation I proudly made this announcement. But this approval was short-lived. The international pressure to stop this research was then renewed, possibly due to several factors, including my announcement. In an interview with *Wall Street Journal* reporter, Alix Freedman, in Jakarta on January 19, 1998, our Minister of Population informed her that "Indonesia simply cannot fly in the face of world opinion" (Personal communication, Stephen D. Mumford, Dr.P.H., January 19, 1998). No further action has been taken on this second trial. We hope that FIGO will act to counter the opposition to further research of this method. Then when women ask how they may obtain a QS for themselves, we will be able to respond in a satisfactory manner.

References

[1] Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept* 1992; 8:141–151.

[2] Suhadi A, Soejoenoes A. Quinacrine pellet nonsurgical female sterilization in Wonosobo, Indonesia. *Fertil Steril* 1997; 67:966–968.

[3] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[4] Bhatt R, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril* 1985; 44:303–306.

[5] Mullick B, Mumford SD, Kessel E. Studies of quinacrine and tetracycline for nonsurgical female sterilization. *Adv Contracept* 198; 3:245–254.

[6] Agoestina T, Hoesni RHM, Purwara BH, Santoso BI, Siswanto P, Dasuki D, et al. Randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization. *Fertil Steril* 2002; 77:1065–1068.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S133–S135

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) in Syria: a preliminary report on 297 cases

V. Garabedian

Private Practice, Aleppo, Syria

Abstract

Objectives: To evaluate the safety, efficacy and acceptability of quinacrine sterilization (QS) in Syria. *Methods:* From July 2001 to December 2002, 297 women who requested permanent sterilization volunteered for QS either in my private practice or my local family planning center in Aleppo, Syria. The standard protocol was used: 252 mg of quinacrine in the form of 7 pellets are deposited at the uterine fundus with a modified CuT IUD inserter during the proliferative phase of the menstrual cycle. This procedure is repeated 4 weeks later. DMPA was injected at the time of the first insertion for temporary contraception. Every sterilized woman has had a monthly checkup visit until the cut-off date for this report, including a beta HCG pregnancy test. All procedures were performed by the author. The cut-off date for this report was June 11, 2003. *Results:* The single pregnancy was ectopic. Four women (1.3%) complained of severe pain. Moderate pain was experienced by 13.1% while the remaining women felt mild pain, all easily treated. The remaining side effects were minor and also easily treated. Oligomenorrhea and amenorrhea affected 29% of the women and lasted for several months. Immediate side effects are similar to reports from other researchers. *Conclusions:* Results thus far regarding efficacy are encouraging. QS has proven to be acceptable.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

After women have all the children they want, they prefer a permanent method of contraception. However, currently the only option is surgical sterilization which carries with it some serious risks. In Syria, as in many other countries, there is a need for a safe, effective and acceptable alternative to this surgical procedure.

In October 2000, I was introduced to a nonsurgical sterilization method using the antibiotic and antimalarial, quinacrine. This method has been used for a quarter of a century [1] by more than 140,000 women in 34 countries. An informational ad appeared that month in *Fertility and Sterility,* the official journal of the American Society for Reproductive Medicine. After reviewing the literature, I contacted the organization responsible for that ad, the Center for Research on Population and Security. Along with the necessary training materials came an offer from the Center of research quantities of quinacrine pellets and the required modified CuT IUD inserters. After a thorough study of the training materials and local arrangements for a trial were completed, a request was made to the Center for pellets and inserters and they were soon delivered.

* Tel.: 963-21-224-7532, 963-94-443339 (Cell); Fax: 963-21-465-6120.

E-mail address: vanigvanig@postmaster.co.uk (V. Garabedian)

Correspondence address: Muhatet Baghdad Amine Rihani Street, Bazerdji Building 43/8, P.O. Box 4081, Aleppo, Syria

2. Materials and methods

A prospective clinical study of QS is being conducted

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Table 1
Immediate side effects of QS and their treatment in Aleppo, Syria, July 2001 to December 2002 ($N = 297$)

Side effect	N	(%)	Treatment
Lower abdominal pain			
mild	254	85.5	Ibuprofen 400 mg PO three times daily for 3 days
moderate	39	13.1	Diclofenac IM 75 mg twice daily for 3 days
severe	4	1.3	Diclofenac IM 75 mg twice daily for 3 days + Tramadole 100 mg IV twice daily for 3–4 days
Yellow discharge	297	100.0	none
Nausea	142	47.8	oral ondancetron
Headache and dizziness	47	15.8	none
Backache	8	2.7	none
Vomiting	4	1.3	none

in my private practice and at the local family planning center in Aleppo, Syria. From July 2001 through December 2002, 297 women, who gave informed consent, received transcervically 252 mg dose of quinacrine hydrochloride in the form of 7 pellets (Sipharm, Sisseln, Switzerland) during the proliferative phase of the menstrual cycle. Four weeks later this process was repeated. All insertions were made by the author. The insertion technique first described by Hieu [2] was used, placing all pellets at the uterine fundus. To provide contraception for three months following the first insertion, as called for in the standard protocol for QS, all 297 women received a DMPA injection on the day of the first dose of quinacrine.

All women seeking surgical sterilization were counseled on both this method and QS. If they expressed an interest in QS, the study was explained and they were invited to participate. Since initiating the study, about 65% of the women have chosen QS and 35% surgical sterilization. Not a single woman was excluded from the study because of a pre-existing condition. A follow-up examination is given every month including a medical history, a physical exam, ultrasonography and a beta HCG test for pregnancy. Women were also told that we would see them at any time if they had complications or concerns. The cut-off date for the analysis for this preliminary report was June 11, 2003.

3. Results

As of June 11, 2003 there continues to be 100% follow-up. There has been only one pregnancy. This was an extra-uterine pregnancy that occurred 4 months after the second insertion. It was successfully treated with two doses of methotrexate. Table 1 shows the side effects that occurred immediately after quinacrine insertion and the treatment given. The only side effects encountered were the same as those reported by other investigators, and, thus, anticipated. Four women were hospitalized for observation and treatment for severe pain. None of the four exhibited rebound tenderness on palpation of the abdomen nor was there any other suggestion of perforation of the uterus. Since great care had been taken with each patient to avoid such an eventuality, I am confident there were no perforations among these four women, nor in any patient in this series. Three levels of pain were encountered as shown in Table 1, which also relates the course of treatment prescribed for each.

Either oligomenorrhea or amenorrhea was experienced by 30% (88 of 297) of the patients. However, this may have been due to the DMPA injection, not necessarily the QS insertion. Patient demand for this procedure grew steadily throughout the study period. Side effects only occasionally reported by others, such as pelvic inflammatory disease and hematometra, were not seen.

4. Discussion

This preliminary analysis of our experience in Aleppo suggests that the performance of QS here will not differ

from that seen in the other 33 countries where this method has been offered. QS has already been proven to be acceptable in this trial, as the demand for it continues to grow. The risks of surgical sterilization are a serious drawback for that method. Our experience thus far confirms that QS is much safer than the surgical procedure, a finding that all investigators of QS have reported. It is too early to draw any conclusions regarding the failure rate. The use of DMPA in our series insured that there were no early failures. That it was not necessary to exclude a single woman from this study is an important feature of QS. Thus far, QS is meeting our expectations. A definitive assessment of this method will only come from a much larger series and a much longer period of monitoring.

References

[1] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. *Int J Gyn Obstet* 1980; 18:275–279.

[2] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S137–S139

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

10-year follow-up of women who elected quinacrine sterilization (QS) in Wonosobo, Central Java, Indonesia

A. Suhadi[a,*], M. Anwar[b], A. Soejoenoes[c]

[a]*Department of Obstetrics and Gynecology, Wonosobo General Hospital, Wonosobo, Central Java, Indonesia*
[b]*Department of Obstetrics and Gynecology, Gadjah Mada University Faculty of Medicine, Dr. Sardjito Hospital, Yogyakarta, Indonesia*
[c]*Department of Obstetrics and Gynecology, Diponegoro University Faculty of Medicine, Dr. Kariadi Hospital, Semarang, Indonesia*

Abstract

Objectives: To evaluate the safety and efficacy of quinacrine sterilization (QS) in Indonesia. *Methods*: During the period, August 1992 to October 1993, 200 women who had requested surgical sterilization volunteered for QS at the Wonosobo Regency Hospital, Central Java Province, Indonesia. The protocol called for transcervical insertion of 252 mg of quinacrine in the form of 7 cylindrical pellets and 55.5 mg of ibuprofen with a CuT-IUD (Kimia Farma) inserter during the proliferative phase of the menstrual cycle. A second procedure was done 4 weeks later. The technique used is essentially the same as inserting a CuT-IUD. Follow-up was scheduled at 6, 12, 24 and 48 months after the last insertion. In March 2003 additional monitoring was completed. *Results*: The 10-year cumulative pregnancy rate was 4.3 per 100 women with a follow-up rate of 93%. No pregnancies had occurred among these women since the 4-year follow-up. No long-term side effects or complications were reported. *Conclusions*: After 10 years of use, QS was found to be safe and reasonably effective.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

When this study was initiated 10 years ago, quinacrine sterilization (QS) was a promising method of nonsurgical female sterilization because of its safety, acceptability and effectiveness. Today, it is even more promising. The number of cases performed has tripled as has the number of countries where it has been offered. Yet no clinician has reported a bad experience with this method. This growing experience with QS is particularly important to Indonesia. When this study was initiated in 1992, Indonesia had a very low prevalence of female sterilization, 2.9% [1] and an unacceptably high maternal mortality of 390 per 100,000 live births [2]. These indicators have changed little in the last decade. Surgical sterilization requires trained personnel, adequate medical care facilities and acquisition and maintenance of sophisticated equipment. Most Indonesian women do not have access to these resources nor will they in the foreseeable future. This predicament is recognized by the National Family Planning Coordination Board (NFPCB) which consequently organized and conducted a QS clinical trial in 6 academic centers located throughout Indonesia in 1993–1995. The results of that study were recently published and contributed significantly to the growing body of evidence showing that this method is safe, reasonably effective and acceptable to women [3].

Research on the long-term effects of QS is also expanding and thus far, none have been identified. This report on a 10-year follow-up will add to the collective

* Corresponding author. Fax: 62-286-325371;
E-mail address: agungspogyahoo.com (A. Sahudi)
Correspondence address: Department of Obstetrics and Gynecology, Wonosobo General Hospital, Wonosobo 56311, Indonesia

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

experience. Earlier results from this study are reported elsewhere [4,5].

2. Materials and methods

A prospective clinical study of QS was conducted at the Wonosobo Regency Hospital, Central Java Province, Indonesia, with the approval of the NFPCB of Wonosobo Regency, Central Java Province which served as the institutional review board. From August 1992 through October 1993, 200 women, who gave informed consent, received transcervically 252 mg of quinacrine hydrochloride in the form of 7 cylindrical pellets (Sipharm, Sisseln, Switzerland) followed by 55.5 mg ibuprofen in three pellets during the proliferative phase of the menstrual cycles. This process was repeated 4 weeks later. Pellets were provided by the Center for Research on Population and Security. All insertions were made by the senior author. The procedure was essentially the same as for inserting a CuT-IUD (Kimia Farma, Bandung, Indonesia).

Women seeking surgical sterilization were advised of the QS option and of the study in which they were invited to participate. Excluded were women who had pathologic pelvic conditions (except cervicitis), such as upper tract infection, or gross distortion of the uterine cavity or who appeared unusually nervous. Those who could not participate in the trial were offered a choice of surgical sterilization or other methods of contraception. Monitoring of the QS patients was scheduled at 6, 12, 24 and 48 months after the last insertion and at any time when complications or complaints occurred. In February and March 2002 we undertook an additional follow-up visit. Data were collected on standardized forms developed by the International Federation for Family Health. Life-table analysis was used to calculate efficacy.

3. Results

Less than 2% of the women who opted for QS were excluded as a result of our criteria. Their mean age was 33.2 years (SD 9.75), and they were between 24 and 40 years old. The mean number of live births was 3.5 (SD 0.5) and ranged from 2 to 8. All 200 women completed the first insertion but 3 declined the second and were offered an alternative method. One month after the first insertion, 116 women (58%) reported that they had experienced lower abdominal pain. Two women complained of severe abdominal pain and required antibiotic and analgesic treatment, 26 (13.5%) had fever, 15 (7.5%) leukorrhea, 7 (3.5%) menorrhagia, and 2 (1.0%) amenorrhea. At the 1-year follow-up, two women informed us that they had had amenorrhea for 4 months and then resumed menstruation. More detailed results are provided in our two-year [4] and four-year reports [5].

Four women became pregnant during the 2-year follow-up period, at 4, 5, 14 and 18 months after the second insertion. Before the 4-year follow-up there were 4 additional pregnancies for a total of eight. No additional failures were documented and, thus, the 10-year cumulative pregnancy rate was 4.3 per 100 women. The follow-up rate was 93% at 10 years.

Two of the 8 pregnancies were terminated by vacuum aspiration; one aborted spontaneously. The other five ended in spontaneous full term deliveries. No major malformations were noted.

At the 10-year follow-up, 2 women had amenorrhea. No cancers or long-term side effects had occurred.

4. Discussion

The fact that less than 2% of the volunteers requesting QS were excluded from the study is in itself an important finding. All but a few women will be good candidates for this procedure. The side effects recorded are similar to those mentioned by other investigators. The two cases of amenorrhea during the 10-year follow-up could be anticipated. Ten years later, some of these women who had QS could be expected to be menopausal. When this study was initiated in 1992, there was some evidence that ibuprofen might enhance the effectiveness of QS. This has now been convincingly disproved [6] and is no longer recommended.

An accurate explanation for the distribution of failures over time may assist in improving the efficacy of QS. That all 8 failures would occur in the first 4 years is an observation of interest and may be of significance if substantiated by other studies. More investigators are needed to evaluate all aspects of the procedure and arrive at solutions. For example, after our study

was initiated, Hieu and his colleagues [7] made an important discovery in recognizing the importance of placing the pellets at the fundus and, in turn, lowering the failure rate. There will be other such advances. The failure rate of this study of 4.3 per 100 women at 10 years is most acceptable given the alternatives available to women in Indonesia and elsewhere. We found QS to be safe, indeed, much safer than surgical sterilization and there was no hint that QS might cause any long-term side effects, including cancer. We conclude that QS has great promise. It is safe, effective and acceptable.

References

[1] Central Bureau of Statistics (CBS) [Indonesia]; State Ministry of Population/National Family Planning Coordinating Board (NFPCB); Ministry of Health (MOH); Micro International, Inc. (MI). Indonesian Demographic and Health Survey 1994: Calverton, Maryland: CBS and MI: 1995:73.

[2] Central Bureau of Statistics (CBS) [Indonesia]; op. cit., p. 211.

[3] Agoestina T, Hoesni RHM, Purwara BH, Santoso BI, Siswanto P, Dasuki D, et al. Randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization. *Fertil Steril* 2002; 77:1065–1068.

[4] Suhadi A, Soejoenoes A. Quinacrine pellet nonsurgical female sterilization in Wonosobo, Indonesia. *Fertil Steril* 1997; 67:966–968.

[5] Suhadi A, Anwar M, Soejoenoes A. Four-year clinical evaluation of quinacrine pellets for non-surgical female sterilization. *Adv Contracept* 1998; 14:69–77.

[6] Randic L, Haller H, Sojat S. Nonsurgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen. *Fertil Steril* 2001; 75:830–831.

[7] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S141–S145

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine sterilization (QS) in Costa Rica: 694 cases

F. Alpizar

Department of Obstetrics and Gynecology (retired), Hospital San Rafael, Alajuela, Costa Rica

Abstract

Objectives: To evaluate the safety, efficacy and acceptability of quinacrine sterilization (QS) in Costa Rica. *Methods:* From 1989 though August 1993, 694 women volunteered for QS in my private practice. All were referred by a family planning clinic or a local hospital obstetric service. The protocol used involved the transcervical insertion of 216 mg of quinacrine hydrochloride in the form of 6 pellets. A second dose was given 4 weeks later. All insertions were done in the first 14 days of the menstrual cycle. The procedure was similar to the CuT IUD placement. Temporary contraception was recommended for 3 months after the last insertion. The cut–off date for this analysis was April 1994. *Results:* With 7 months to 5 years of follow-up, the gross pregnancy rate was 2.5%. Side effects were relatively minor, none requiring hospitalization. *Conclusion:* QS was found to be safe, effective and acceptable.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

This method has been in development since 1977, when Zipper and his colleagues began to experiment using quinacrine for nonsurgical female sterilization [1]. Since then, the procedure has been widely studied by other investigators [2–4]. The system involves the transcervical intrauterine placement of approximately 250 mg of quinacrine hydrochloride through a modified IUD inserter. Quinacrine introduced into the uterus has a sclerosing effect that normally causes occlusion of the opening of the fallopian tubes, through inflammation and fibrosis [5]. This use of quinacrine was introduced in Costa Rica in 1989, and interest in the method has grown from that time. It has been used and investigated as an alternative to a surgical procedure.

Costa Rica is a small country in Central America with a population of 3,099,063 inhabitants in 1992. Of them, 1,532,400 were females, whose life expectancy was 74.7 years [6]. According to a National Survey of Reproductive Health, the specific fertility rate/1000 (SFR), by age and the differentiation between rural and urban women in 1990 is shown in Table 1. This rate is higher in rural than in urban areas [7]. Table 2

Table 1
Births by age, specific fertility rate and total births by geographic area, Costa Rica National Survey of Reproductive Health, 1992

Age (years)	Rural	Urban	Total
15–19	113	69	87
20–24	193	168	179
25–29	180	149	159
30–34	121	94	105
35–39	79	65	71
40–44	43	23	31
Specific fertility rate	3.64	2.84	3.16
Total births (%)	43	57	100

* Tel.: 506-441-4174; Fax: 506-441-1596.
E-mail address: falpizar@bytecr.com (F. Alpizar)
Correspondence address: Calle 5, Av. 1–3, Alajuela, Costa Rica

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

Table 2
Ideal number of wanted children, Costa Rica National Survey of Reproductive Health, 1992

Age (yr)	Current number of children (mean)				Wanted (mean)
	0	1–2	3–4	5 or more	
15–24	2.7	2.6	3.6	–	2.7
25–34	2.6	2.7	3.6	4.5	3.1
35 or older	2.9	2.8	3.7	4.7	3.6
Mean	2.7	2.7	3.7	4.7	3.1

Table 3
Surgical sterilization by age in urban and rural areas, Costa Rica National Survey of Reproductive Health, 1992

Age (yr)	Cumulative percentage (%)		
	Urban	Rural	Total
15–19	–	–	–
20–24	0.6	3.9	2.2
25–29	8.0	7.4	7.8
30–34	21.4	16.7	19.4
35–39	38.5	29.3	33.8
40–44	47.9	32.0	40.4
45 or older	55.8	3.9	45.3
All	24.0	17.0	20.7

reveals the number of wanted children compared to actual live births according to the age of the woman, with a mean of 3.1 wanted children. These figures are declining among the younger women with an increasing potential demand of family planning and sterilization services [3]. Twenty-four percent of urban women compared to 17% in rural areas used the surgical sterilization method for family planning. This preference is clearly shown in Table 3 [3].

The potential demand for surgical female sterilization in women over 34 is estimated to be around 200,000. The actual cost of each of these procedures in our Social Security System is between $500 and $800. The total amount, to satisfy this demand, would be between 100 and 160 million US dollars.

2. Materials and methods

Between 1989 through August 1993, 694 women elected to have QS in my private practice. All of them were referred by a family planning clinic or the local hospital obstetric service. The procedure and the possibility of failure was explained in detail to each patient. All 694 women wrote and signed an acceptance and discharge of responsibility agreement. All of them had a gynecologic examination.

The protocol used involved the transcervical insertion of 216 mg of quinacrine hydrochloride in the form of 6 pellets (International Federation for Family Health). A second dose was given 4 weeks later. All insertions were done in the first 14 days of the menstrual cycle. Lactation or use of DMPA were not contraindications. The procedure was carried out in the same way as the CuT IUD insertion, pulling the sheath back rather than pushing the pellets in, leaving a column of pellets along the midline of the uterus. If there was significant bleeding at the end of either the first or second insertion, then a third insertion was done four weeks later. Temporary contraception was recommended for 3 months after the last insertion. In order to check patients for tubal obstruction, hysterosalpingograms (HSG) were performed. Only when both tubes were obstructed in the cornual area were HSG reported as positive. The cut-off date for this analysis was April 1994.

3. Results

A total of 694 women accepted the procedure. An increase in demand for QS began after 2 years of offering this method as shown in Table 4, and this is evidence that it is acceptable and popular. The mean age of women who accepted the method is 33.4 years

Table 4
Quinacrine sterilization acceptance by year 1989–1993, Costa Rica ($N = 694$)

Year	Number	Percentage (%)
1989	47	6.8
1990	32	4.6
1991	91	13.1
1992	294	42.4
1993	230[a]	33.1
Total	694	100.0

[a] Until August.

Table 5
Quinacrine sterilization (QS) by age, 1989–1993, Costa Rica ($N = 694$)

Age	Number	Percentage (%)
16–19	2	0.3
20–24	49	7.0
25–29	135	19.4
30–34	191	27.5
35–39	211	30.4
40–44	101	14.5
45 or older	5	0.7
Total	694	100.0

Table 6
Parity of quinacrine sterilization (QS) acceptors, 1989–1993, Costa Rica ($N = 694$)

Parity	QS acceptors (N)	Percentage (%)
1	22	3.2
2	174	25.1
3	239	34.4
4	131	18.9
5	61	8.8
6	37	5.3
7	13	1.9
8	7	1.0
9	4	0.6
10	6	0.9
Total	694	100.0

(Table 5). The percentage of women between 25 and 39 years of age is 77.3%. The mean number of live births is 3.4. Table 6 shows that 78.4% of the women had between 2 and 4 live births and 18.5% had 5 or more live births. Of the 694 patients, 510 (73.5%) never had an abortion.

A total of 653 women completed 2 insertions of pellets. The 41 women who had only a single dose were excluded from the remainder of the analysis. Three women received a third dose of quinacrine because they had significant bleeding after one of the two insertions. A total of 116 were lactating during the insertions.

In April 1994, the gross cumulative pregnancy rate was 2.5% for the 653 patients who completed the treatment of two or three insertions (Table 7). There was a total of 16 pregnancies. Two ended in miscarriage, and one woman was pregnant at the time of the analysis. Five patients were lost to follow-up after they became pregnant and the outcome of their pregnancies is unknown. Eight known pregnancies finished in spontaneous birth at term with healthy children, except one, who had an esophageal atresia. All 8 of these women elected postpartum surgical sterilization. No ectopic pregnancy is reported in this series.

Table 7
Quinacrine sterilization failure rate by year, 1989–1993, Costa Rica ($N = 653$)

Year	Number	Pregnancies	Percentage (%)
1989	41	2	4.9
1990	25	1	4.0
1991	88	4	4.5
1992	269	7	2.6
1993	230	2	0.9
Total	653	16	2.5

The post-insertion symptoms are shown in Table 8. Lower abdominal pain was the major complaint in the 24 hours after the application, of which 83 were reported as minor, 46 as mild and 6 as severe pain for which oral medication such as acetaminophen or ibuprofen were prescribed. None of the patients had to be hospitalized. One perforation occurred and no insertion was carried out at that time. In this case, it was done the following month.

Table 8
Immediate side effects of quinacrine sterilization (QS) by severity, 1989–1993, Costa Rica ($N = 653$)

Side effect	Severity			Total
	Minor	Mild	Severe	
Lower abdominal pain	83	46	6	135
Fever	16	32	0	48
Headache	6	3	1	10
Dizziness	9	1	0	10
Bleeding	48	20	3	71
Discharge	2	1	0	3

Of the 108 QS patients who were lactating, 6 (5.6%) became pregnant as opposed to the 545 non-lactating women who experienced 10 pregnancies for a failure rate of 1.8% (Table 9). This represents a relative risk of 3.1. Among the 653 women, 129 (19.8%) had hysterograms. Bilateral obstruction was found in 115 cases (89.1%), 13 (11.3%) had unilateral obstruction, and 1 (0.8%) had no obstruction. Another family planning method was recommended to these last 14 patients. Of the 115 women who had bilateral obstruction, as shown on the hysterogram, 5 later became pregnant, for a failure rate of 4.3% (Table 10), compared to 2.0% among those who did not have a hysterogram, a relative risk of 2.4.

Table 9
Pregnancy rates following quinacrine sterilization (QS) of non-lactating women versus lactating women, 1989–1993, Costa Rica ($N = 653$)

Year	No lactation			Lactation		
	N	Pregnancies	%	*N*	Pregnancies	%
1989	21	0	0	20	2	10.0
1990	13	0	0	12	1	8.3
1991	66	1	1.5	22	3	13.6
1992	236	7	3.0	33	0	0
1993	209	2	1.0	21	0	0
Total	545	10	1.8	108	6	5.6

Table 10
Pregnancy rate following hysterogram versus no hysterogram, 1989–1993, Costa Rica

Year	No hysterogram			Hysterogram			Total women (*N*)	Total pregnancies	Total pregnancy rate (%)
	N	Pregnancies	Rate (%)	*N*	Pregnancies	Rate (%)			
1989	17	1	5.9	24	1	4.2	41	2	4.9
1990	6	0	0	19	1	5.3	25	1	4.0
1991	33	2	6.1	55	2	3.6	88	4	4.5
1992	252	6	2.4	17	1	5.9	269	7	2.6
1993	230	2	0.9	0	0	0	230	2	0.9
Total	538	11	2.0	115	5	4.3	653	16	2.5

Table 11
Temporary contraceptive use during and for 3 months after quinacrine insertion and risk of pregnancy, 1989–1993, Costa Rica ($N = 653$)

Method	Number	Pregnancies	Percentage (%)
Condom	227	7	3.1
IUD	45	1	2.0
Pill	246	5	2.0
Depo Provera	27	0	0
Rhythm	108	3	2.8
Total	653	16	2.5

In the 41 cases, there were women who were lactating and had a hysterogram. Four pregnancies were observed in this unique group. This represents a failure rate of 9.8%. No differences were observed in pregnancy rates according to the temporary contraceptive method they were using (Table 11).

4. Discussion

In an effort to satisfy the demand for female sterilization services that exceeds the supply, researchers are investigating the use of a safe, nonsurgical method that can be performed easily and at a significantly lower cost. The quinacrine method is safe; no deaths are reported in this series. All complications were resolved at home and no major problems were detected.

In this series, the quinacrine pellet method with 2 insertions had a gross cumulative failure rate of 2.5%. When the insertion was carried out during the lactation period, the gross cumulative failure rate increased to 5.6% (Table 9). When a hysterogram was used to demonstrate tubal obstruction, there was also an increase of the pregnancy rate to 4.3%, even though the hysterogram showed bilateral occlusion, compared to 2.0% among women who had no hysterogram (Table 10). When women were lactating and a hysterogram

was done, the gross failure rate increased to 9.8%. The possibility of recanalization of tubes as a result of the hysterogram is pointed out in order to explain the gross failure rate, which was less when this procedure was not used.

The quinacrine pellet method is safe and effective for female sterilization, with an increased failure rate for women who are lactating. Surgical sterilization cannot possibly satisfy the demand for the foreseeable future. A simpler nonsurgical sterilization method is needed, and that method is QS. In rural areas, where the fertility rate is higher and the surgical facilities more scarce, it is an excellent option. The main advantages of this method are the possibilities of raising contraceptive prevalence among women who want no more children, while providing more effective contraception than temporary methods.

Acknowledgments

I am grateful to Gerardo Herrara and Maureen Solano for review of the paper, helpful suggestions and editorial assistance.

References

[1] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet* 1980; 18:275–279.

[2] Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31 781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. *Lancet* 1993; 342:213–217.

[3] Guzman-Serani R, Bernales A, Cole LP. Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. *Contracept Deliv Syst* 1984; 5:131–135.

[4] Zipper J, Cole LP, Rivera B, Brown E, Wheeler RG. Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for nonsurgical female sterilization. *Adv Contracept* 1987; 3:255–256.

[5] Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM. Quinacrine-induced pathologic changes in the fallopian tube. *Fertil Steril* 1980; 33:666–667.

[6] Costa Rica Office of Statistics and Census. San José, 1992. In Spanish.

[7] Costa Rica, National Survey of Reproductive Health, Preliminary Report. Program of Reproductive Health, 1993. In Spanish.

International Journal of Gynecology and Obstetrics 83 Suppl. 2 (2003) S147–S159

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Quinacrine Sterilization (QS): Informed Consent[1]

Informed Consent Working Group

Abstract

Informed consent is a basic human right for any medical procedure. It is particularly important that women know what is involved in any sterilization method, and how it will affect their health and their emotional life. Over 140,000 QS procedures have been performed in 34 countries. In no country has there been any formal effort to advance the acceptance of this method. Instead, satisfied users have been the promoters. Thoroughly informed consent is vital to patient satisfaction. A working group undertook an initiative to create an ideal consent form. The product of that initiative is presented.

Keywords: Quinacrine sterilization, female sterilization, non-surgical sterilization

1. Introduction

An informed consent is a fundamental human right for any medical procedure. It is critical for an elective procedure, particularly a permanent one like sterilization. Detailed knowledge of every aspect of a method on which a woman bases her decision is essential to her ultimate peace of mind.

Quinacrine sterilization (QS) providers have an additional reason to be deeply concerned, because success of their program depends on patient satisfaction. More than 140,000 women in 34 countries have chosen QS. Nowhere have practitioners made a formal effort to advance its acceptance. Instead, contented users themselves have been the promoters of this method. Thoroughly informed consent is vital to patient satisfaction. These women have been happy with the service they received and the results of their QS procedure. They recommend it to others because of their own experience.

One of the lessons learned in family planning over the past 40 years is that women who find fault with a contraceptive method can seriously undermine its acceptance, especially in regard to sterilization, because of its permanence. We have learned that incentives for sterilization usually lead to an increasing number of women (or men) in the population who are unhappy to have elected such a procedure. They have been tempted into choosing sterilization, before they were ready for it, by the incentive payment. They then become increasingly regretful of their decision, which had been made prematurely. They often complain bitterly about their sterilization and attribute any number of maladies to it. In their misery, they concoct rumors, which they spread abroad. Eventually, they go out of their way to discourage others from seeking sterilization.

The same applies to women who have second thoughts about their sterilizations because they lacked a

* Correspondence:
E-mail address: editor@quinacrine.com

[1] Note to Readers: This questionnaire had more than 30 authors. It is the product of an initiative to create the best possible consent form for quinacrine sterilization (QS). From the beginning, the goal of the designers of this document has been to do our best to insure that women are so well informed about the procedure and its sequelae that they will be content with their decision whether or not to undergo QS. One contributor to developing this consent form was the late Dr. Michael Burnhill, Vice President for Medical Affairs, Planned Parenthood Federation of America. He played a key role in advancing the acceptance of QS in the United States and bringing this method to American women and consequently to women everywhere. This article is dedicated to Dr. Burnhill.

0020-7292/03/$ – see front matter
PII: S0020-7292(03) 00000-0

complete understanding of the procedure and the risks. You can count on them to frustrate your efforts to offer a QS program. The most effective way to minimize this trend is to insure that your patients are well informed. These satisfied QS users not only present the method in a positive way to others who may then seek it, but they also constitute a pool of accurate first-hand QS information in the community.

Well-informed women are more apt to comply with the protocol. They are more likely to use the necessary alternative contraception for 3 months following the first insertion and return to the clinic for a second one, without a pregnancy intervening between the first and second quinacrine insertion. Thus, failure of the QS procedure will be reduced. In the long run, program success depends on thorough informed consent. The more people who have reliable facts about the method, the greater the demand will be for QS services. Experience with QS in country after country has shown that satisfied QS users are sufficient for program success. No other promotion is needed.

Toward this end, a working group of more than 30 people undertook an initiative to create an ideal consent form. The product of that initiative follows. We realize that local conditions may necessitate alterations in the ideal informed consent procedure but every effort should be made to maximize understanding of the QS procedures. To facilitate alterations, this document is available in an electronic form and can be easily modified to meet local needs.

Quinacrine Non-Surgical Female Sterilization (QS)

Introduction and Summary

You are considering a very serious decision.
Please read and consider everything you have been given.
Ask questions.
Take your time.

HOW DOES TUBAL STERILIZATION OCCUR?

One kind of sterilization occurs when there is no way for the egg and the sperm to meet. This happens when the Fallopian tube between the ovary and the uterus becomes blocked. Although there can continue to be normal ovulation, the egg cannot pass through the tube and cannot meet a sperm. Occasionally this blockage happens after an infection causing unwanted infertility. It also happens intentionally when the tubes are cut during surgical sterilization.

WHAT IS QUINACRINE?

Quinacrine is also known as Atabrine or Mepacrine.

It was first introduced in the 1930s to be taken by mouth to prevent and treat malaria. Since then, doctors all over the world have prescribed it for millions of people to treat and prevent malaria. It is also used to treat giardiasis, lupus, tapeworm and other medical conditions.

It is the only drug in the United States approved by the FDA (Food and Drug Administration) to treat giardiasis.

There has been a great deal of research on oral quinacrine over the past 65 years. Oral use of quinacrine is safe, especially in doses under 3000 mg per month. Millions of Americans have taken as much as 36,500 to 52,000 milligrams of it by mouth each year. In some cases they have done so for years to prevent malaria, with few lasting side effects.

WHAT IS QUINACRINE STERILIZATION (QS)?

QS is a non-surgical sterilization procedure for women. It cannot be reversed. Do ***not*** agree to have this procedure done if you may want more children. On the other hand, although the QS method is intended to prevent pregnancies permanently, it can sometimes fail and you could become pregnant.

Permanent sterilization results when pellets of quinacrine are put into the uterus (womb). The pellets dissolve and some of the liquid makes its way into the Fallopian tubes. The action of the Quinacrine that reaches the Fallopian tube causes scar tissue, which blocks the tube.

The QS method requires two doses about 1 month apart of 252 milligrams of quinacrine to be inserted into the uterus.

WHAT IS THE HISTORY OF QS?

The QS method was first developed in Chile in 1977. Since then, over 130,000 women in 34 countries have undergone the procedure.

Even though quinacrine is an FDA approved drug for giardiasis, the FDA has not approved its use for female sterilization. Using quinacrine for this purpose is considered an "off-label" use. Off-label use of drugs is legal, acceptable, and common practice by providers. For example, treating lupus with quinacrine is an off-label use. The United States Pharmacopeia, a national text, lists female sterilization as a use of quinacrine.

WHAT HAPPENS DURING THE QS PROCEDURE?

QUINACRINE INSERTION

The quinacrine may only be inserted into your uterus between the 6th and 12th day of your period (beginning with the first day of your menstrual period). This reduces the risk that you may be pregnant and not know it. It is also that part of the cycle when the height of the endometrium, which may interfere with the action of the quinacrine, is the lowest.

Before insertion, your clinician will perform a pelvic examination. Its purpose is to determine the size, shape, and position of the uterus and to be sure that there are no contraindications. An instrument called a speculum will hold your vagina open so that the cervix (the entrance to the uterus) can be seen. You will probably feel pressure from the speculum throughout the insertion procedure.

The cervix is then cleaned with an antiseptic solution and an instrument called a tenaculum is attached to it. This instrument helps hold the uterus steady during insertion. You may feel pain or a pinching sensation as the tenaculum is attached. Then the clinician will guide a narrow instrument called a sound through the opening of the cervix into the uterus. The sound measures the depth and position of the uterus. Some women feel cramping similar to menstrual cramps as the sound is inserted and withdrawn.

Then the clinician will guide the inserter containing the quinacrine pellets through the vagina and the cervix into the uterus. The pellets are placed inside at the top of the uterus.

During insertion, you may have some pain or cramping. Occasionally, some patients feel nauseated, weak or faint. After the inserter is removed from the cervical opening, the tenaculum and speculum will then be removed. Following the insertion, you should remain lying down quietly for a while and rise slowly to avoid the possibility of fainting.

FOLLOW-UP PROCEDURES

For one or two days after insertion you will likely have a discharge that is yellow or green and itching may follow. Itching can be prevented by douching as soon as you see the yellow discharge.

You will have a follow-up appointment in a week.

If you have any event that worries you, you should feel free to call us.

REPEAT OF PROCEDURES

The insertion process will need to be repeated in one month.

Occasionally, for special reasons it may be necessary to repeat the insertion a third time.

There is currently no reliable test to learn if the blockage is complete. There is one test called a hysterosalpingogram (HSG), an x-ray with instillation of a dye under pressure, but when it is used, it can reduce the effectiveness of QS.

CONTRACEPTIVE BACKUP METHODS

Another contraceptive method should be used starting the day of the first insertion and continuing for two months after the second insertion or third if needed. In other words, it should be used for a total of at least 12 weeks. This ensures that during the period when the plug of scar tissue is forming, the chances of pregnancy will remain low. If you have already been using a contraceptive method that you are comfortable with before you had your QS, you should keep using it for the required time.

HOW EFFECTIVE IS THE QS METHOD?

QS is not as effective in the first year as surgical sterilization or as some temporary methods such as an IUD, the Pill (when used correctly), Norplant® and Depo-Provera®.

QS is more effective than some well known birth control methods such as condoms, the diaphragm or spermicides (used alone).

Early studies reported that 9 out of 100 women who had QS, became pregnant: 3 in year 1; 2 more in years 2 to 5; and 4 more in the next 5 years. Changes in the insertion procedure have improved effectiveness.

To see how the failure rate of QS compares with all methods of birth control during the first year of use, see Table 1. A failure means that the woman has become pregnant in spite of using a particular method. Failures continue to occasionally occur throughout a woman's reproductive years with QS because the body never stops striving to repair itself, just as we see in women who have been surgically sterilized. With surgery, about two women out of 100 will become pregnant in the first 10 years.

Table 1 *Typical Failure Rates for All Methods during the First Year of Use*

Oral Contraceptives	less than 5%
ParaGard® T 380A (IUD)	less than 1%
Diaphragm + Spermicide	18%
Vaginal Sponge	18% to 28%
Condom alone	12%
Periodic abstinence	20%
Norplant®	less than 1%
Injections	less than 1%
Surgical Sterilization	less than 1%
QS	1% to 2%
No Method	85%

WHAT ARE THE PERMANENT STERILIZATION CHOICES?

SURGICAL STERILIZATION

The most common method is surgical sterilization. In terms of safety, quinacrine sterilization is safer.

QUINACRINE STERILIZATION

In over 130,000 sterilizations, no deaths have been reported, unlike surgical sterilization, "tying the tubes," which requires surgery. In industrialized countries, the death rate for surgical sterilization is three to ten per 100,000 women. In less developed countries, the death rate for surgical sterilization can be as high as 20 per 100,000 women. QS also has fewer serious complications that require hospitalization than surgical sterilization. The QS rate is 0.03% compared to 1.7% for laparoscopic sterilization. The risks of complications with the surgical method are even greater for women with certain health problems such as respiratory disease, diabetes and obesity, or if they have had abdominal or pelvic surgery.

It is also much less risky to have a QS than to become pregnant, carry a child to full term and give birth.

OTHER

There are a few other experimental methods. The safety and the effectiveness of these methods are not yet established.

WHAT ARE THE RISKS AND DISCOMFORTS TO BE CONSIDERED?

Death

In over 130,000 Quinacrine sterilizations, no deaths have been reported.

Surgical sterilization (tying the tubes) requires surgery and anesthesia. In industrialized countries, the death rate for surgical sterilization is 3 to 10 for 100,000 women. In less developed countries, the death rate for surgical sterilization can be as high as 20 per 100,000 women.

It is also much less risky to have a QS than to become pregnant, carry a child to full term and give birth.

Available data from numerous sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death include the combined risk of the contraceptive method plus the risk of pregnancy or abortion in the event of method failure.

Table 2 *Annual number of birth-related or method-related deaths associated with control of fertility per 100,000 non-sterile women, by fertility control method, according to age.*

Age	15-19	20-24	25-29	30-34	35-39	40-44
Method of control and outcome						
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives,, nonsmokers**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives,, smokers**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6
Surgical female sterilization**	2.0	2.0	2.0	2.0	2.0	2.0
Surgical male sterilization**	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
QS**	**<1.0**	**<1.0**	**<1.0**	**<1.0**	**<1.0**	**<1.0**

* Deaths are birth related only

** Deaths are method related or birth related

Potential for Regret

Some women regret getting sterilized. This regret is almost always due to changing circumstances, usually divorce or remarriage. QS is not reversible. If you believe there is any chance that you may regret your decision, QS might not be your best option. A temporary method would be more appropriate for you. Before agreeing to be sterilized you should be comfortable with your decision. Ask yourself these questions.

- Am I sure that I never want any more children?
- What action would I take if I found myself pregnant?
- Would temporary methods or a surgical sterilization be better for me?
- Is my family or a clinician or anyone else pressuring me to get sterilized?
- Why am I choosing QS?

Ectopic Pregnancy

An ectopic pregnancy is one in which the fertilized egg implants in the tube or on the ovary instead of the uterus. As the tube will not grow, this is extremely dangerous.

Ectopic pregnancies also occur in women who have not been sterilized. Although QS (and surgical sterilization) prevents many ectopic pregnancies, a greater percentage of the pregnancies that do occur after sterilization failure are ectopic.

If you have ever had an ectopic pregnancy, you have an increased risk of having another one. You also have an increased risk of an ectopic pregnancy if you have ever had certain types of infections. These infections include pelvic inflammatory disease (PID) or any venereal disease (VD) or sexually transmitted disease (STD) caused by, for example, gonorrhea or chlamydia.

Ectopic pregnancy can cause death, so it is very important to know the symptoms!

They are:

- Vaginal bleeding
- Lower abdominal pain
- A missed period
- Dizziness
- Weakness
- Fainting
- Shoulder pain

If you have any of these symptoms or suspect that you may be pregnant because of a missed period you must immediately contact your doctor or nurse and go to a hospital or clinic to find out if it is an ectopic pregnancy. Ectopic pregnancy may require surgery to save your life. Ectopic pregnancies are also treated medically.

Serious problems requiring hospitalization

QS also has fewer serious complications that require hospitalization than surgical sterilization. The QS rate is 0.03% (3 per 10,000) compared to 1.7% (1.7 per 100) for laparoscopic sterilization. The risks of complications with the surgical method are even greater for women with certain health problems such as respiratory disease, diabetes, and obesity, or if they have had abdominal or pelvic surgery.

Birth Defects

In over 130,000 QS sterilizations, no birth defects have been reported in any infant exposed to quinacrine in early pregnancy -- that is, when a woman was not aware that she was pregnant at the time of quinacrine insertion or when she became pregnant in the weeks following quinacrine insertion.

Potential Risk of Cancer

QS researchers believe that if there is any risk of cancer with QS, that risk is very small. Quinacrine has been taken orally by more than 100 million people during its first 65 years of use, always in larger doses than for QS. There was never any mention that this drug might cause cancer because clinical experience did not indicate any link. No cancer clusters were ever reported in this vast human experience. One QS study in Chile that has followed 1500 women for 19 years, has found no increase in the risk of cancer.

Severe Allergic Reaction to Quinacrine

Severe allergic reactions that could be life threatening are known to occur occasionally with every drug used by humans. Quinacrine is no exception.

Thus far, two severe allergic reactions with QS have been reported, or one per 50,000 cases. Both women had the allergic

response within an hour of use and fully recovered within a few hours.

Uterine Perforation

Uterine perforation occurs once every 1000 to 1500 cases. Partial or total perforation through the wall of the uterus may occur as the quinacrine is put in the abdominal cavity. Perforation could result in abdominal adhesions (scars), severe pain, and loss of contraceptive protection. Perforation and its complications may require surgery and, in very rare cases, could possibly result in serious illness or death. No deaths have ever been reported with QS. Nor has any QS complication ever required abdominal surgery in over 130,000 documented cases.

Side Effects

Side effects are those temporary and expected problems that accompany a treatment. Their severity ranges from almost nothing to severe, and they are not predictable.

Side effects in QS are common but they are usually minor, temporary and easily managed. It is extremely important that you know about these possible side effects before you decide to have the procedure, so you will know what to expect.

If any of these side effects bother you after QS is administered, you should contact your health care provider for treatment.

The following may occur during the insertion of the quinacrine and shortly afterwards.

- Pain, usually uterine cramps, low backache, headache, dizziness, vaginal itching or irritation and fever may occur at the time of insertion or shortly afterwards and may persist. If pain is severe, becomes worse, or persists, contact your clinician. Pain during sex is a rare side effect that disappears within a few months. Pain during urination is also rarely reported and disappears without treatment.
- Dizziness or fainting may occur at the time of insertion.
- A small amount of bleeding occurs following insertion in some women. If the amount of blood is more than 4 milliliters (about a teaspoon), the insertion may need to be repeated in the next cycle as an additional insertion.
- Bleeding between menstrual periods may occur during the first two or three months after insertion. The first few menstrual periods after insertion may be heavier and longer than usual or they may be lighter and shorter. Some women will miss their period for as much as several months after the first insertion. If these conditions continue for longer than two or three months, consult your clinician.
- Occasionally, you may miss a menstrual period while using QS. It is important to determine if you are pregnant; report this immediately to your clinician.
- You will experience a bright yellow discharge from the vagina during the first 24 hours following insertion. The bright yellow color comes from the quinacrine itself. This side effect is harmless but will stain clothing and bedding, as quinacrine is also a dye. This may cause itching which is relieved or prevented by douching.
- Abdominal adhesions (scar tissue)
- Backache
- Cervical infection
- Miscarriage
- Pelvic infection (PID), which may result in surgical removal of your reproductive organs, including hysterectomy
- Hematometra, accumulation of menstrual blood in the womb, an easily-treated condition

WHAT SHOULD YOU LET THE CLINICIAN KNOW?

The clinician needs the truth. You will be interviewed and a checklist will be used for all of these points.

Contraindications

There are 12 conditions that will prevent or delay your QS procedure. In some cases you can be treated for the condition and have the QS later.

- Pregnancy. You must be absolutely certain that you are not pregnant before QS can be performed. If there is any reason to suspect pregnancy, you will need a pregnancy test first.
- Infection - uterine or cervical
- Unexplained vaginal bleeding
- Tumor in the reproductive tract (fibroid, etc.)
- Severe uterine distortion (bicornate uterus, etc) that will not allow proper placement of the pellets
- Active pelvic inflammatory disease (PID)
- Psoriasis. Quinacrine may cause a severe attack of psoriasis
- Porphyria. Quinacrine may cause this condition to worsen
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Use of alcohol or alcohol-containing medications within 24 hours before the procedure and 24 hours after
- Use of primaquine
- Use of hepatotoxic (liver damaging) drugs

Information

There are many other conditions that the clinician should know about in order to better understand your health.

- Heart disease
- Heart murmur
- Hepatitis or severe liver disease
- Diabetes
- Leukemia
- Fainting spells
- Steroid therapy
  Anemia or blood clotting problems
- Current suspected or possible pregnancy
- Ectopic pregnancy (pregnancy outside of the uterus)
- Recent pregnancy
- Abnormalities of the uterus
- Bleeding between periods
- Cancer of the uterus (womb) or cervix
- Suspicious or abnormal Pap smear
- IUD in place now
- Heavy menstrual flow
- Severe menstrual cramps
- Multiple sexual partners
- A sexual partner who has multiple sexual partners, or is at high risk for acquiring HIV
- Pelvic infection (including pus in Fallopian tubes)
- Infection of the uterus (womb) or cervix
- Genital sores or lesions
- Sexually transmitted disease (venereal disease), such as herpes, gonorrhea, chlamydia, or acquired immune deficiency syndrome (AIDS)
- Unexplained genital bleeding
- Uterine or pelvic surgery
- Vaginal discharge or infection
- I.V. drug abuse
- Alcoholism

A COMPARISON OF THE ADVANTAGES AND DISADVANTAGES

This is a list made up by someone else. You may have your own considerations to add to this list.

Advantages

- Less risky than surgical sterilization. No deaths or life-threatening complications have been reported in over 130,000 cases. With surgery, 3 to 10 deaths per 100,000 procedures have been recorded. No surgery means less risk of infection, injury and death.
- QS is an outpatient procedure. No hospitalization is needed. Usually you can leave the clinic or office in about an hour after the pellets are inserted.
- No general anesthetic.
- Less pain than with surgery.
- Recovery is faster.
- Many types of trained health care practitioners, not just doctors, can provide this method.
- It is the least expensive contraceptive method – 1/10th the cost of surgical sterilization.
- It is permanent after the insertions are complete.
- There is no visible scar.
- It does not change the user's sex drive or interfere with her ability to feel sexual pleasure.
- No ongoing use of hormones is required.

Disadvantages

- It is not reversible, which means that a woman cannot expect or hope to undergo another procedure that would make her fertile again.
- Nearly half of all women having this procedure complain of a side effect. The most common are lower abdominal pain, headache, dizziness and backache. Sometimes users experience mild fever or vaginal itching. These symptoms usually stop a few hours or days after the treatment. Also, menstrual periods may be irregular for a few months after quinacrine sterilization.
- Some patients report a yellow vaginal discharge for up to 24 hours. This is not a sign of infection. It is due to the yellow color of the quinacrine, which is a brilliant yellow dye. It will stain clothing and bedding. Feminine protection should be used to prevent this staining. Douching helps.
- Quinacrine sterilization is still new at least in the United States; there may be risks that are not yet known. Only one study has tried to establish long term risks. For up to 19 years, it followed 1500 women who had had QS. There was no increase in the incidence of cancer. No long term risks have been identified.
- Life-threatening complications of QS are very rare. However, this does not mean that you will not experience a life-threatening complication. In such a case, it is possible that you would have to undergo major surgery for some unforeseen reason, which could place you at risk of death.
- QS requires 2 and possibly 3 insertions one month apart.
- The failure (pregnancy) rate has been variously reported between 1% to 2% at the 2-year mark.
- You may become pregnant in a tube (ectopic pregnancy). This condition has also been reported for women who are using no contraceptive method, or using temporary methods, and in those women who have been sterilized surgically or with the quinacrine method.
- Does not protect against AIDS or other sexually transmitted diseases.

WARNINGS

Call your clinician immediately for any of the following reasons:

- A missed period. You may be pregnant.
- Unexplained or abnormal vaginal bleeding or discharge. This could indicate a serious complication, such as an infection or ectopic pregnancy.
- A delayed period followed by scanty or irregular bleeding. You may have an ectopic pregnancy.
- Pelvic or lower abdominal pain or cramps or unexplained fever. An ectopic pregnancy or infection may have developed, requiring immediate treatment.
- Exposure to venereal disease (VD) also called sexually transmitted disease (STD).
- *QS does not prevent venereal disease.* If exposure to venereal disease is suspected, call for examination and prompt treatment. Failure to do so could result in serious pelvic infection. **QS does not protect against diseases transmitted sexually such as HIV (AIDS), chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B and syphilis.**
- If your relationship ceases to be mutually monogamous or if your partner becomes HIV positive or gets a sexually transmitted disease, you should report this change to your clinician immediately. It is advisable to use a condom as a partial protection against STDs.
- Genital sores or lesions, or fever with vaginal discharge. You may have an infection.
- Severe or prolonged menstrual bleeding.

Glossary

Adhesions – Scarring within a body cavity or between organs in the abdominal cavity

Cervicitis – Infection of the cervix.

Cervix – Lower portion of the uterus visible in the vagina

Contraceptive – Means of preventing conception

Ectopic or tubal pregnancy – Pregnancy outside of the uterus

Endometrium – Lining of the uterus. The endometrium is shed every month and expelled during the menstrual period.

Fallopian tubes – Tubes through which the egg passes from the ovary to the uterus

Fertilization – The process of the sperm penetrating the egg of the female

G6PD – Glucose 6 phosphate dehydrogenase. A metabolic disorder in which quinacrine is contraindicated

Genital – Referring to organs concerned with reproduction

Giardiasis – An intestinal infection caused by a protozoan parasite

HIV – Human Immunodeficiency virus that causes AIDS

Infection – Invasion of the body by microscopic (tiny) organisms, such as bacteria. Can cause illness.

Intermenstrual Bleeding – Bleeding between periods

Intrauterine – Within the uterus

Menstruation – A woman's monthly period.

Monogamous – Practicing sexual relations with only one partner

Mutagenic – The ability to cause genes to mutate (change)

Off-label use – When a doctor prescribes a drug for a treatment that is not indicated on the drug's package insert (or label). Any drug that is FDA approved can legally be used in this way. Approximately 60% of all prescriptions are for off-label uses

Ovary – Almond-shaped organ. One ovary is located on each side of the uterus. Produces and releases human eggs

Ovulation – Release of an egg by the ovary

Porphyria – A metabolic disorder

QS (Quinacrine pellet method for non-surgical female sterilization) – Name for the quinacrine sterilization procedure

Quinacrine (Atabrine) – A synthetic anti-protozoal drug. Originally used to treat malaria. When placed in the uterus, it can prevent pregnancy by scarring the Fallopian tubes

STD – Sexually transmitted disease - also called VD or venereal disease

Spermicide – Chemical that kills male reproductive cells (sperm)

Uterine Perforation – A tear, hole or puncture of the uterus

Uterus (womb) – Pear-shaped organ located deep in the pelvis that contains and nourishes a fetus during pregnancy

CONSENT TO HAVE QUINACRINE STERILIZATION

You have come to this clinic seeking information about permanent methods of contraception. You were given information about temporary methods of birth control and two methods of permanent sterilization: surgical and QS. You have had time to read and view the information. You read or viewed:

_____ QS brochure _____ QS video

_____ QS information sheet _____

There are some basic points you must understand before agreeing:

- Being sterilized is an irreversible choice. If you have any hesitation about wanting children at all you should not do this.
- It is not 100% effective. A pregnancy could be dangerous and you may be advised to have an abortion. If you are opposed to abortion, now is the time to think about this.
- Being sterilized does not protect you from sexually transmitted diseases, including Acquired Immune Deficiency Disease (AIDS), gonorrhea, chlamydia, syphilis and others.
- The FDA has not approved this use of quinacrine for female sterilization. It is however, a legal use of the drug.
- There is no money available from any source, including from the doctors or the clinic, to cover the cost of treating any complications or for any additional costs resulting from the quinacrine sterilization method.
- There is no penalty for saying no at this point. You will still be treated in this clinic and receive its services. You may drop out of this program at any time and dropping out will not affect your receiving medical care now or in the future.

You may sign this form only if the following points are totally true.

- No one has forced or pressured me to undergo this procedure. I am making this choice freely.
- I feel comfortable that the information I have at this point about the risks, benefits and alternatives is sufficient for me to choose this method.
- I have had the opportunity to ask questions and all of my questions have been answered to my satisfaction.
- I have answered all of the clinician's questions truthfully, and as completely, and accurately as I can.

After reading the material checked above or viewing the video I, choose to be permanently sterilized by the quinacrine sterilization method.

	Signature	Printed Name	Date
Patient	_____	_____	_____
Witness 1	_____	_____	_____
Witness 2	_____	_____	_____

Section 3: Human Studies (1970 - 2002)

ELSEVIER

Contraception

Contraception 64 (2001) 281-286
Original research article

Quinacrine non-surgical female sterilization in Bangladesh

Syeda Nurjahan Bhuiyan*, Rokeya Begum

Department of Obstetrics and Gynecology, Chittagong Medical College, Chittagong, Bangladesh

Abstract

This study was undertaken to evaluate the efficacy, safety, and acceptability of transcervical applications of quinacrine along with other adjuvants, such as ampicillin and ibuprofen, for sterilization. The cohort consisted of 750 normal women who requested sterilization and volunteered for this method at the family planning clinic of a tertiary hospital and community clinics in Chittagong, Bangladesh.

Several different protocols were followed from October 1989 to April 1999. Each woman received one or two insertions of 180 mg or 252 mg quinacrine with or without adjuvants including 55.5 mg ibuprofen or 125 mg ampicillin. Supplementary contraception was given in the form of combined oral contraceptive pills, barrier methods, or injection of depot medroxyprogesterone acetate for 3 months. Details of each protocol are described in the text.

The gross pregnancy failure rate for insertion of 180 mg in 590 women was 3.9% compared to 1.9% for the 160 who received 252 mg. There were no serious complications, and side effects were transient. We conclude that quinacrine non-surgical sterilization is a safe, acceptably effective method when two insertions of 252 mg quinacrine with medroxyprogesterone injection as a supplement is used.

Keywords: Quinacrine sterilization; Female sterilization; Quinacrine

1. Introduction

Bangladesh has a population of 120 million, growing by 2.2% annually, with a per capita income of less than US $310 [1]. Fertility has been declining because of an increased use of modern contraception, which has reached 50% of married women today. Nevertheless, about one third of pregnancies are reported as unplanned [2]. This is partly the consequence of irregular use of the oral pill, which accounts for 20.8% of contraceptive users. Female sterilization prevalence is 7.6% and has recently declined even further [2], no doubt due to lack of trained physicians and surgical facilities in predominantly rural areas of Bangladesh. A simple, non-surgical sterilization method is needed to fulfill unmet contraceptive demand.

In 1970, Zipper and his coworkers began to experiment with quinacrine and other drugs with scarring properties as an alternative to surgical sterilization. Among them, transcervical application of quinacrine pellets produced the best result [3] Quinacrine was originally introduced in 1931 to prevent and cure malaria. Today, it continues to be prescribed for giardiasis and lupus erythematosus. This drug has sclerosant properties for some tissues and has been used for the management of recurrent pleural effusion. Controversy concerning its use for sterilization has been reviewed by Benagiano [4]

Quinacrine pellets for sterilization are introduced transcervically to the uterine fundus via a modified copper-T intrauterine device (IUD) inserter during the proliferative phase of the menstrual cycle. The procedure is similar to an IUD insertion and requires comparable technical skill. The pellets dissolve in uterine fluid within 30 min, and some flows into the proximal tubes. Quinacrine produces an aseptic inflammation and fibrosis of the intramural segment of fallopian tubes leading to occlusion of the lumen. Scarring requires 6-12 weeks [5] Women are counseled to use a backup method of contraception for that period. We initiated use of quinacrine in our centers in Bangladesh to determine whether this method is an appropriate technology for our needs by assessing safety factors, efficacy, method acceptance, cost-effectiveness, and ease of delivery in a rural-based community.

2. Patients and methods

Clinical trials of quinacrine sterilization (QS) were started in October 1989. Initial encouraging results led to an

* Corresponding author. Tel.: +880-31-610064; fax: +880-31-681392.

E-mail address: unigmt@ctg.dolphi.net (S.N. Bhuiyan).

0010-7824/01/$ - see front matter
PII: S0010-7824(01)00263-3

Table 1
Age distribution among 750 QS acceptors

Age (years)	Number	Percent
<25	19	2.5
26-30	182	24.3
31-40	460	61.3
>40	89	11.9

Table 3
Educational status among 750 QS acceptors

Level of education	Number	Percent
Illiterate	304	40 5
Primary	252	33 6
Secondary	141	18.8
Higher secondary	36	4.8
Graduation and above	17	2.3

expanded trial involving 750 women who requested sterilization and volunteered for this method. Trials were carried out in the family planning clinic of a tertiary hospital and in two community clinics in Chittagong, a major port city of Bangladesh. Participants were selected on the basis of national criteria for surgical sterilization, such as the woman's age being no less than 30 years and that she have no fewer than two living children, the youngest being at least 1 year old. Younger women of high parity were also accepted.

All the women were sexually active. They received quinacrine in the proliferative phase of the menstrual cycle (eighth to twelfth day) at least 6 weeks after termination of a pregnancy. Before admission to the study, the risks and benefits of the method and details of the procedure were carefully explained to those who chose this option. They then signed an informed consent form that acknowledged its permanent character as well as the candidate's preference for this method over others that were available.

The client's history was taken. She was then given a careful physical examination to rule out any uterine abnormality or pregnancy. Doctors trained in the copper-T IUD insertion technique carried out the procedure. Quinacrine pellets were introduced with a cold sterilized copper-T IUD inserter that had been air-dried after a spirit wash. The pellets were kept clean but not sterilized because quinacrine is known to be bactericidal, fungicidal, and antiviral [6] A vaginal speculum was used to expose the cervix. The anterior lip was held with volsellum forceps. The utero-cervical length was measured with a uterine sound. The loaded inserter was gently introduced up to the uterine fundus It was then withdrawn 5 mm and, while holding the outer sheath steady, the plunger was advanced to release all the pellets at the fundus

Additional contraceptives, such as condom, combined oral contraceptive pill, or injection of depot medroxyprogesterone acetate (Depo Provera, Upjohn, Kalamazoo), were prescribed for 3 months after quinacrine insertion. A follow-up schedule at 3, 6, and 12 months and yearly intervals thereafter was established. The clients were asked to report accordingly and in-between if necessary.

In an attempt to increase the efficacy of QS, several different protocols were tried as follows:

1. Quinacrine (252 mg) for two insertions plus a combined oral contraceptive pill for 40 women, from October 22, 1989 to May 19, 1991.
2 Quinacrine (180 mg) plus ibuprofen (55.5 mg) for two insertions plus a combined oral contraceptive pill for 110 women, from May 20, 1991 to December 19, 1991.
3 Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for two insertions plus a combined oral contraceptive pill for 215 women, from December 22, 1991 to December 8, 1993.
4 Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for one insertion plus a combined oral contraceptive pill for 228 women, from January 1, 1994 to October 2, 1996.
5 Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for two insertions plus injection of 150 mg Depo Provera [intramuscular (im)] for 37 women, from March 15, 1997 to April 9, 1997.
6 Quinacrine (252 mg) for two insertions plus injection of 150 mg Depo Provera (im) for 120 women, from April 9, 1997 to December 31, 1998.

Ibuprofen was used as an adjuvant when suggested by colleagues in Chile [7] A small, randomized trial showed ampicillin to improve efficacy (B. Mullick, personal communication, 1991). The adjuvants such as ibuprofen and ampicillin were administered in an intrauterine fashion along with quinacrine.

Table 2
Distribution of 750 QS acceptors according to living children

Living children	Number	Percent
2	28	3.7
3	139	18.5
4	238	31.x
≥5	345	46.0

Table 4
Socioeconomic status of 750 QS acceptors

Income in US$ per month	Number	Percent
<20	136	18.2
20-40	218	28.9
41-60	188	25.1
>60	208	27 8

Table 5
Distribution of 750 QS acceptors by method of contraception before sterilization

Method used	Number	Percent
IUD	105	14.0
Pill	291	38.8
Condom	55	7.3
Injection	48	6 4
Safe period	22	2.9
Failed surgical sterilization	3	0 4
None	226	30.1

3. Results

Of the 750 women who volunteered for this procedure, **182 (24.3%)** were 26-30 years of age, 460 (61.3%) were **31-40** years old, and 89 (11.9%) were over 40. Only 19 (3.3%) of the women who received quinacrine were younger than 25 years (Table 1). Twenty-eight (3.7%) of them had two living children, 139 (18.5%) had three, and 583 (77.7%) had four or more (Table 2). Among quinacrine acceptors, 304 (40.6%) were illiterate. Of the remaining educated women, 17 (2.3%) were graduates of higher secondary schools or above (Table 3). QS acceptors were mainly lower income people (72.1%) who earned less than US $60 per month (Table 4).

Previous contraceptive users (524) accepted quinacrine more often than did non-users (226) (Table 5). Interval QS (70.3%) was more common than post menstrual regulation (26%) and postnatal cases (3.7%; Table 6). Women were lost to follow-up after quinacrine insertion in 396 (52.8%) cases, and the rest were followed through April 1999. The main side effects were lower abdominal pain (1.9%) and vaginal discharge (2.5%). These symptoms lasted a few hours to a few days. No changes in menstrual flow were reported by 95% of the women, 0.9% reported an increase in menstrual flow, 0.9% experienced spotting, and 3.2% of the cases were amenorrheic. Amenorrhea lasted not more than 6 months and required no treatment (Table 7). No uterine perforation, major complications, or deaths occurred in this study. There were 26 intrauterine pregnancies but no extrauterine ones (crude pregnancy failure = 3.4%). Pregnancy failures by protocol is shown in Table 8. Among all failure cases, conceptions in 21 cases were aborted by menstrual regulation. The rest of the pregnancies were carried to term. All these babies were examined at birth, and no malformations were noted.

Table 6
Time of insertion for 750 QS acceptors

Time	Number	Percent
After menstrual regulation	195	26 0
Interval	527	70.3
Postnatal	28	3.7

Table 7
Side effects/complications for 750 QS acceptors

Side effects/complications	Number	Percent
Menorrhagia	7	0 9
White vaginal discharge	19	2.5
Spotting	7	0 9
Secondary amenorrhea	24	3.2
Lower abdominal pain	14	1.9
Ectopic pregnancy	0	—
Fetal abnormality	0	—

Efficacy of quinacrine was not remarkably increased by decreasing the dose of quinacrine or with addition of adjuvants such as ibuprofen and ampicillin ($p > 0.5$; Tables 9 and 10). Pregnancy failure of quinacrine was not related to number of insertions, i.e., single versus twice in this series ($p > 0.5$; Table 11). Statistical analysis did not show any significant difference between use of additional contraceptives, such as combined oral pill, condom, or injectable contraception ($p > 0.1$; Table 12). Pregnancy failures occurred early after insertion and with the passage of time gradually declined (Fig. 1). Pregnancy failure for women younger than 35 years was higher than that for the women older than 35 (23 vs. 3).

4. Discussion

In daily life we are constantly required to make judgments based on a balance between the risks and benefits of our activities. This is especially true of medical decisions in both therapy and prevention Risks and benefits change over time for various local situations. A developing nation such

Table 8
Pregnancy failure among 750 QS acceptors by protocol

Protocol Type	Failures		
	Number	Number	Percent
1 Quinacrine (252 mg) for 2 insertions + oral pill	40	1	2.5
2 Quinacrine (180 mg) + ibuprofen (55 5 mg) for 2 insertions + oral pill	110	3	2.7
3 Quinacrine (180 mg) + ibuprofen (55 5 mg) + ampicillin (125 mg) for 2 insertions + oral pill	215	11	5.1
4 Quinacrine (180 mg) + ibuprofen (55 5 mg) + ampicillin (125 mg) for 1 insertion + oral pill	228	9	3.9
5 Quinacrine (180 mg) + ibuprofen (55.5 mg) + ampicillin (125 mg) for 2 insertions + injection medroxyprogesterone (150 mg)	37	(–)	0
6 Quinacrine (252 mg) for 2 insertions + injection medroxyprogesterone (150 ma)	120	2	1.7

Table 9
Effect of dose of quinacrine pellets on efficacy of sterilization of 522 QS acceptors having two insertions*

	Doses of quinacrine					
	180 mg		252 mg		Total	
	#	%	#	%	#	%
Success	567	96.1	157	98.8	724	96.7
Failure	23	3.9	3	1.3	26	3.3
Total	590	100.0	160	100.0	750	100.0

* Chi-square with Yates correction = 0 90, p > 0 5 (NS)

as Bangladesh, with low contraceptive use, high population growth, and high maternal mortality, benefits greatly from increased contraceptive use. Risks and benefits of QS were analyzed in the form of safety, efficacy, acceptability, ease of delivery, and possibility of cancer and birth defects.

4.1. Safety

Maternal mortality in Bangladesh is 4 per 1000 live births, and each additional sterilization is estimated on average to prevent two births [2] In this situation, each 1000 additional sterilizations using quinacrine would prevent eight maternal deaths. On the other hand, for an industrialized country with high contraceptive use, low population growth, and low maternal mortality, the benefits of QS are not as significant. The method is an outpatient procedure and does not need anesthesia, which, when used for surgical sterilization, can be associated with serious side effects and even death Studies of such surgery in developing countries report rates of 50-100 deaths per 100,000 procedures [8] In Bangladesh, 19 deaths per 100,000 surgical procedures have been documented [9], and in India it is 20 [10], compared to 3 in the United States [11]. There were no deaths in the present series, and no death has been reported for this method anywhere in the world [12] Serious complications are also rare. Their reported rate with laparoscopic sterilization is 1.7% [13], so in a series of this size, 13 serious complications would be expected. Side effects were mainly lower abdominal pain, oligomenorrhea, amenorrhea, discharge, and pruritus vulvae. All were transient and of short duration, as found by others [5,14].

4.2. Efficacy

Zipper and his co-workers have reported a pregnancy failure rate of 3.1 per 100 women at 1 year, using three insertions of 252 mg quinacrine pellets [15]. Other investigators have observed that two or three insertions have given similar results [14,161. Our crude pregnancy failure rate was 3.4%. Hieu and his co-workers noted great variation in efficacy among inserting clinicians and hypothesized that this was due to different insertion techniques [5] In the present series, insertion technique was uniform. The trial of Hieu et al. [5] showed improved efficacy by number of insertions, Our series shows only a moderate increase in failures for single compared to double insertion. Our failure to confirm efficacy reports of others may be due to our large lost-to-follow-up rate and to use of crude pregnancy rates, which is the main deficiency of the report since such rates do not distinguish between different durations of use Most study participants attended the tertiary hospital that draws patients from a wide rural area. As they know menstrual regulation is free at the center, failures are more likely to return for follow-up, which would distort life table rates. Sokal and his co-workers [17] have documented improved efficacy for women 35 years of age or older. This is similar to the present study. Merchant's study also revealed an expected direct relationship between quinacrine dose and efficacy [18], which our data support; however, higher doses extend tubal damage beyond the intramural segment. Dr. Ljiljana Randic has shown that addition of ibuprofen to quinacrine does not improve efficacy [19] In this series, the use of adjuvants along with low dose quinacrine (180 mg) did not improve the efficacy significantly ($p > 0.5$), and the data suggest ampicillin may increase failures. Failure rates of QS appeared to be higher in the early months of use. The pre-hysterectomy study of Merchant and her associates [18] shows that it takes 6 weeks for tubal closure to occur in a high proportion of cases. A randomized trial with and without an additional contraceptive has not yet been reported A standardized protocol recommends 3 months of additional

Table 10
Effect of 125 mg ampicillin on efficacy of QS cases with two insertions of 180 mg quinacrine plus 55 5 mg ibuprofen

	With ampicillin		Without ampicillin		Total	
	#	%	#	%	#	%
Success	231	95.5	107	97.3	238	96.0
Failure	11	4.5	3	2.1	14	4.0
Total	242	100.0	110	100.0	352	100.0

Table 11
Number of insertions in relation to success of sterilization for 750 QS acceptors*

	Number of insertions					
	Single		Two		Total	
	#	%	#	%	#	%
Success	219	96.1	505	46.8	724	96.5
Failure	9	3.9	17	3.2	26	3.5
Total	228	100.0	522	100.0	750	100.0

* Chi-square = 0 20, p > 0 5 (NS)

contraceptive from first insertion [20]. In this series Depo Provera showed superior efficacy over oral pill and condom, hut not to a significant level. Our recommendation is for use of medroxyprogesterone because of its assured effectiveness for 3 months.

Failure of surgical sterilization is frequently due to fistula formation [21], which does not occur with the quinacrine method [18] It appears that QS is an all or none response. If the drug reaches the tube, it nearly always results in closure, and most failures occur if it does not enter the tubal lumen. This could be because of tubal ostial spasm or a layer of endometrium covering the ostia. In this series, there was no report of ectopic pregnancy, a risk that is similar for surgical [22] and QS [5]

4.3. Acceptability

It is usual that a non-surgical method is more acceptable to women than one involving surgery In Bangladesh, where both procedures have been performed in the same settings and despite government financial incentive to opt for the surgery, more than 750 QSs have been carried out.

4.4. Ease of delivery

The pellets and inserters cost less than 25 cents (US) per sterilization, which is affordable to the world's poorest women if it is made accessible. This procedure can be done by anyone trained in IUD insertions. Expansion of the services can be very rapid in a rural-based community with an inadequate doctor to population ratio because the method requires no anesthesia, surgery, or hospitalization.

4.5. Birth defects

There is limited human experience reported to date for accidental quinacrine insertion in pregnancy. For a birth defect to occur with this method would require insertion of quinacrine during early pregnancy, a teratologic effect of quinacrine, and the pregnancy to be carried to term. An estimate of the probability of these events occurring together [23] suggests the risk of a birth defect is very low.

4.6. Cancer

Cancer risk was not evaluated in this study, but long-term follow-up of cases in Chile shows no increased risk of cancer [24]. Long-term use of this drug for malaria suppression has revealed no increased risk of any malignancy [25].

5. Conclusion

The plight of poor women worldwide who are desperate to feed their children is such that they desire nothing more than safe and effective methods to curtail an addition to their family. QS would satisfy such an unmet need for those who have reached their desired family size. The failure rate of this method is somewhat higher than that of surgical sterilization, but it is much safer. Long-term evaluations to date confirm that it is not hazardous to health. QS is a safe, effective method when two insertions of 252 mg quinacrine with Depo Provera (150 mg) as 3 months of supplementary contraception is used. It should be an option for a well-informed woman.

Table 12
Effect of supplementary contraception on efficacy of quinacrine sterilization for 750 acceptors*

	Type of contraceptive					
	Oral pill + condom		Injection		Total	
	#	%	#	%	#	%
Success	569	96 0	155	98.7	724	96.5
Failure	24	4 0	2	13	26	3.5
Total	593	100.0	1.57	100.0	750	loo 0

* Chi-square with Yates correction = 2.04. p > 0.10 (NS)

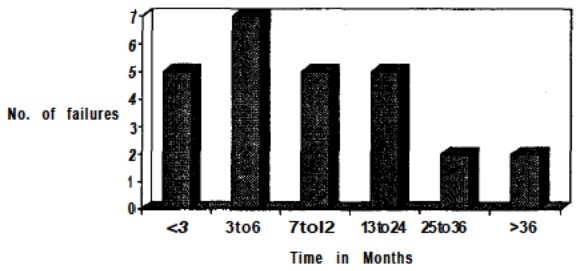


Fig 1. Pregnancy failures over time among 750 QS acceptors

Acknowledgments

Quinacrine and ibuprofen pellets were provided by the International Federation for Family Health.

References

[1] Bangladesh Bureau of Statistics Statistical pocketbook of Bangladesh 1996 Dhaka, 1997 p. 149

[2] Mitra SN, Ahmed AI-S Cross AR, Jamil K Bangladesh demographic and health survey, 1996-1997 Dhaka and Calverton Maryland: National Institute of Population Research and Training (NIPORT), Mitra and Associates and Macro International Inc, 1997

[3] Zipper J, Medel M Stachetti E, Pastene L, Rivera M, Prager R Chemical agents for transvaginal sterilization In: Richart RM, Prager DJ, editors Human sterilization Proceedings of the Conference Cherry Hill, New Jersey Springfield, Illinois: Charles C Thomas, 1972. p 339-52

[4] Benagiano G Non-surgical female sterilization with quinacrine: an update Contraception 2001;63:239-45

[5] Hieu DT, Tan TT Tan DN, Nguyet PT Than P, Vinh DQ 31,781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam Lancet 1993:342:213-27

[6] Ciak J, Hahu FE Quinacrine (Atabrine): mode of action Science 1967;156:655-6

[7] Trujillo V, Zipper J, Viel B, Rivera M Sterilisation feminine, non chirugicale avec l'emploi de quinacrine: efficacite de deux insertions de pellets de quinacrine Rev Fr Gynecol Obstet 1993;88:147-50

[S] Green CP Voluntary sterilization: world's leading contraceptive method Pop Reports 1978;March:M57

[9] Peterson HB, Lubell I, DeStefano F, Ory HW The safety and efficacy of tubal sterilization: an international overview Int J Gynecol Obstet 1983;21:139-44

[10] Bhatt RV Camp laparoscopic sterilisation deaths in Gujarat State, India, 1978-80 Asia Oceanic J Obstet Gynecol 1991;17:297-301

[1 I] Dorfman SF Death from ectopic pregnancy United States, 1979 to 1980 Obstet Gynecol 1983:62:334-8

[12] Kessel E 100,000 quinacrine sterilizations Adv Contracept 1996;12: 69-76.

[13] DeStefano F, Greenspan JR, Dicker RC, Peterson HB, Strauss LT, Rubin GL Complications of interval laparoscopic tubal sterilization Obstet Gynecol 1983;61:133-8

[14] Agoestina T, Kusuma I Clinical evaluation of quinacrine pellets for chemical female sterilization Adv Contracept 1992;8:141-51

[15] Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstt 1980;18:265-9

[16] Suhadi A, Anwar M Soejoenoes A Four-year clinical evaluation of quinacrine pellets for non-surgical female sterilizaiton Adv Contracept 1998;14:69-77

[17] Sokal DC Zipper J, King T Transcervical quinacrine sterilization: clinical experiences Int J Gynecol Obstet 1995;51(Supp1):556-69

[18] Merchant NR, Prabhu SR, Kessel E Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets Int J Fertil 1995; 14:47-54

[19] Randic L Nonsurgical female sterilization: comparison of intrauterine application of quanacrine alone or in combination with ibuprofen Fertil Steril 2001;75:830-1

[20] Female voluntary nonsurgical sterilization: the quinacrine method Chapel Hill, NC: Institute for Development Training, 1997

[21] Rock JA, Parmley TH, King TM Laufe LE Su BC Endometriosis and the development of tuboperitoneal fistulas after tubal ligation Fertil Steril 1981;35:16-20

[22] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Taylor LR, Trussell V The risk of ectopic pregnancy after tubal sterilization N Engl J Med 1997;336:762-7

[23] Kessel E Quinacrine sterilization: an assessment of risk for ectopic pregnancy, birth defects, and cancer Adv Contracept 1998;14:8-10

1241 Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1988-1991 Fertil Steril 1995;64:324-34

[25] Tice RR, Griffith J, Recio L An evaluation of the mutagenicity and carcinogenicity of quinacrine Research Triangle Park, NC: Family Health International, 1990 p 27

Y"
VOL. 75, NO. 4, APRIL 2001

Nonsurgical female sterilization: comparison of intrauterine application of quinacrine alone or in combination with ibuprofen

In many parts of the world, sterilization has become the leading method of fertility control (1). The need to make this procedure simpler, safer, and less expensive-and thereby more acceptable, even in countries with limited surgical facilities-is well recognized. Consequently, in the past three decades, various chemicals have been used to accomplish tubal occlusion through transcervical intrauterine application. Use of quinacrine pellets has become the most widely adopted method of nonsurgical female sterilization, with more than 100,000 cases reported (2).

Since this approach is less effective than surgical procedures in prevention of pregnancy, different adjuvants have been used to improve its performance. We sought to compare the results of nonsurgical female sterilization with quinacrine hydrochloride pellets alone or in combination with ibuprofen.

Patients requesting sterilization at our institution must apply to a legally formed Joint Committee for approval. The application specifies that the patient has been fully informed of the risks and benefits of both surgical and quinacrine sterilization, and the patient must note her choice of sterilization method.

From February 12,, 1988 to September 9, 1992,150 women 35 years of age or older under went intrauterine application of quinacrine hydrochloride (Sipharm, Sissein, Switzerland), 7 pellets of 36 mg each (group 1). The pellets were administered by using a modified copper T intrauterine device (IUD) inserter during the early proliferative phase of two consecutive menstrual cycles. From September 11, 1992 to May 14, 1998, the same protocol was used in 222 women of similar age, except that 3 pellets each containing 18.5 mg of ibuprofen were added (group 2). The insertion technique was simiar to copper T IUD insertion. After intrauterine application of the drugs, the women lay supine with the pelvis elevated for 2 hours and were advised to use additional contraception (condom plus 5% nonoxynol-9 in vaginal cream [Delfen; Ortho Pharmaceutical Corp., Raritan, NJ), between the first and second applications and for 2 months after the second application.

All relevant patient data, such as age, number of previous deliveries and abortions, contraceptive practice, coital frequency in the last 3 months, and years of formal education of the women and their partners, were registered. During ths study, the women were monitored 3 months after the last drug application and at yearly interv als thereafter. All participants were successfully monitored after May 1998 by clinic visit, telephone call, or home visit.

In terms of the efficacy of sterilization, the most relevant characteristic of the women is their mean age: 37.3 years in group I and 37.4 years in group 2. This indicates that age did not affect the number of sterilization failures.

More than 50% of the women in both groups had not used any contraceptive method in the 3 months before the first application. Most of the women in groups 1 and 2 (40.7% vs. 61.7%) had had four or more previous abortions and two 01 more previous deliveries (86.7% vs. 83.8%). Formal education in sterilized women and their partners was relatively high (mean [±SD], 10.9±2.5 vs. 11.6±3.0 years for women and 12.0±2.3 vs. 1 1 .0±3.9 for partners.).

The cumulative pregnancy rates after these methods of sterilization, calculated by using the life table method, are shown in Table 1. Cumulative pregnancy rates did not differ between the two groups (log-rank test: $t = .24$; $P = .4$). All 23 pregnancies that resulted after sterilization failure were intrauterine and were ended with induced abortion. The first pregnancy occurred 4 months after the first quinacrine application, and the last one occurred almost 5 years later.

In group 2, two cases of hematometra resulted from quinacrine sterilization; the women were successfully treated with the introduction of uterine sound through the cervical canal. In both groups, women had an unpleasant yellowish vaginal discharge of which the duration varied, but only a few experienced mild pruritus of the vulvar area. On the day after insertion, especially in the first application, about 5% of the women in group 2 and 7% in group 1 had fever that did not exceed 38°C.

Received July 21, 2000; revised and accepted October 17, 2300.
Reprint requests: Ljiljana Randic, Department of Obstetrics and Gynecology, University hospital of Rijeka, Cambierieva 17/5, 51000 Rijeka, Croatia (FAX: 365 51-675-806).

0015-0282/01/$20.00
PII S0015-0282(01)01671-5

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 1

Life-table cumulative pregnancy rate per 100 women for each group of women (Q and Q + 1) sterilized by transcervical insertion of quinacrine pellets.

Months	Women at risk (No.)	*Q* Pregnancies (No.)	Cumulative pregnancy rate	Women at risk (No.)	*Q+I* Pregnancies (No.)	Cumulative pregnancy rate
12	150.0	3	2.00	222.0	5	2.25
24	146.0	4	4.68	214.0	6	4.99
36	142.0	0	4.68	198.0	1	5.47
48	142.0	0	4.68	179.0	2	6.53
60	142.0	2	6.02	142.0	0	6.53
72	140.0	0	6.02	91.0	0	6.53
84	135.5	0	6.02	31.0	0	6.53
96	109.5	0	6.02			

Q: quinacrine.
Q + I: quinacrine + ibuprofen.

Randic Adjuvant for quinacrine sterilization. Fertil Steril 2001

Nonsurgical female sterilization, such as with intrauterine application of quinacrine pellets, is generally less successful than surgical methods in prevention of pregnancy. Therefore, many attempts have been made to improve its effectiveness. These attempts had developed in four directions: modifications of the quantity of quinacrine used per application, the number of applications, or the technique for intrauterine application or use of various adjuvant agents.

Our study, in which the 2-year cumulative pregnancy rates were 4.68% among women sterilized with quinacrine alone and 4.99% among those sterilized with quinacrine plus ibuprofen, failed to show any beneficial effect of ibuprofen on the efficacy of quinacrine sterilization. The 5-year cumulative pregnancy rates of 6.02% and 6.53% further confirm this finding. Our pregnancy rates are higher than those reported by Bairagi et al. (3), regardless of whether antiprostaglandins were used as adjuvant agents. The lower pregnancy rates in the latter study need to be confirmed, especially since all women in our study were older than 35 years of age. Age is clearly a key determinant of the pregnancy rate after quinacrine sterilization, as was pointed out by Sokal et al. (4).

Although the addition of antiprostaglandins has not improved the efficacy of quinacrine sterilization, other adjuvant agents should be considered. In addition, new chemicals for nonsurgical female sterilization can be tested with the primary objective of approaching the low failure rates obtained by surgical sterilization.

Acknowledgment: Quinacrine and ibuprofen pellets were provided by the International Federation for Family Health.

Ljiljana Randic, M.D.
Herman Haller, M.D.
Silva Sojat, M.D.
University of Rijeka, School of Medicine and Department of Obstetrics and Gynecology, University Hospital of Rijeka, Rijeka, Croatia

References

1. Church A. Geller JS. Voluntarv female sterilization: number one and growing. Popul Rep C 1990;10:3-15.
2. Kessel E. 100 000 quinacrine sterilizations. Adv Contracept 1996;12: 69-76.
3. Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical sterilization. Adv Contracept 1995;11:303–8.
4. Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experience. Int J Gynecol Obstet 1995(51);Suppl 1:57–69.

Retrospective Study on the Efficacy and Safety of Quinacrine Sterilization

《生殖与避孕：英文版》2000年 第4期 | 丁菊红 陆卫群 丁婉华 朱红 童建孙
Family Planning Institute of Jiangsu Province Nanjing 210029
China Family Planning Institute of Guizhou Province Guiyang 550001 China

Dissertation service：

Summary：Objective To observe and evaluate the efficacy and safety of quinacrine sterilization Methods A total of 572 cases of quinacrine sterilization preformed during the 4 years from 1993 to 1997 in Jiangsu and Guizhou Provinces were employed in this study. The efficacy and safety of quinacrine sterilization in those case were studied and evaluated, with 588 cases of surgical sterilization performed at the same time being the control group. Results Both groups were with identical demographic and gynecological characteristics. The result of multiple decrement life table analysis showed the 12th gross cumulative failure rates for quinacrine sterilization was 3.13% and serious side effects occurred in only 2 cases accounting for 0.35%. One was ectopic pregnancy (20 months after treatment).The other was due to anaphylaxis in 10 minutes after the second insertion). No difference in the liver and nephic functions was detected and no suspected cancer cells or cancer cells were found in the two groups. 99.6% of the 572 women interviewed accepted the quinacrine sterilization. Conclusions Quinacrine sterilization method is with high acceptability but comparatively low effectiveness. It has been proved to be a safe method of contraception in short term. However, the safety of long term still needs further study.

【分　类】 【医药、卫生】 > 药学 > 药品 > 计划生育药物 > 避孕药物

【关键词】 安全性 QUINACRINE 避孕药物 有效性

【出　处】 《生殖与避孕：英文版》2000年 第4期 209-215页 共7页

【收　录】 中文科技期刊数据库

CONTRACEPTION

Long-term follow-up after quinacrine sterilization in Vietnam. Part I: interim efficacy analysis

David Sokal, M. D.,[a] *Do Trong Hieu, M.D.,*[b] *Debra H. Weiner, M.P.H.,*[a] *Dao Quang Vinh, M.D.,' Trinh Huu Vach,* Ph.D.,[d] *and Robert Hanenberg, Ph. D.*[a]

Family Health International, Research Triangle Park, North Carolina; Ministry of Health, Hanoi; and Thai Binh Medicai College, Thai Binh, Vietnam

Objective: To determine the long-term efficacy of nonsurgical sterilization with quinacrine.

Design: Observational cohort study.

Setting: Rural provinces in northern Vietnam.

Patient(s): Two thousand seven hundred and nine women who had quinacrine insertions between 1989 and 1993.

Intervention(s): Interviews in 1994, 1995, and 1996 and review of available medical records. Pregnancy rates were corrected for problems in detecting and confirming pregnancies.

Main Outcome Measure(s): Pregnancy rates.

Result(s): Over 90% of women were interviewed at least once. Uncorrected cumulative pregnancy rates were 12.9% at 5 y after two insertions and 27.3% after one insertion. Effectiveness varied by age group: the partially corrected pregnancy rates after two insertions were 6.8% in women 35 or older at the time of insertion and 13.0% in women under 35. A subgroup of women who received oral papaverine at the time of quinacrine insertion had lower pregnancy rates, with a cumulative uncorrected rate of 5.3% at 4 years among women of all ages.

Conclusion(s): Efficacy of quinacrine appears reasonable for two insertions of quinacrine in women 35 and older. It may be possible to improve efficacy by the use of papaverine or the Hieu insertion technique. (Fertil Steril® 2000;74: 1084-91. 02000 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, tubal sterilization, nonsurgical, pregnancy, follow-up studies

Received February 18, 2000; accepted June 15, 2000.

Supported in part by Family Health International (FHI). FHI is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, STDs, and AIDS. Views expressed in this report do not necessarily reflect those of FHI.

Reprint requests: David Sokal, M.D., Family Health International, P. 0. Box 13950, Research Triangle Park, North Carolina 27709 (FAX: 203-785-7134; E-mail: dsokal@fhi.org).

[a] Family Health International, Research Triangle Park, North Carolina.

[b] Director, MCHFP Department, Ministry of Health, Hanoi, Vietnam, at the time of the study; currently retired.

[c] Ministry of Health, Hanoi, Vietnam.

[d] Research Center for Rural Population and Health, Thai Binh Medical College, Thai Binh, Vietnam.

0015-0282/00/$20.00
PII S0015-0282(00)01596-X

Nonsurgical sterilization has the potential to be an inexpensive, safe, and well-accepted procedure that would be of benefit to women in both developed and developing countries. One nonsurgical approach, first described in 1980 (I), involves the use of quinacrine pellets to produce occlusion of the fallopian tubes In the most commonly studied regimen, seven pellets, each containing 36 mg of quinacrine dihydrochloride dihydrate, are inserted into the uterus with a modified intrauterine device (IUD) inserter. A second insertion is done 1 mo later.

Quinacrine sterilization was first offered by the Vietnamese Ministry of Health (MOH) in 1988 as a pilot study with 200 volunteers selected from two provinces near Hanoi, in the Red River Delta, namely Hai Hung and Ha nam Ninh. (These two provinces have since been divided into a total of five smaller provinces, four of which are involved in the current study)

The results of this pilot study were reported in a joint meeting organized by the Vietnamese MOH and the National Committee for Population and Family Planning in April 1989. In that meeting, the MOH decided that quinacrine sterilization should be introduced more widely in those two provinces, which had a combined population of over five million people. Because of the ease of service delivery and good acceptability, MOH clinics in a number of provinces subsequently decided to use quinacrine sterilization.

By October 1992, 31,781 women in 24 provinces had received quinacrine sterilization (2). The total number of quinacrine steriliza-

tions in Vietnam is not known, but it has been estimated that a cumulative total of about 50,000 women were sterilized before the program was terminated. The MOH halted the program in December 1993 because of concerns voiced by the World Health Organization (WHO) (3) that quinacrine might be a carcinogen. Subsequently, in July 1994, WHO held a consultative meeting on the development of new technologies for female sterilization (4). The report of that meeting included recommendations for additional toxicologic testing of quinacrine and for additional follow-up of women who had already received quinacrine (5).

After the quinacrine program was halted, the MOH invited Family Health International (FHI) to help evaluate the program because of FHI's experience with quinacrine research (6). In 1994, FHI and Vietnamese researchers conducted a retrospective study to address concerns about whether women had given informed consent before accepting quinacrine insertions and to evaluate other service delivery-related aspects. (Katz K, Waszak C, Hieu D, Vinh D, Sokal D. The lessons of quinacrine introduction in Vietnam. Manuscript submitted for publication.) In 1995, in keeping with WHO recommendations (5), we began a long-term follow-up study, to consist of five annual interviews of the women first interviewed in 1994. One of the study objectives was to estimate long-term pregnancy rates after transcervical quinacrine pellet sterilization. In this paper, we report pregnancy rates from the interim analysis, based on data through the second annual interview in 1996. An accompanying paper presents the interim analysis of the safety data, including rates of ectopic pregnancies (7).

MATERIALS AND METHODS

Study Population and Sampling Methods

This is a long-term, observational cohort study of a.sample of women who had quinacrine insertions in Vietnam between 1989 and 1993 (2). We chose three provinces near Hanoi and the four districts within each province with the greatest number of quinacrine acceptors. Since the study began, two of the provinces have been split, but for this analysis. we are using the original grouping.

For the 1994 survey, we prepared sampling frames from logbooks of 6,535 quinacrine acceptors. We then selected a random sample of quinacrine acceptors, stratified by province, district, and 5-year age group. The sampling frame included women who had one, two, or more insertions.

In 1995. we added more one-insertion women to the sample to have better statistical power for comparing one vs. two quinacrine insertions. This expansion group included all the remaining one-insertion women in the sampling frame. The data from the 1994 interviews and the current study were pooled to determine participants' pregnancy rates from the date of quinactine insertion up to the date of last contact

A participant flow chart is included in the accompanying paper (7). Women found to be ineligible or duplicates (e.g., more than one entry in the sampling frame) were removed before analysis. *The intent-to-interview* population consists of all women selected for the study, whether or not they were ever interviewed. The *interviewed* population is the subset who were interviewed at least once in 1994 (for our retrospective study), 1995, or 1996. In all, 95% of women were interviewed at least once. We excluded six one-insertion quinacrine women because of invalid insertion dates (e.g., missing year).

Questionnaires and Interview Methods

Questionnaires were initially drafted in English, translated into Vietnamese, and then reviewed, revised, and finalized in Vietnam. The questionnaires asked about pregnancies and the occurrence of any health problems.

In 1994, schoolteachers interviewed 1,679 women for the retrospective survey. In 1995, we used schoolteachers again to interview 2,621 women, including the added sample of one-insertion women. In addition, physicians conducted 536 follow-up interviews to get more information about health problems. In 1996, to improve reporting of medical problems, we used physicians to conduct both the initial and follow-up interviews-of 2,520 and 313 women, respectively. If a woman had died, we interviewed relatives and local health workers. For selected cases involving hospitalization, surgery, or death, we sought copies of hospital records

Other Data Sources

In addition to the annual interviews, we used two additional sources of data:

1. Data regarding the use of drug combinations with quinacrine, collected in July and August 1997, from the original quinacrine insertion logs We found adjuvant data on 88% of the women from the original insertion logs in the provincial health offices
2. Passive surveillance data regarding pregnancy tests, menstrual regulations (MR), and abortions. (An MR is an early abortion procedure, often done within a week or two of a missed period and commonly done without a pregnancy test [8].)

To collect the passive surveillance data, we initiated regular distribution of pregnancy tests to hospitals and clinics in the study area and gave each woman in the study a document entitling her to free pregnancy tests. After this distribution, most of the women in our study had access to pregnancy tests. Clinic staff reported the results of pregnancy tests and whether a woman had an abortion or MR. Only pregnancies reported in the annual interviews were included in the analysis, but we used the passive surveillance data to calculate two correction factors: [1] one for unnecessary menstrual regulations and [2] one for unreported MRs or abortions (see Technical Appendix).

Women interviewed in 1996 were asked their current age, either by Vietnamese animal year or (if animal year was not available) by month and year of birth. The Vietnamese calendar has a cycle of 12 animal years. Women reporting an animal birth year were then assigned a specific age by interviewer observation, in other words, either x years of age or x + I2 years of age. An improved measure of age at insertion, based on the 1996 data (but using the logbook value if the 1996 data were missing), was created. The 1996 age data were available for 93% of the women. We used the improved estimate of age at insertion to categorize women for pregnancy analysis (<35 vs. ≥35). We used the original age strata when accounting for sampling design and in the table of baseline characteristics (see Table I).

Baseline Characteristics

Percentages, means, and standard deviations (see Table I) are weighted for differential sampling probability and nonresponse. Almost all women were married and literate. The proportions of one- vs. two-insertion quinacrine women are quite different across provinces, and the years since quinacrine insertion at the time of last interview are slightly different. This is probably due to the combined effects of oversampling for women with one insertion and the limited practice of one-insertion trials. Obstetric and contraceptive history and age at insertion were similar in both groups. Most women in both groups had three or four living children In both groups, 90% of women were 30 years of age or older at the time of insertion, with 40% in the 35to-39-year age group

Pregnancy Analysis

We estimated the date of conception as the date of the last menstrual period (LMP) plus 14 days. If we had more than one date for the LMP, we chose the earlier date. For the few cases with missing data, we used various algorithms to estimate the date of conception.

Follow-up times ranged from less than I year to 8 years. Annual cumulative pregnancy rates through 5 y were calculated using the life-table method (monthly intervals), stratified by the sampling stratification variables (province, district, and 5-year age group). We originally specified that sampling and nonresponse should be taken into account in the pregnancy estimates (i.e., weighted). Later, we considered the possible effects of unnecessary menstrual regulations and underreporting of abortions, and we calculated correction factors for both of these effects (see Technical Appendix).

Pregnancy estimates corrected for unnecessary menstrual regulation and underreporting of abortions are our best estimate of the true contraceptive effectiveness of the method, and we designated these a priori as the gold standard estimates. However. because most studies do not correct for underreporting and have no need to correct for unnecessary MRs (because pregnancy status is typically known), partially corrected rates, corrected only for unnecessary MRs, are more appropriate for comparison with other studies. Except as noted below, we have calculated pregnancy rates by the reported number of insertions, not by the intended number.

For five women, the only evidence of pregnancy was a positive response to an item in 1996 about whether they had gotten pregnant between insertions. Because related items were not answered and they had reported no pregnancies when interviewed in 1994, we assumed that these were form completion errors.

Statistical Methods

We computed weighted percentages, means and standard deviations of baseline characteristics using SAS software, version 6.12 (SAS Systems, Cary, NC). We computed weighted, stratified, annual cumulative pregnancy rates and 95% confidence intervals, both corrected and uncorrected, using the method described in the Appendix, programmed via SAS data steps. (Survival analysis estimates are more accurately called ***cumulative probabilities*** of an event [e.g., pregnancy] rather than ***rates.*** However, because the latter term is more commonly understood, these terms will be used interchangeably in this report.) For better comparability with the CDC Collaborative Review of Sterilization (CREST) study of sterilization failure (9), we revised the planned method of calculating time to pregnancy so as not to censor on either age or menopause status. Standard errors were computed by Greenwood's method, modified to handle weighted and stratified observations and pregnancy corrections (details available upon request) Results are not given if the number at risk was substantially less than 30 because such estimates may be unstable. We then did Cox proportional hazards regression using SUDAAN version 7.0 (Research Triangle Institute, Research Triangle Park, NC) to account for sampling design, in order to compare one- vs. two-insertion groups for overall uncorrected pregnancy rates (α = 0.05, two-tailed).

RESULTS

The gold-standard 5-year cumulative pregnancy rate was 12.6 (95% confidence interval [CI]: 10.6, 14.5) per 100 women receiving two insertions. The 5-year rate for women receiving one insertion was 25.8 per 100 women (95% CI: 23.5, 28.1).

The weighted, uncorrected 5-year cumulative life-table pregnancy rate for women receiving two insertions of quinacrine was 12.9 per 100 women (95% CI: 11.1, 14.7) vs. 27.3 (95% CI: 25.1.29.5) for women receiving one insertion. The one-insertion group had a 2.47 times higher risk of pregnancy than did the two-insertion group (95% CI: 2.04,2.98), $P<0.001$.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 1

Participant characteristics,[a] interviewed population.

Parameter	Quinacrine two insertions (n = 1 329) wt %	Quinacrine, one insertion (n = 1,380) wt %	Quinacrine, overall (n = 2,709) wt %
Insertion history			
Age at insertion[b]			
20-24	0 0	0 5	0.1
25-29	10.1	9 0	9 8
30-34	36 4	31 7	35 2
35-39	39 6	40 3	39 8
≥40	14.0	18.5	15.1
Mean age (SD)	34 7 (7 71)	35 2 (4 59)	34 9 (6 32)
Median (min/max)	35 (25148)	35 (20/48)	35 (20/48)
Years since insertion at last interview			
<2	1.0	I 0	1.0
2-3	16.5	13.2	15.6
4-5	71 0	84.7	74 5
≥6	11.5	LI	8.8
Mean years (SD)	4.9 (1.94)	4 5 (0 76)	4.8 (I 49)
Median (min/max)	5 (0/8)	4 6 (2/7)	4 6 (0/8)
Sociodemographic			
Marital status'			
Married	99.3	93 9	97 9
Not married	0.5	0 6	0 6
Unknown	0.2	5 4	1.5
Education			
illiterate	0.3	0 7	0 4
Primay school (1-5)	14.9	11.7	14.0
Basic school (6-9)	77.3	80.7	78 2
Secondary school (10-12)	5 9	5.8	5.8
Technical/vocational	1.5	1.0	1.4
College/university	0.2	0 2	0 2
Province[d]			
1: Nam Ha	58.2	25 9	49 9
2: Hai Hung	28.5	22 9	27.1
3: Thai Binh	13.3	51 2	23 0
Obstetrical history			
Age at first pregnancy			
<20	14.0	16.2	14.6
20-24	68 7	66 6	68 2
25-29	16.1	15.1	15.9
≥30	1.2	2.1	1.4
Number of pregnancies'			
I	0 0	0 2	0 0
2	2.1	4.2	2.3
3	14.5	12.8	14.3
4	23 8	20 4	23 5
5	21.8	22 6	21 8
≥6	37.8	39 8	38 0
Number of live births'			
None	0 2	0.3	0 2
I	0 2	0 5	0 2
2	7.9	13.1	8 4
3	37 6	39 4	37 7
4	31 8	31 0	31 8
5	14.9	9.7	14.4
≥6	7.4	6.1	7.2
Number of living children'			
None	0 0	0 0	0 0
I	0.3	0 5	0.3
2	8.9	14.3	9.5

Continued on following page

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 1—CONTINUED

Participant characteristics,[a] interviewed population.

Parameter	Quinacrine two insertions (n = 1,329) wt %	Quinacrine one insertion (n = 1 380) wt %	Quinacrine overall (n = 2 709) wt %
3	42 6	43 4	42 7
4	31.5	28 2	31 2
5	11.6	9 7	11.4
≥6	5 0	3 9	4 9
Contraceptive history: method used immediately before insertion			
None	19.9	19.1	19.8
IUD	57.8	45.1	56.5
oral contraceptives	1.1	2 9	1.3
Condoms	3.5	3.3	3.5
Other	17.7	29 6	18.8

[a] Percentages means medians, and standard deviations are weighted for differential probabilities of selection and nonresponse.
[b] Based on logbook/sampling frame.
[c] At the 1994 interview If not available then at the 1996 interview
[d] Provinces as they existed at the time sample selection was conducted
[e] As of the 1994 retrospective study interview

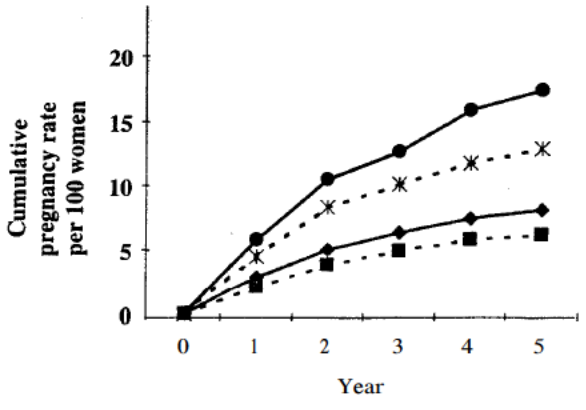
Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

Women Who Received Two Insertions at Age 35 and Above

Quinacrine would probably be most appropriate for women aged 35 years and above (6). For women 35 years and above who received two insertions. the 5-year gold-standard rate was 9.0% per 100 women (95% CI: 6.5, I 1.5). Women aged 35 and above at the time of insertion had substantially lower pregnancy rates than did younger women (see Figure 1); for example. partially corrected rates of 6.8 per 100 women (95% CI: 4.5, 9.0) vs. 13.0 (95% Cl: 10.3, 15.7) at 5 y. Figure 1 shows two rates for each age group: the fully corrected, gold-standard rates and the lower, partially corrected rates that are more appropriate for comparison with other studies.

FIGURE 1

Five-year cumulative pregnancy rates per 100 women with two quinacrine insertions, by age, with either full or partial correction* of pregnancy rates * Full correction corresponds to the gold-standard pregnancy rate, correcting for both unnecessary menstrual regulations and unreported abortions. The partial rates are corrected for unnecessary menstrual regulations but not for unreported abortions. —●— <35, fully corrected; --✳--, <35, partially corrected; —◆—, ≥35, fully corrected; --▫-- ≥35, partially corrected.



Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

Intent-to-Treat Analysis

Classifying women by the number of insertions actually received gives a somewhat idealized failure estimate for the two-insertion group. that is. analogous to a **perfect-use** rate because only those women who came back for their **second** insertion and who did not get pregnant **between** insertions are included. Among the 1.279 one-insertion women for whom we have information regarding reasons for only one insertion, 221 (17.3%) reported that they were supposed to receive two insertions but did not return for the second They gave the following reasons for not returning: 24% were busy; 11% reported side effects from the first insertion; 10% forgot the appointment; 10% were ill. menstruating, or pregnant; 10% did not give a reason; and the remaining 34% gave a variety of miscellaneous other reasons.

We recalculated the gold-standard pregnancy rates. classifying women on the basis of the number of insertions that they were supposed to receive; in other words. an intent-to-treat analysis. The 5-year cumulative pregnancy rate increased somewhat for the 1.530 women in the two-insertion protocol (14.8 per 100 women: 95% Cl: 13.0. 16.7) **and**

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 2

Ad hoc analysis: use of adjuvants by number of quinacrine insertions, interviewed population.

Adjuvant	Quinacrine, two insertions[a] n	(%)	Quinacrine, one insertion n	(%)
Ampicillin only (intrauterine)	580	(57 5)	207	(22 4)
NET-EN or DMPA	19	(1 9)	466	(50 4)
Oral contraceptives only	42	(4 2)	33	(3.6)
Pnpaverine only (oral)	237	(23 5)	114	(12 3)
Other	2	(0.2)	1	(0.1)
None	129	(12 8)	103	(11 1)
Total[b]	1009		924	

[a] Number of insertions at time of pregnancy Frequencies and percentages are unweighted

[b] Information on 215 two-insertion and 152 one-insertion women is not available; 93 two-insertion and 316 one-insertion women could not be classified into "pure" types

Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

decreased somewhat for the 1,055 women in the one-insertion protocol (24.3 per 100 women; 95% CI: 21.9, 26.8). For older, two-insertion women, the partially corrected 5-y pregnancy rate shown in Figure 1 would increase from 6.8 to 8.2 per 100 (95% CI: 5.9, 10.5) on the basis of an intent-to-treat analysis.

Drug Combinations and Insertion Techniques

Several drugs were administered in combination with quinacrine. whether orally, uanscervically, or **by** injection. We classified 1.933 quinacrine acceptors into mutually exclusive categories by type of drug combination received (see Table 2). Most women received an additional drug. In the two-insertion group, intrauterine ampicillin (125 mg) was the most commonly added **drug**. Antibiotics are routinely given in Vietnam at the time of IUD insertion. and some physicians thought ampicillin, either oral or intrauterine, should also be given with quinacrine to reduce the risk of infection. In the one-insertion group. intramuscular injections of 150 mg of depo-medroxyprogesterone acetate. which is manufactured under the brand name Depo-Provera. or 200 mg norethisterone enanthate. manufactured with the brand name Noristerat. were most frequently given to prevent pregnancies immediately after the insertion.

Oral papaverine is routinely, used in Vietnam to reduce the painful uterine cramping often associated with IUD insertions and was given to some women at the time of their quinacrine insertions. In most cases. health providers gave each woman four 40-mg pills. Although the exact regimen to be used was not documented in writing, discussions with health providers indicate that women were probably advised to take one pill twice a **day** to **reduce** pain from **uterine cramping**, though some providers recommend two pills twice a day

We conducted post hoc calculations of **unweighted** and uncorrected life-table pregnancy rates and 95% confidence intervals for the most common drug combinations.

Because of the highly exploratory nature of this analysis, generalization beyond the cohort was not advisable; hence the use of unweighted and uncorrected estimates.

The follow-up times in the life-table analyses for these subgroups are shorter and of different lengths, either 2 or 4 years, because of the small number of women in these subgroups. Women with two insertions who got papaverine had a lower pregnancy rate than did women who received ampicillin (see Figure 2). The 129 women who had no added drug had a 2-year pregnancy rate of 11 .O per 100 women (95% CI: 5.6, 16.5), similar to the rate among women who received intrauterine ampicillin.

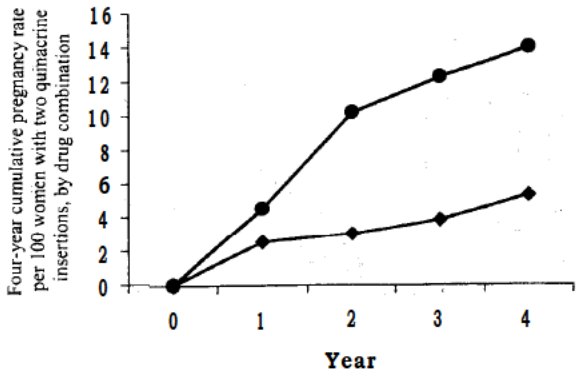
Among women who received one quinacrine insertion, the 2-year cumulative life-table pregnancy rates were 23.5 per 100 women (95% CI: 17.7, 29.3) for ampicillin; 22.6 (95% CI: 18.8, 26.4) for injectable progestogens; I 1.5 (95% CI: 5.6, 17.4) for papaverine; and 21.0 (95% CI: 13.0. 29.0) for no added drug.

After both one or two insertions, women receiving papaverine had substantially lower pregnancy rates than the other groups. Looking at the two-insertion papaverine group by age, women 35 years of age or older at the time of quinacrine insertion had a 4-year cumulative pregnancy rate of 2.7 per 100 women (95% CI: 0, 5.7).

The use of papavcrine was recommended by Hieu, so it is possible that the Hieu insertion technique, rather than papaverine use, was responsible for the low pregnancy rate in this subgroup. In the original report of the quinacrine pro-

FIGURE 2

Four-year cumulative pregnancy rates per 100 women, with two quinacrine insertions, by drug combination. Papaverine use may have been associated with the Hieu insertion technique. —●— ampicillin only; —◆— papaverine only.



Sokal. Interim quinacrine efficacy analysis. Fertil Steril 2000.

gram in Vietnam, Hieu described a new insertion technique: gently advance the inserter to the fundus, withdraw it about 5 mm, and then advance the plunger to deposit the pellets at the fundus (2). This is different from the method previously used by Zipper and other investigators, who used a standard IUD insertion technique, in which the inserter is advanced to the fundus and the outer tube is withdrawn, which would leave the quinacrine pellets dispersed throughout the uterus (6). We have no data as to which insertion technique was used for particular women. To try to disentangle this confounding, we conducted stratified Mantel-Haenszel tests, done separately by insertion group, on the association of pregnancy to papaverine, controlling for health care provider, and vice versa. When controlling for health care provider, the odds ratios for papaverine remained low but were no longer statistically significant. Controlling for papaverine, the health care provider factor was highly significant for the one-insertion group but not for the two-insertion group.

DISCUSSION

A number of small clinical studies of quinacrine pellet sterilization have been conducted in various countries (6) and in the United States (10) during the past 20 years. but many of them have had limitations in study design. Some long-term follow-up data on efficacy have been reported from Chile (6, 11-13). This study is the largest long-term follow-up study of quinacrine pellet sterilization.

Because other studies of pregnancies after sterilization have not corrected for underreporting of abortions, the overall rate that should be used when comparing our data to studies of surgical sterilization is 9.8 per 100 women at 5 years. The CREST study found an overall pregnancy rate of 1.4 per 100 women at 5 y and 1.9 per 100 women at 10 y (9). Participants at the WHO meeting on female sterilization discussed the issue of what would be an acceptable pregnancy rate following a nonsurgical method, but did not come to any conclusions (5).

We found that two quinacrine insertions were clearly better than one. A previous review of clinical data on quinacrine sterilization (6) suggested that quinacrine sterilization was likely to be most appropriate for women ages 35 and above because pregnancy rates are lower and the risk of regret is lower (14). The results of the present study are consistent with that suggestion The pregnancy rate at 5 y for women 35 y of age and above who had two or three insertions in Chile was only 2.8%; the comparable figure from the current data would be 6.8%. There are at least two possible explanations for this difference:

1. Relative lack of training in Vietnam: at the time the quinacrine program began in Vietnam, there was a desperate need for new contraceptive method.., and it was felt that the quinacrine method was not technically difficult and required little or no formal training for providers already experienced in IUD insertions However, it was later clear that there was considerable variation in pregnancy rates by health provider (2, 15).
2. Better reporting: the use of carefully designed survey procedures with home visits and an independent system of passive surveillance may have resulted in better reporting of pregnancies than in other long-term studies of quinacrine sterilization

The use of drug combinations may have also affected the efficacy rates in unknown ways. The most striking finding was among women who received papaverine, who had substantially lower pregnancy rates than other women. Papaverine is known to inhibit uterine smooth-muscle contractions and was used with the intention of preventing painful uterine contractions after quinacrine insertion. Although the number of women who received papaverine was relatively small. the pregnancy rates in this subgroup were much lower in both the one- and two-insertion groups. Our exploratory analytic attempt to determine whether the lower pregnancy rate was due to the influence of (a) papaverine or (b) better insertion techniques used by certain providers was inconclusive.

The limitations of this interim analysis include limited statistical power and the conduct of exploratory analyses, designated in the tables as ad hoc if requested generally before other results were known or as post hoc if clearly following up observed findings. Given the retrospective collection of data about the insertion procedures, it was difficult to determine whether women were supposed to receive one or two insertions. Our intent-to-treat estimates may be conservative because our sample over-represents one-insertion women. On the other hand. we may have underestimated the number of one-insertion women who were supposed to receive two insertions.

CONCLUSIONS

Among women of all ages. our best estimate of the 5-year cumulative pregnancy probability is 12.6 per 100 women (95% CI: 10.6. 14.5) for women receiving two quinacrine insertions: and 25.8 per 100 (95% CI: 23.5.28.1) for women receiving one insertion.

In women with two insertions at age 35 or above, the partially corrected pregnancy rate was 6.8% at 5 years, compared with 2.8% for similarly aged women in Chile. The higher pregnancy rate in Vietnam could be due to several factors, including less uniform insertion techniques by a larger number of providers and better reporting.

In a subgroup of two-insertion women who received oral papaverine to prevent painful uterine cramping, we found that the pregnancy rate was markedly lower. with an uncorrected four-year rate of 5.3% among all women. and 2.7% in women 35 years of age and above. The use of papaverine may have been confounded with insertion technique or inserter skill.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Because these results are from an interim analysis and are from an observational study rather than a clinical trial, they are. by definition, preliminary, and they should be interpreted cautiously

TECHNICAL APPENDIX

Calculation of Pregnancy Correction Factors

Correction for Unnecessary Menstrual Regulations

When pregnancy tests are not readily available and the woman's pregnancy status is not clinically obvious, it is possible that a menstrual regulation will be performed when, in fact, the woman is not pregnant. Counting all such cases as pregnancies will overestimate rates, whereas counting none of them will underestimate rates. To correct for this, the following steps were taken.

Passive-surveillance data were used to estimate the proportion of menstrual regulations that were likely not to have been true pregnancies. By late 1995, pregnancy tests were more generally available, particularly to study participants. These data showed that 58% of women in the quinacrine sample who sought pregnancy tests had a negative test. Assuming that before the availability of pregnancy tests, these women would have received a menstrual regulation. we estimated that for 58% of "uncertain" menstrual regulations (menstrual regulations not confirmed by a pregnancy test and conducted within 7 wks of last menstrual period, before clinical signs would be apparent), the woman was not really pregnant. We implemented this correction by counting study pregnancies that met this definition as .42 of a pregnancy in the life-table, with the remaining 58 censored at the time of the pregnancy.

Correction for Underreporting of Menstrual Regulations and Abortions

Underreporting of menstrual regulations and abortions was estimated by comparing menstrual regulations and abortions recorded via passive surveillance with events reported by women during the regular yearly interview for the same period (November 1. 1995, through November 1. 1996).

An underreporting ("U") correction factor is defined as: $1/(N_a/N_t)$

where

N_a = number of menstrual regulations or abortions reported during annual interviews and

N_t = number of known number of menstrual regulations or abortions detected by either system.

For the present analysis, U = 1.46. Thus, for every 100 menstrual regulations or abortions that were reported, it is estimated that there were another 46 that were not.

Underreporting of menstrual regulations and abortions was incorporated into the life-table analysis by assuming that for each menstrual regulation or abortion in a given interval, another .46 unreported menstrual regulation or abortion occurred

References

1. Zipper J, Cole LP, Goldsmith A Wheeler R, Riven M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstet 1980:18:275-9
2. Hieu DT, Tan TT, Tan DN, Nguyet PT Than P, Vinh DQ 3 I ,78 I cases of non-surgical female sterilisation with quinacrine pellets in Vietnam Lancet 1993:342:2 13-7
3. AnonymouS Death of a study: WHO what and why Lancet 1994:343: 987-8
4. Benagiano G, Sciarra J Introduction: WHO consultation on the development of new technologies for female sterilization Int J Gynaecol Obstet 1995;51(suppl 1):S1.
5. Wilson EW The development of new technologies for female sterilization: conclusions and recommendations for research Int J Gynaecol Obstet 1995;51(suppl 1):S71–4.
6. Sokal D, Zipper J King T Transcervical quinacrine sterilization: clinical experience Int J Gynaecol Obstet 1995;51(suppl 1):S57–69.
7. Sokal D, Hieu DT Weiner DH, Vinh DQ, Vach TH, Hanenberg R Long-term follow-up after quinacrine sterilization in Vietnam Part II: interim safety analysis Fertil Steril. 2000;74:1092–101.
8. Vach T Bishop A Hoa V, Hien L Chien T, Nguyen TI The potential impact of introducing pregnancy testing into menstrual regulation services in Vietnam Int Fam Plann Perspect 1998;24:165–9.
9. Peterson HB, Xia Z, Hughes JM Wilcox LS, Tylor LR, Trussell J The risk of pregnancy after tubal sterilization: findings from the US Collaborative Review of Sterilization Am J Obstet Gynecol 1996;174: 1161–70.
10. Laufe LE, Sokal DC, Cole LP, Shoupe D, Schenken RS Phase I prehysterectomy studies of the transcervical administration of quinacrine pellets Contraception 1996;54: 181-6
11. Zipper J Dabancens A Guerrero A Trujillo V Quinacrine revised Hum Reprod Update 1995: 1:324–42.
12. Trujillo V Zipper J, Viel B, Rivera M Nonsurgical female sterilization using quinacrine: efficacy of two insertions of quinacrine pellets Rev Fr Gynecol Obstet 1993;88: 147–50 (in French)
13. Feldblum PJ Hays M Zipper J, Guzman-Serani R Sokal DC Pregnancy rates among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989 Contracept 2000;61: 379-84
14. Chi IC Jones D Incidence, risk factors and prevention of poststerilization regret in women: an updated international review from an epidemiological perspective Obstet Gynecol Surv 1994;49:722–32.
15. Sokal D Hanenberg R Quinacrine family planning method (letter) Lancet 1994;343:1426–7.

Fertility and Sterility 2001;75:830-31.

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Long-term follow-up after quinacrine sterilization in Vietnam. Part II: interim safety analysis

David Sokal, M.D.,[a] *Do Trong Hieu, M.D.,*[b] *Debra H. Weiner, M.P.H.,*[a] *Dao Quang Vinh, M.D.,*[c] *Trinh Huu Vach, Ph. D.,*[d] *and Robert Hanenberg, Ph. D.*[a]

Family Health International, Research Triangle Park, North Carolina; Ministty of Health, Hanoi; and Thai Binh Medical College, Thai Binh, Vietnam

Objective: To determine the long-term safety of nonsurgical sterilization with quinacrine

Design: Observational cohort study

Setting: Rural provinces in northern Vietnam

Patient(s): Two thousand eight hundred forty women who had had quinacrine insertions and an age-matched comparison group of I658 women who had an intrauterine device (IUD) insertion between 1989 and 1993

Method(s): Interviews in 1994, 1995 and 1996 and review of available medical records This is a planned interim analysis

Main Outcome Measure(s): Ectopic pregnancies and the occurrence of other adverse health events

Result(s): Over 90% of women were interviewed at least once Despite matching on age, the groups differed on baseline parity The ectopic pregnancy rates were similar after either one or two insertions and were similar to the rate of ectopic pregnancies after surgical sterilization in the United States The quinacrine group reported more gynecologic health problems than the IUD group However, after correcting for information bins there was no dose-response effect between the one- and two-insertion quinacrine groups, suggesting the possibility of recall bias or differing baseline health status

Conclusion(s): Ectopic pregnancies do not appear to be increased compared with US surgical sterilization rates. The data on other adverse events are more difficult to interpret. (Fertil Steril ® 2000:74:1092–101. ©2000 by American Society for Reproductive Medicine.)

Key Words: Quinacrine. tubal sterilization. nonsurgical. pregnancy, follow-up studies, safety, intrauterine devices

Received February 18, 2000: accepted June 15, 2000.

Supported in part by Family Health International (FHI). FHI is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, STDs. and AIDS. Views expressed in this report do not necessarily reflect those of FHI.

Reprint requests: David Sokal, M.D., Family Health International, P.O. Box 13950, Research Triangle Park, North Carolina 27709 (FAX: 919-544-7261; E-mail: dsokal@fhi.org).

[a] Family Health International, Research Triangle Park, North Carolina.

[b] Director. MCHFP Department, Ministry of Health, Hanoi, Vietnam, at the time of the study: currently retired.

[c] Ministry of Health, Hanoi, Vietnam.

[d] Research Center for Rural Population and Health. Thai Binh Medical College, Thai Binh, Vietnam.

0015-0282/00/$20.00
PII S001 5-0282(00)01594-6

Nonsurgical sterilization has the potential to be an inexpensive. safe. and well-accepted procedure that would be of benefit to women in both developed and developing countries. One nonsurgical approach. first described in 1980 (1). involves the use of quinacrine pellets to produce occlusion of the fallopian tubes. In the most commonly studied regimen. seven pellets. each containing 36 mg of quinacrine dihydrochloride dihydrate, are inserted into the uterus with a modified intrauterine device (IUD) inserter. A second insertion is done l month later. It has been estimated that 100.000 women have undergone a quinactine pellet sterilization procedure (2).

The short- and medium-term side effects of quinacrine pellet insertions have been reviewed (3), and a risk assessment has estimated the potential risks of ectopic pregnancy. birth defects. and cancer from quinacrine use (4). A long-term follow-up study of women in Chile examined the risk of gynecologic cancers after quinacrine pellet sterilization (5. 6). Close examination of a cancer cluster in Chile showed no plausible relationship between the cancer cluster and quinacrine. The sole remaining finding at the end of that analysis was a single case of uterine leiomyosarcoma, the same case that had led to the investigation.

In this study, our goal was to compare the rates of ectopic pregnancy and other adverse events between women who received quinacrine and a comparison group, as well as between women who received one vs. two quin

acrine insertions We chose IUD acceptors as the comparison group. We considered the use of a surgical sterilization comparison group, but surgical sterilizations were rarely done when the quinacrine program began in Vietnam, so there were few women who had had surgical sterilization in the same time frame. In this report, we present the scheduled interim analysis of long-term safety data, including data on ectopic pregnancies. The interim analysis of overall pregnancy rates and additional background information are in an accompanying article (7). As noted in that article, Family Health International (FHI) had not been involved in the quinacrine insertion program in Vietnam.

METHODS

This is an observational cohort study of a sample of women who had quinacrine insertions in Vietnam between 1989 and 1993. The study also includes a comparison group of women who had IUD insertions in the same provinces during the same time period. We obtained approval from Family Health International's (FHI's) institutional review board to conduct this study on August 26, 1994. Enrollment and observations began several years after the quinacrine and IUD insertions had taken place. Most of the women in this cohort were initially recruited during a 1994 retrospective survey

Sampling Methods

The methods for the 1994 survey are described in more detail in another report (Katz K. Waszak C, Hieu D, Vinh D, Sokal D. The lessons of quinacrine introduction in Vietnam. Manuscript submitted for publication.). We will summarize them briefly here. We chose three provinces near Hanoi and the four districts within each province with the greatest number of quinacrine acceptors. Since the study began, two of the provinces have been split, but for this analysis, we are using the original grouping.

Sampling frames were developed from logbooks of 6,535 quinacrine acceptors and 6.446 IUD acceptors. A random sample of quinacrine acceptors was selected. stratified by province. district, and 5-year age group. The sampling frame included women who had one or two quinacrine insertions. We selected a frequency-matched IUD sample using the same three variables.

When we began this study, we recruited an expansion group composed of women who had had only a single quinacrine insertion. in order to have better statistical power for comparing long-term effects of one versus two quinacrine insertions, especially with respect to ectopic pregnancies. This expansion group included all the remaining one-insertion women in the sampling frame.

Questionnaires and Interview Methods

Although the 1994 survey focused on issues of regret and informed consent. it did include limited items regarding health problems, which were used in the present analysis. Questionnaires for the current study were initially drafted in English, translated into Vietnamese, and then reviewed, revised, and finalized in Vietnam. We reviewed data quality after each annual round of interviews and made minor revisions to the questionnaires as needed We found that the best way to gather accurate age data was to ask women for their animal year of birth, using the Vietnamese 12-year cycle of animal years.

We conducted interviews in June 1995 and in November 1996. Annual interviews continued through 1999. During the interviews, women were asked to describe any health problems. The definition of a health problem was any problem that led a woman to see a health worker or kept her from her usual activities for 2 days or more. Thus, the reported health problems include many minor health problems. If a woman had died, we interviewed relatives and local health workers.

For serious health problems or health problems related to the reproductive system in which the diagnosis was unclear, a physician conducted a follow-up interview. The decision on whether or not to conduct a follow-up interview was made by FHI staff masked to study group. For selected cases involving hospitalization, surgery, or death. we sought copies of hospital records.

In 1995, schoolteachers conducted the initial interviews, as had been done during the retrospective study. For the second year, in order to improve reporting of medical problems. physicians conducted both the initial and follow-up interviews. We conducted 536 medical follow-up interviews in 1995 and 313 in 1996.

We coded the questionnaire data after translation by an independent translator. We used the Co-Start coding system (8). We conducted an audit of the medical codes as part of the interim analysis.

Other Data Sources

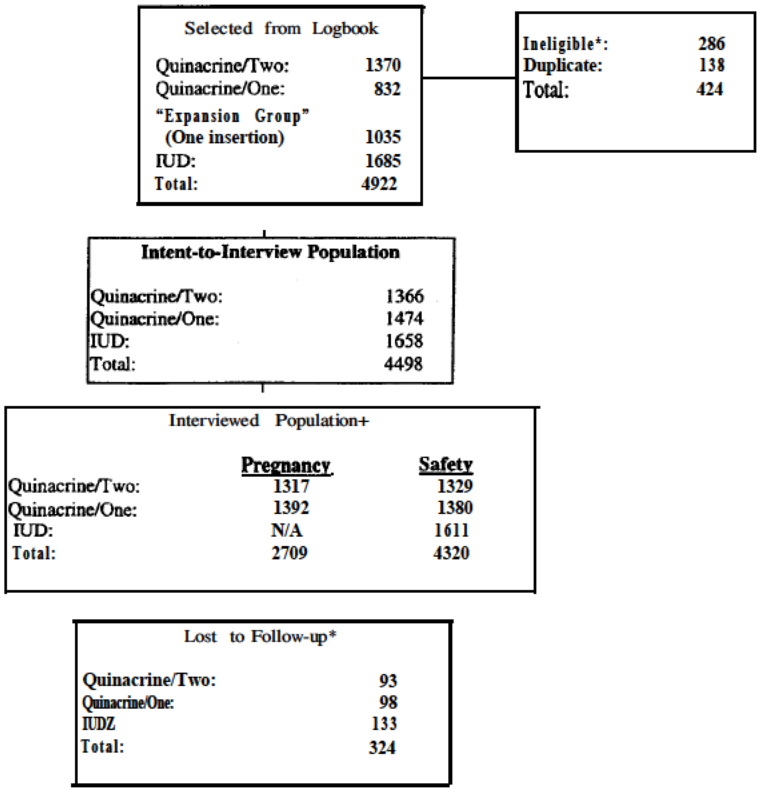
The data from the retrospective study and the current study were pooled to determine participants' health experiences from the date of insertion of either an IUD or quinacrine pellets to the date of last contact. The 1994 data set included specific information on ectopic pregnancies and hysterectomies but did not include detailed descriptions of other gynecologic health problems. Thus, we could not categorize those health problems, other than to say they were gynecologic in nature.

In addition to the annual and follow-up interviews, we used an independent passive-surveillance system to identify ectopic pregnancies and other serious health events. We describe the passive-surveilhmce system in more detail in the accompanying article (7). We also reinterviewed women who were reported to have received hospital care. for suspected pelvic inflammatory disease (PID).

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

FIGURE 1

Flow chart diagram of patient follow-up. *Ineligibles; women selected for the one-insertion expansion sample who reported having received two insertions. †Interviewed population; persons who were interviewed in 1994, 1995, or 1996. For the various pregnancy analyses, women with invalid insertion dates are excluded, whereas they are kept in the safety analysis. Quinacrine acceptors who got pregnant after one insertion and then had additional insertions are counted in the one-insertion group for pregnancy analysis and in the two-insertion group for safety analysis. This will create some differences in group sizes between this paper and the pregnancy analysis paper (7). ‡Lost to follow-up; these women were not interviewed in 1996.



Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

Study Populations

As shown in the participant flow chart (see Figure I), women found to be ineligible or duplicates (e.g., more than one entry in the sampling frame) were removed before analysis. The intent-to-intenticw population consisted of all women selected for the study, whether or not they were ever interviewed. The interviewed population is the subset who had been interviewed at least once in 1994 (for the retrospective study), 1995, or 1996. Of the eligible women, 96% were interviewed at least once. Only 7.5% of women interviewed in 1994 or 1995 were not interviewed in 1996; the percentages were similar in the three study groups.

Baseline Characteristics

Percentages means and standard deviations (see Table 1) are weighted for differential sampling probability and nonresponse. Almost all women were married and literate. The age distributions in the quinacrine and IUD groups were similar, but quinacrine users had higher parity. Among IUD women, only 12.4% of women reported five or more live births compared with 21.6% of quinacrine women. Quinacrine users were more likely to have used IUDs than other birth control methods immediately before undergoing their nonsurgical sterilization.

Safety Analysis

Protocol Endpoints

We initially specified four categories of serious adverse events to be evaluated in the interim analysis: ectopic pregnancy, hysterectomy, hospitalizations, and deaths. During the interim analysis, we found that participants sometimes

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 1

Participant characteristics[a], interviewed population.

Parameter	Quinacrine, overall (*n* = 2,709), wt %	IUD (n = 1,611), wt %
Insertion history		
Age at insertion[b]		
20 24	0.1	0 0
25 29	9.8	10.1
30 34	35.2	35.2
35 39	39.8	39.2
≥40	15.1	15.4
Mean (SD)	34.9 (6.32)	34.3 (4.42)
Median age (min/max)	35 (20/48)	35 (25/40)
Years since insertion at last interview		
<2	1.0	1.8
2 3	15.6	26.5
4 5	74.5	45.3
≥6	8.8	26.5
Mean years (SD)	4.8 (1.49)	4.9 (1.46)
Median years (min/max)	4.6 (0/8)	4.8 (1/8)
Sociodemognphic		
Marital status[c]		
Married	97.9	97.7
Not married	0.6	1.4
Unknown	1.5	0.9
Education		
Illiterate	0.4	0.3
Primary school (grades 1–5)	14.0	10.2
Basic school (grades 6–9)	78.2	75.1
Secondary school (grades 10–12)	5.8	9.4
Technical/vocational	1.4	3.7
College/university	0.2	1.2
Province[d]		
I: Nam Ha	49.9	50.9
2: Hai Hung	27. 1	26.2
3: Thai Binh	23.0	23.0
Obstetrical history		
Age at first pregnancy		
<20	14.6	9.7
20–24	68.2	62.3
25 29	15.9	24.9
30+	1.4	3.1
Number of pregnancies[e]		
1	0.0	4.3
2	2.3	17.4
3	14.3	25.2
4	23.5	22. 1
5	21.8	15.5
6+	38.0	15.5
Number of live births[e]		
None	0.2	0.0
1	0.2	6.3
2	8.4	29.7
3	37.7	33.4
4	31.8	18.3
5	14.4	8.3
≥6	7.2	4.1

Continued

TABLE 1

Continued.

Parameter	Quinacrine, overall (*n* = 2,709). wt %	IUD (*n* = 1,611), wt %
Number of living children[e]		
None	0 0	0.1
1	0.3	6.6
2	9.5	32.4
3	42.7	35.2
4	31.2	16.4
5	11.4	6.7
≥6	4.9	2.7
Contraceptive history: method used immediately before insertion		
None	19.8	38.6
IUD	56.5	36.7
Oral contraceptives	1.3	2.1
Condoms	3.5	5.7
Other	18.8	16.9

[a] Percentages, means, medians, and standard deviations ore weighted for differential probabilities of selection and nonresponse Frequencies ore unweighted

[b] Based on logbook/sampling frame

[c] At the 1994 interview If not available, then at the 1996 interview

[d] Provinces as they existed at the time sample selection was conducted

[e] As of the 1994 retrospective study interview

Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

cited outpatient hospital visits as hospitalizations because of ambiguous wording in the questionnaire. thereby blurring the distinction between inpatient stays (for presumably more serious events) and outpatient visits. This endpoint was therefore changed to any hospitalized or nonhospitalized health problem. The questionnaire was modified to avoid this problem with data collection in later years.

The diagnoses of ectopic pregnancies, deaths, hysterectomies, pelvic and abdominal surgeries, and cancer hospitalizations were confirmed by data reviews conducted independently by Thai Binh Medical College and FHI clinicians. Diagnoses for minor, nonhospitalized events were added later, with diagnoses agreed upon by the Thai Binh and FHI clinicians. One of the authors (D.S.) and other FHI clinicians not involved in this study reviewed medical codes for accuracy and consistency across cases. Clinicians were generally masked to method group. but sometimes the descriptions of the health problems referred to either quinacrine or IUD use.

Other Clinical Endpoints: Pelvic and Abdominal Surgeries as Well as Gynecologic Health Problems

During the course of clinical review, we decided to tabulate. but not compare statistically, *pelvic and abdominal surgeries* as a separate category. These are defined as surgeries reported in the 1995 or 1996 interviews. We also added another new endpoint, *gynecologic health problems.* in the multivariable analysis described below. For events reported during the retrospective study, this was defined as any gynecological illness because precise diagnoses were not available For events reported during the current study, in which detailed medical coding was used. this was defined as

[1] any genital health problem (excluding breast and pregnancy disorders) or [2] pelvic pain or endocrine ovarian problems. Health problems in this category include diagnoses such as menstrual disorders, vaginitis, cervicitis, pelvic inflammatory disease, ovarian cysts, and uterine fibroids.

Statistical Methods

We computed weighted percentages, means, and standard deviations using SAS, version 6.12 (SAS Systems, Cary, NC). We computed weighted, stratified annual cumulative ectopic pregnancy rates and 95% confidence intervals using the life-table method (with monthly intervals) using customized SAS programs. For better comparability to the CDC Collaborative Review of Sterilization (CREST) study of pregnancies after sterilization (9), the planned method of calculating time in pregnancy analysis was revised so as not to censor on either age or menopause status. We computed standard errors using modifications of Greenwood's method to allow for weighted observations and stratification. We do not present results if the number at risk was substantially less than 30 because such estimates may be unstable. We used Cox proportional hazards regression using SUDAAN (release 7.0, Research Triangle Institute, Research Triangle Park, NC) to account for sampling design and to compare one- versus two-insertion groups for ectopic pregnancy ($a = 0.05$, two-tailed).

Our interim analysis plan was to test safety events by comparing proportions of groups experiencing the end points, whereas our final analysis will conduct a time-to-event analysis. This decision is supported by the fact that follow-up time did not differ significantly across groups.

We calculated odds ratios (OR), 95% confidence intervals, and tests of significance for comparison of the study groups using logistic regression analyses, using SUDAAN to account for the sampling design The analysis assumed stratified random sampling, with replacement, with stratification on province, district, method group (quinacrine/IUD), and logbook age category. The comparison between groups was tested by the Wald χ^2 statistic. Because of the rarity of ectopic pregnancies, hysterectomies, and deaths, these ORs approximate relative risks.

Small numbers of events are a concern for logistic regression because the overall type I error rate can be inflated. Poisson regression is preferable, but methods for dealing simultaneously with unequal sampling weights and Poisson regression are not readily available. We therefore decided to analyze the data by logistic regression but to use a more stringent alpha criterion (0.01) to avoid inappropriate inference. We made this decision before the analysis was conducted

Covariate Adjustment

Although we originally did not plan to include a covariate adjustment of safety events in the interim analysis, we later decided to add some basic potential confounders to the logistic model, mainly because of the unanticipated difference in parity between the two groups. The study clinician (D.S.) selected three potential confounders: age at insertion (using an improved age measure based on animal year of birth), parity at insertion (defined as number of live births at time of insertion), and education. These covariates were specified before knowing their impact on the comparison.

Subgroup Analysis to Handle Information Bias

The expansion group of one-insertion women had only two chances to be interviewed (1995 and 1996), as compared with other one-insertion women and all of the two-insertion women, who had three chances to be interviewed (1994, 1995, and 1996). This created an information bias: women in the expansion group reported far fewer health problems than did other one-insertion women: 28% vs. 64% ($\chi^2 = 160.10$. $P \ll .001$). Presumably, because of the longer recall period at the first interview, minor illnesses may have been forgotten. This information bias will artificially decrease the difference in health problems between the quinacrine and IUD groups and artificially increase the difference in health problems between the one-insertion and two-insertion groups To eliminate this bias, we conducted subgroup analyses including only women interviewed in 1994 but using all available data for this subset of women.

RESULTS

Primary Analysis

The primary safety analysis (see Table 2) was conducted on the intent-to-interview population, including women who were never interviewed because they had died before contact. A woman was counted only once in each category but could contribute to more than one category. For example, the tabulation of *any health problems* includes women who had ectopic pregnancies or hysterectomies. Percents are weighted for differential probability of selection **and** for nonresponse

Quinacrine-treated women had more ectopic pregnancies and hysterectomies than did IUD-treated women, with ORs of 2.33 (95% CI: 0.84, 6.51) and 2.62 (95% CI: 0.85, 8.09), respectively. But these differences were not significant, perhaps because of the small numbers of events. The numbers of deaths were similar in both groups, with an OR of 1.33 (95% CI: 0.49, 3.59). and none of the deaths were attributed to either quinacrine or IUD use. A fatality due to a choriocarcinoma occurred in a woman who had received quinacrine about a year after having a molar pregnancy. A fatality due to a uterine cancer occurred in an IUD user, but we were unable to locate her hospital records to determine the type of uterine cancer.

We repeated these analyses, excluding the 62 women in the IUD sample who later received quinacrine and the 181

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 2

Comparison of study groups reporting selected adverse events: intent-to-interview population, all participants.

Event	Quinacrine, two insertions (n = 1,366)		Quinacrine, one insertion (n = 1,474)		Quinacrine, overall (n = 2,840)		IUD (n = 1,658)		Overall quinacrine vs. IUD		
	n	(wt %)	n	(wt %)	n	(wt %)	n	(wt %)	Odds ratio (95% CI)	Chi square[a]	P value
Ectopic pregnancy	9	(0.7)	9	(0.6)	18	(0.6)	5	(0.3)	2.33 (0.84. 6.5 1)	2.66	0.1031
Hysterectomy	7	(0.5)	11	(0.7)	18	(0.6)	4	(0.2)	2.62 (0.85, 8.09)	2.83	0.0924
Any health problems	865	(63.2)	547	(37.0)	1412	(56.3)	789	(47. I)	1.45 (1.27. 1.65)	31.68	<<.0001
Death	5	(0.4)	13	(0.9)	18	(0.5)	6	(0.4)	1.33 (0.49. 3.59)	0.32	0.5738
Post hoc: my abdominal or pelvic surgery	14	(1.0)	17	(1.2)	31	(1.1)	7	(0.4)	—	—	—

Note: Ectopic pregnancy, hysterectomy. hospitalization, and death were specified in protocol as key safety events for interim analysis. Frequencies are unweighted: percentages are weighted for sampling and nonresponse. Because of concerns regarding misinterpretation of the question. the hospitalization endpoint was revised to include all health problems. See text.

[a] Wald χ^2 for study group (quinacrine vs. IUD) from logistic regression model. Takes sampling design and nonresponse into account.

Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

women in the quinacrine sample who later used an IUD (data not shown). Such cross-overs might blur the distinction between groups and underestimate the effect of the method. However, because cross-over could be related to method problems, the exclusion itself can introduce bias. Results were similar, except that the risk of ectopic pregnancy in quinacrine users appeared to increase because of the elimination of two ectopic pregnancies from the IUD group. In fact, one of those two women had had her ectopic pregnancy before her quinacrine insertion. The other woman's quinacrine insertion status is uncertain, but she was eliminated because we used a very liberal definition of cross-over

In case a woman's decision not to come back for a second insertion stemmed from health problems after the first insertion, we also conducted a post hoc analysis to compare IUD women with quinacrine women who were intended to receive two insertions. Results were similar to those of the main analysis (data not shown).

The most common reasons for "any abdominal or pelvic surgery" were enlarged uterine fibroids, ectopic pregnancies, appendicitis, and ovarian cysts. This post hoc tabulation includes women who had hysterectomies and ectopic pregnancies, but the numbers are less than the totals of hysterectomies and ectopic pregnancies given in the upper rows of the same table. That is because the post hoc tabulation includes only surgeries reported in the 1995 and 1996 interviews, for which more detailed clinical data were available. A higher percentage of quinacrine than IUD acceptors had surgery: 1.1% compared with 0.4%. Comparing women who had two vs. one quinacrine insertions, the percentages are similar: 1.0% vs. 1 2%, respectively.

Quinacrine acceptors were more likely than IUD acceptors to report "any health problem," and women who had two quinacrine insertions reported more health problems than women who had one insertion. However, further analysis controlling for information bias (see below) showed that the difference between the one- and two-insertion quinacrine groups was most likely due to information bias.

Ectopic Pregnancies: Two vs. One Quinacrine Insertions

We identified nine ectopic pregnancies in each quinacrine insertion group. All the ectopic pregnancies were identified by both the annual interviews and the passive-surveillance system. We identified only one ectopic pregnancy among women who received two insertions at age 35 or older (data not shown). The cumulative life-table ectopic pregnancy rate at 5 years was 0.7 per 100 women after both the one- and two-insertion groups (see Figure 2). Though the rate at 5 years was identical. one-insertion women tended to have their ectopic pregnancies sooner than two-insertion women, giving a hazard ratio of 0.77 (95% CI: 0.25, 2.41).

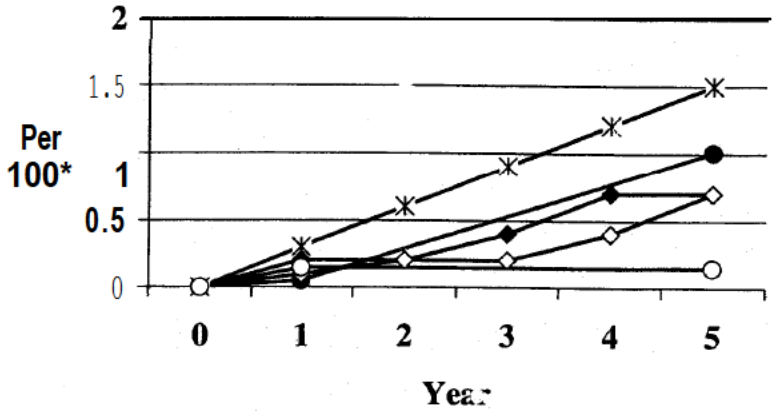
Multivariate Logistic Analysis of Health Problems

Adjusting for age, education, and parity, we compared quinacrine versus IUD and one- vs. two-insertion groups for odds of experiencing [I] any health problems, [2] nongynecologic health problems, and [3] gynecologic health problems (see Table 3). These adjusted analyses were conducted with all participants and then repeated for those who were interviewed in the retrospective study, as a way to control for information bias among the one-insertion group. A tabula-

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

FIGURE 2

Five-year cumulative ectopic rates per 100 women for one- and two-insertion quinacrine groups, compared with a US estimate for nonoontraceptors and with US CREST data for surgical sterilization by bipolar cautery and postpartum partial salpingectomy. CREST = Collaborative Review of Sterilization. CREST data are from Peterson (10); the "no method" estimate is from DeStefano (11). Postpartum partial salpingectomies include the Pomeroy method and similar methods. ✳, No method (11); —●—, CREST, bipolar cautery; —○—, CREST, postpartum partial salpingectomy; —◆—, one-insertion quinacrine; and —◇—, two-insertion quinacrine.



Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

tion of the gynecologic events included in this latter analysis is given in Table 4.

Controlling for covariates and including data from all participants, we found that quinacrine-treated women reported more gynecologic health problems than did IUD women, OR 1.45 (95% CI: 1.13, 1.86) and reported more nongynecologic health problems, OR 1.64 (95% CI: 1.42, 1.90). When the analysis was restricted to those interviewed in 1994. this pattern did not change.

Comparing women who received two insertions **versus** those who received one insertion and including data from all participants, we found that two-insertion women reported

TABLE 3

Post hoc analysis: comparisons between quinacrine and IUD groups and between two- and one-insertion quinacrine groups on overall health problems and gynecologic health problems.

	Quinacrine vs. IUD3				Two insertions vs. one insertion[b]			
Analysis group	Odds ratio	95% CI	Chi-square[c]	*P* value	Odds ratio	95% CI	Chi-square	*P* value
All participants								
Overall health problems	1.39	(1.21. 1.61)	20.26	<0.0001	2.13	(2.32.3.22)	143.55	<<0.0001
Nongynecologic problems	1.64	(1.42. 1.90)	45.06	<<0.0001	2.77	(2.35, 3.26)	146.1	<<0.0001
Gynecologic health problems	1.45	(1.13, 1.86)	8.54	0.0035	1.49	(1.15. 1.94)	8.81	0.003
Participants in retrospective study[d]								
Overall health problems	1.84	(1.56, 2.16)	52.01	<0.0001	1.10	(0.86. 1.40)	0.56	0.4540
Nongynecologic problems	2.15	(1.83. 2.53)	84.49	<<0.0001	1.17	(0.92. 1.48)	1.61	0.2044
Gynecologic health problems	1.60	(1.23, 2.09)	12.04	0.0005	0.90	(0.64. 1.26)	0.40	0.5263

Note: Adjusted for age at insertion. number of live births at insertion. and education of interviewed population.

[a] 2.5 13 quinacrine women and 1.477 IUD women had nonmissing data and are included in the analysis.

[b] 1.234 two-insertion women and 1.279 one-insertion women had nonmissing data and are included in the analysis.

[c] Wald χ^2 from logistic regression analysis. I df. Takes sampling design and nonresponse into account.

[d] The retrospective study participants include women who were interviewed in the 1994 retrospective study and exclude an expansion group of one-insertion women who were first interviewed in 1995.

Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

TABLE 4

Gynecologic health problems[a] reported 1994-l 996 by women interviewed in the retrospective study.

Gynecologic problem	Quinacrine two insertions (n = 1,271): wt %, (n)	Quinacrine, one insertion (n = 405): wt %, (n)	Quinacrine overall (n = 1,676): wt %, (n)	IUD (n = 1 499): wt %, (n)
From the 1994 survey	8 25 (105)	10 34 (42)	8 45 (147)	4 94 (75)
Repotted in 1995 or 1996	5 70 (72)	3 80 (15)	5 52 (87)	3 02 (47)
Amenorrhea	0 00	0 24	0 02	0 00
Cervicitis	0 23	0 27	0 24	0 30
Cervix disorder	0 08	0 00	0 07	0 00
Dysmenorrhea	0 79	0 24	0 74	0 56
Endometriosis	0 00	0 00	0 00	0 06
Endometritis	0 56	0 00	0 50	0 26
Hypomenorrhea	0 08	0 25	0 09	0 06
Leukorrhea	0 55	0 76	0 57	0 37
Menopause	0 24	0 00	0 22	0 06
Menorrhagia	0 16	0 00	0 15	0 37
Menstrual disorder	1.01	0 27	0 94	0.31
Ovarian cyst	0 40	0 24	0 38	0 06
Pelvic pain	0 32	0 54	0 34	0 12
Premenstrual syndrome	0 16	0 00	0 15	0 00
Salpingitis	1.34	1.55	1.36	0 48
Uterine disorder	0 16	0 00	0 14	0 00
Uterine fibroids enlarged	0 24	0 49	0 27	0 13
Vaginal moniliasis	0 08	0 00	0 07	0 00
Vaginitis	0 16	0.51	0 19	0 24
Vulvovaginitis	0 08	0 00	0 07	0 00

[a] Based on definition of gynecologic end point used for multivariable analysis

Sokal. Interim quinacrine safety analysis. Fertil Steril 2000.

more gynecologic health problems than did one-insertion women, OR 1.49 (95% CI: 1. 15, 1.94). and more nongynecologic health problems. OR 2.77 (95% CI: 0.92. 1.42). When the analysis was restricted to those interviewed in 1994. the findings changed substantially. Two-insertion women did not report more gynecologic health problems than did one-insertion women, OR 0.90 (95% CI: 0.64, 1.26). nor nongynecologic health problems. OR 1.17 (95% CI: 0.92. 1.48).

Although the two-insertion group initially appeared more likely than the one-insertion group to report gynecologic or nongynecologic health problems, this difference disappeared when we controlled for information bias.

Pelvic Inflammatory Disease

Table 4 shows a list of the problems and the percentages of women who reported gynecologic problems among the women in the restricted analysis. About 8% of women who received quinacrine reported gynecologic problems in the retrospective survey, but we did not have the clinical details needed to permit detailed categorization.

Based on the interviews in 1995 and 1996, women who received a diagnosis of either salpingitis or endometritis (see Table 4) were considered to have had pelvic inflammatory disease (PID). PID was the most commonly reported gynecologic health problem; it was found in 1.86% (n = 30) of quinacrine acceptors and 0.74% (n = 12) of IUD acceptors. However, the clinical diagnosis of PID is difficult and often inaccurate. Without careful confirmation, a clinical diagnosis of PID may actually reflect lower-genital tract infection such as cervicitis. vaginitis or other gynecologic or even gastrointestinal disease

To try to clarify the data, FHI and Thai Binh clinicians reviewed the questionnaires of women that reported receiving hospital care for gynecologic or abdominal illness, blinded to study group. We identified 39 women with symptoms suggestive of PID reported in a 1994, 1995. or 1996 interview. Of 17 women identified from the 1994 survey, I I were IUD users, and six were quinacrine users. Of 22 women identified from the 1995 and 1996 surveys, three were IUD users, and 19 were quinacrine users.

The women who reported events during 1995 or 1996 were then interviewed again to gather additional details concerning their illnesses. We did not reinterview women who were identified from the 1994 interviews because of concerns about recall because those events could have occurred anytime between 1989 and 1994. Among the 22 events reported in 1995 or 1996. we found that eight of the 22 women who reported hospital care for PID had been hospitalized. Thirteen women had visited a hospital but had been treated as outpatients, and information was unavailable

for one woman who had moved to Hanoi. In reviewing the description of the illnesses, two of three reviewing physicians doubted the diagnosis of PID in four of the nonhospitalized women. We did not identify the occurrence of any abortions before the suspected PID events. Two of the hospitalized women had had surgical sterilizations after entry into this study and within a year or two before being diagnosed with PID.

We did a post hoc breakdown of the 39 PID cases by time of report (either before or after increased publicity about quinacrine in 1994; cases are divided by diagnosis or onset dates before vs. on or after January I, 1994) to see whether the data were compatible with a reporting bias. We found that in the earlier period, there were eight cases (0.3%) among quinacrine users and IO cases (0.6%) among IUD users. In the later period, IO cases (0.4%) occurred among quinacrine users, and only one case (0.1%) occurred among IUD users. The proportion of quinacrine women with PID was comparable before and after 1994, whereas the proportion of IUD women with PID was higher during the-earlier versus the later period. To see whether the episodes of PID among IUD acceptors might have been attributed to IUD insertions, we reviewed the intervals between IUD insertion and diagnosis of PID and found exact dates of both events for six women. For these women, the intervals ranged from 2 to 22 months. All but one of the intervals were greater than 6 months, suggesting that the cases were not related to the IUD insertion procedures.

DISCUSSION

Ectopic Pregnancy Rates

Despite the relatively high pregnancy rate after one insertion (7), the ectopic pregnancy rate after one insertion was similar to the ectopic pregnancy rate after two insertions. Although the risk of ectopic pregnancy in the quinacrine group was higher than that of the IUD group. it was similar to ectopic rates reported in the CREST study (IO) and lower than an estimate for the rate among noncontracepting women in the United States (1 I). For women in the CREST study who had bipolar coagulation, the most common form of surgical sterilization in the United States, the rate at 5 years was IO per 1,000 women, slightly higher than the rate of 7 per 1,000 women for women receiving quinacrine. For women in the CREST study who had postpartum partial salpingectomy, the rate at 5 years was 1.5 per 1.000 women, lower than the quinacrine rate. A recent more detailed analysis of the CREST data (12) suggests that the original CREST report (10) may have overestimated the risk of ectopic pregnancy after bipolar cautery when improved surgical techniques are used. Based on more detailed analysis by year of the procedure, the pregnancy rate after bipolar cautery sterlizations that were performed more recently with at least three bum points per tube is estimated to be 3.2 per 1.000 women at five years. This would necessarily mean lower rates of ectopic pregnancy than the curve shown in Figure 2, which is based on the earlier CREST report.

Another way to look at ectopic pregnancies is as a proportion of all pregnancies. As would be expected given the higher pregnancy rate after quinacrine, the proportion of ectopic pregnancies among all pregnancies after quinacrine was lower than after surgical sterilizations in the CREST study, 5.8% vs. 32.9%, respectively.

The CREST study gathered data by telephone rather than by home visits and did not evaluate possible underreporting of pregnancies, as we did with our passive-surveillance system (7). We are confident of the accuracy of the number of ectopic pregnancies identified since 1995 because we identified all the ectopic pregnancies in both the annual interviews and the passive-surveillance system. In addition. the ectopic rates reported here appear similar to rates reported from Chile. 2 per 1,000 women at 5 y and 9 per 1,000 at 10 y (13).

Hysterectomies

We found an increase in the risk of hysterectomy in the quinacrine group compared with the IUD group (OR 2.6) that was not statistically significant. A recent CREST report showed a statistically significant 4-fold higher rate of hysterectomy among women who underwent surgical sterilization compared with women whose husbands had had a vasectomy (14). However, the authors note that "biologic factors are unlikely to be responsible for this association." The increase in the rate of hysterectomies in the CREST study probably involves patient and physician behavior rather than adverse biologic effects of the sterilization procedure. It is possible that an analogous effect could be operating in Vietnam with respect to quinacrine sterilization: however, biologic factors cannot be ruled out.

Limitations

Major limitations of this study with respect to safety issues are its observational nature and the use of an IUD comparison group rather than a group of women who had had surgical sterilizations. Although matching and multivariate analysis can adjust for certain differences between groups, women who choose permanent vs. temporary methods may have intrinsic differences that defy statistical adjustment. For example, physicians often advise women with serious systemic diseases to be sterilized. In addition, the abrupt halt of the quinacrine program and associated adverse publicity about quinacrine may have produced a reporting bias.

Media publicity about contraceptives has been clearly shown to have substantial effects on women's health concerns, perceptions. physician visits and contraceptive preferences. Adverse publicity can lead to abrupt and sometimes disproportionate changes in contraceptive practice when the media report medical problems. For example. publicity about oral contraceptives and the risk of breast cancer has periodically caused fluctuations in the use of oral contraceptives,

and problems with the Dalkon Shield caused the virtual disappearance of all IUDs from clinical use in the United States. Media reports of a potential increase in prostate cancer risk following vasectomy may have caused a leveling off of the demand for vasectomy, but the evidence is inconclusive (15). In this study, we did not attempt to control for possible reporting bias due to adverse publicity about quinacrine

Other limitations of this interim analysis include limited statistical power and the conduct of exploratory analyses, designated in the tables as ad hoc if requested generally before other results were known or as post hoc if clearly following up observed findings.

CONCLUSIONS

First, the proportion of quinacrine acceptors with ectopic pregnancies was higher than among IUD acceptors. However. the ectopic pregnancy rate in quinacrine acceptors was similar to the rate among women who had surgical sterilizations in the United States. Within the quinacrine group, women who had received either one or two insertions were at similar risk for ectopic pregnancy.

Second, a higher proportion of quinacrine acceptors reported gynecologic and nongynecologic health problems, compared with the IUD group. Because this was observed for nongynecologic events unlikely to be associated with quinacrine use, this may be due to intrinsic differences between the two groups or to reporting bias associated with the adverse publicity about quinacrine Within the quinacrine group. a similar proportion of women who had received either one or two insertions had gynecologic problems once we controlled for information bias. We emphasize the preliminary nature of the results at this stage of the study.

References

1. Zipper J Cole LP, Goldsmith A Wheeler R Riven M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstet 1980: 18:275–9.
2. Kessel E 100,000 quinacrine sterilizations Adv Contracept 1996;12: 69-76
3. Sokal D, Zipper J King T Transcervical quinacrine sterilization: clinical experience Int J Gynaecol Obstet 1995:51(suppl 1):S57-69
4. Kessel-E Quinacrine sterilization: an assessment-of risks for ectopic pregnancy, birth defects and cancer Adv Contracept 1998;14:81-90
5. Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991 Fettil Steril 1995;64:325–34.
6. Dabancens A, Sokal DC, Pruyas M Riven M, Zipper J Prevalence and standardized incidence rates of preclinical cervical pathology among 1 061 women sterilized with tmnscervical quinacrine hydrochloride pellets Fertil Steril 1995;64:444-6
7. Sokal D, Hieu DT, Weiner DH, Vinh DQ, Vach TH Hanenberg R Long-term follow-up after quinacrine sterilization in Vietnam Part I: interim efficacy analysis Fertil Steril 2000:74: 1084-91
8. US Food and Drug Administration COSTART: coding svmbols for thesaurus of adverse reaction terms 5th ed Rockville, MD: National Technical Information Service (NTIS); 1995 Publication PB95-269023.
9. Peterson HB, Xia Z, Hughes JM Wilcox LS Tylor LR, Trussel J The risk of pregnancy after tubal sterilization: findings from the US Collaborative Review of Sterilization Am J Obstet Gynecol 1996;174: 1161-70
10. Peterson HB Xia Z, Hughes JM, Wilcox LS Tylor LR Trussell J The risk of ectopic pregnancy after tubal steri'ization. N Engl J Med 1997:336:762–7.
11. DeStefano F Peterson H Layde P Rubin G Risk of ectoqic pregnancy, following tubal sterilization -Obstet Gynecol 1982;60:326–30.
12. Peterson HB Xia Z Wilcox LS. Taylor LR Trussell J Pregnancy after tubal sterlization with bipolar electrocoagulation. US Collaborative Review of Sterilization Working Group Obstet Gynecol 1999;94: 163-7
13. Feldblum PJ, Hays M Zipper J, Guzman-Serani R Sokal DC Pregnancy mtes among Chilean women who had non-surgical sterilization with quinacrine pellets between 1977 and 1989 Contracept In press
14. Hillis SD Marchbanks PA, Tylor LR Peterson HB Higher hysterectomy risk for sterilized than nonsterilized women: findings from the US Collaborative Review of Sterilization Obstet Gynecol 1998;91: 231-6
15. Magnani RJ, Haws JM, Morgan GT, Gargiullo PM Pollack AE, Koonin LM Vasectomy in the United States, 1991 and 1995 Am J Public Health 1999:89:92–4.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

FERTILI
VOL. 74, NO. 4, OCTOBER 2000

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996

David C. Sokal, M.D., [a] Alfredo Dabancens, M.D., [b] Rene Guzman-Serani, M.D.,[c] and Jaime Zipper, M.D. [d]

Family Health International, Research Triangle Park, North Carolina

Objective: To determine whether further follow-up of a cohort of Chilean women would demonstrate an increased risk of invasive cancer associated with quinacrine sterilization.

Design: Cohort study. Cancer cases were evaluated using cohort analyses.

Setting: Santiago and Valdivia, Chile

Subject(s): Fourteen hundred ninety-two women who received transcervical quinacrine pellets for contraceptive sterilization between 1977 and 1989.

Method(s): Interviews and reviews of medical records.

Main Outcome Measure(s): Age- and site-specific incidence of invasive cancers.

Result(s): During 13,444 person-years of follow-up, 25 invasive cancers were identified, including 8 new cases. This compares with 21.9 expected cancers, based on age-specific rates from the Cali, Colombia, cancer registry. Eight cases of cervical cancer were observed, compared with the 6.3 expected. Since the initial study's confirmation of a single case of leiomyosarcoma, no other noncervical uterine cancers have been diagnosed. The number of observed person-years gives an expectation of 0.62 noncervical uterine cancers. One case of ovarian cancer was diagnosed, compared with the 0.99 expected.

Conclusion(s): Rates of cancer among women exposed to intrauterine quinacrine are not significantly different from population-based rates. (Fertil Steril® 2000;74: 169-71. 02000 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, cancer incidence, cohort analysis, tubal sterilization, follow-up studies

Received August 30, 1999; revised and accepted January 24, 200O.

Supported in part by Family Health International (FHI) with funds from the Mellon Foundation. FHI is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, STDs: and AIDS. Views expressed in this report do not necessarily reflect those of FHI or of the Mellon Foundation.

Reprint requests: Dr. David C. Sokal. Family Health International, P:O. Box 13950, Research Triangle Park, North Carolina 27709 (FAX: 919-544-7261).

[a] Family Health International.

[b] Sotero del Rio Hospital, Area Sur Oriente, Santiago, Chile.

[c] Escuela de Medicina, Universidad Austral de Chile, Valdivia. Chile.

0015-0282/00/$20.00
PII S001 5-0282(00)00581-I

The transcervical insertion of quinacrine pellets has been proposed as a potentially safer and less expensive method of voluntary female sterilization than surgery. However, since quinacrine is a mutagen, there has been some concern about the potential risk of cancer. We conducted a retrospective cohort study to evaluate the occurrence of an apparent cancer cluster among women in Chile who had received quinacrine pellets. That study concluded that the cluster was not related to quinacrine (1).

MATERIALS AND METHODS

Since the initial report, we have gathered 4 additional years of follow-up data. The cohort includes 1,341 women from Santiago and 15 1 from Valdivia. In the initial study, we interviewed 138 (9 1.4%) women from Valdivia and 664 (49.5%) women from Santiago. During the additional years of follow-up, we made further efforts to find and interview more women.

The study's procedures involved [l] clinic record reviews of all women; [2] active tracing of these women and interviews with them to identify cancer occurrences through the 1995 calendar year and part of 1996; [3] hospital record reviews for all cancer cases identified; and [4] review of pathology slides for all gynecologic cancers by an independent pathologist.

This follow-up study was initially approved by FHI's institutional review board in June 1990. The collection of the additional follow-up data reported here was approved in August 1993.

We estimated the expected cancer risk for the cohort using direct standardization with the age- and gender-specific incidence rates from

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Cali, Colombia (2). Additional details regarding identification of study participants, choice of the Cali cancer registry for calculation of expected numbers, and survey and statistical methods were described in a previous publication (1). We also used data from nine US cancer registries to calculate the number of expected cases of uterine leiomyosarcomas (3). An independent pathologist reviewed the pathology slides and confirmed the diagnosis for the new cases of gynecologic cancers that we identified.

RESULTS

From 1977 through 1989, 1,492 women in Chile received voluntary sterilization via transcervical quinacrine pellets and thus were eligible for the retrospective cohort. Since the initial report, an additional 441 women were located and interviewed. Thus we located and interviewed a cumulative total of 1,243 (83%) women: 1,100 (82%) from Santiago and 143 from Valdivia (95%). At least 6 months of follow-up are available for 97.5% of the cohort.

We found 8 additional cancers: one new case in Valdivia and 7 in Santiago. Thus the present analysis is focused on a cumulative total of 25 observed invasive cancers: 9 from Valdivia and 16 from Santiago. Of the 25 women with invasive cancers, 9 were dead at the time the data were gathered.

We observed 13,444 person-years and calculated an expected rate of 7.86 gynecological cancers per 10,000 person-years based on data from the Cali, Colombia. cancer registry. Thus, for a one-tailed test with a .05 significance level, our study has 73% power to detect a two-fold or greater excess of all gynecologic cancers (relative risk [RR] = 2) and 65% power to detect an increase of cervical cancers.

Comparisons-Interviewed Versus Noninterviewed Subjects

We compared the characteristics of the 1,100 Santiago cohort members who were interviewed and the 241 who were not interviewed (data not shown). Interview status in Santiago varied sporadically by year with a range of 8.7%-28.5% not interviewed. Women who were younger when they were sterilized were less likely to be interviewed than older women, ranging from 28.0% not interviewed among 257 women ages <30 years to 10.8% among 158 women ages 240. There was no significant difference in interview status by years of education, number of live births, or previous contraceptive method. At the Valdivia site, 143 of 15 1 women were interviewed, so a tabulation of interviewed versus noninterviewed women was not considered useful.

There were two cancers in the noninterviewed women, a cervical cancer and a bile-duct cancer. Using a one-tailed test, there was no significant difference in cancer incidence per 1,000 person-years between the Santiago women interviewed and not interviewed (1.32 vs. 2.89, P = .86).

TABLE 1

Observed and expected cancer diagnoses for all breast, cervical, uterine, and ovarian cancers, quinacrine cohort 1977-I 996.

Site	Observed	Expected[a]	Ratio	95% Confidence limits
All	25	21 92	1.14	0 74-1 .68
Breast	6	6.1 I	0 98	0 36-2 14
Cervix	8	6.25	I .28	0 54-2 53
Ovary	I	0 99	1.01	0 10-5 66
Other uterine	I	0.62	1.61	0 16-9 03

[a] Expected numbers were calculated from age- and gender-specific incidence rates from the Cali, Columbia, cancer registry Volume V rates were used for person-years contributed during 1977-I 98 1 Volume VI rates were used for years 1982-1986 Volume VII See ref (2)

Sofal Cancer risk and quinacrine. Fertil Sfril 2000.

Temporal Evaluations

We examined the time elapsed from sterilization to cancer diagnosis for the most frequent cancers, breast (6 cases) and cervical (8 cases). The women with breast cancer were an average of 45 years of age, and the time elapsed since their first quinacrine insertion averaged 7 years. The women with cervical cancer were an average of 43 years of age, and the time elapsed since their first quinacrine insertion averaged 8 years. Both breast and cervical cancers varied widely in terms of the interval from first quinacrine insertion to cancer diagnosis (data not shown).

Cohort-Observed Versus Expected

Based on the age distribution and person-years of exposure over the 20-year interval, 21.9 new cancer cases would be expected. The 25 cancer cases observed are not significantly different from the number expected (observed/expected ratio = 1.14; 95% CI = 0.74, 1.68). With respect to geographic location, there were 16 observed and 18 3 expected in Santiago, for a ratio of 0.87; 95% CI = 0.51. 1.42, and 9 observed and 3.6 expected in Valdivia, for a ratio of 2.49; 95% CI = 1 .I 1, 4.74.

Site-Specific Evaluation

The 8 new cancers included 3 cervical cancers and one each of the following: breast, ovary, gall bladder, multiple myeloma, and stomach. For breast cancer, the observed/expected ratio was 0.98, with a 95% confidence interval of 0.3-2.14 (Table I) . For cervical cancer the ratio was 1.28 with a 95% confidence interval of 0.54-2.53. Neither of these results provides evidence of a significant association. We observed one case of ovarian cancer in this cohort, while 0.99 cases were expected.

A case of uterine leiomyosarcoma was identified in the first study (1). No additional cases of Ieiomyosarcoma or other non-cervical cancers of the uterus have been identified. Based on the Cali data, one would expect about 0.48 cases of

cancer of the body of the uterus if "unspecified uterine" cancers are excluded or 0.62 cases if unspecified uterine cancers are included. Based on US data, the number of expected uterine leiomyosarcomas would be approximately 0.17 or 0.29, using rates for white or black women, respectively (3). These are not significantly different from the one case observed.

DISCUSSION

In the current analysis, we had a power of 73.5% to detect a two-fold increase in all gynecologic cancers (RR = 2). The results reported here still show evidence of the Valdivia cluster, but the cluster effect has weakened with the inclusion of additional data. Two of us (AD, JZ) recently published an analysis of a slightly larger group of women from Santiago only, using a hospital-based comparison group. That report listed one additional case of cancer, an oral cancer (4). However, on further review of hospital records, we found that that cancer had been diagnosed prior to the woman's quinacrine insertion. The inferences that can be drawn from this study are limited because of the relatively small number of women in this cohort; however, we have not found a significantly increased risk of cancer associated with the transcervical administration of quinacrine pellets.

Compared with our original report, the rate of follow-up interviews has improved. It seems unlikely that the differences between the interviewed and noninterviewed women in Santiago would significantly bias the analysis.

If we followed this cohort for an additional 10 years through 2006, assuming a 20% loss Eo follow-up, the power of the study would increase. We would have 80% power to detect a 40% increase in all gynecologic cancers (RR = 1.4) or a 45% increase in cervical cancers (RR = 1.45). For other uterine cancers and ovarian cancers. we would have the power to detect increased relative risks of about 1.5.

Compared with the United States, cervical cancer rates in the Cali registry are high. However, in comparison with other South American cancer registries, the cervical cancer rates in Cali are about average. Of the five well-established' South American cancer registries whose results have been reported by the International Agency for Research on Cancer (IARC), Cali's cervical cancer rate is in the middle. Two registries, Goiana, Brazil, and Trujillo, Peru, report higher cervical cancer rates than Cali, and two, Quito, Ecuador, and Porto Allegre, Brazil, report lower rates (2). Furthermore, the IARC editors note that three of these five registries, but not Cali or Trujillo, are probably subject to under-ascertainment Cali was chosen for comparison because it has had the best-established cancer registry in South America, with regular reporting to IARC from 1962 through 1991 (2).

Despite the reassuring results of this follow-up study, additional animal studies of quinacrine's carcinogenic potential are needed before the US Food and Drug Administration would consider approving quinacrine pellets for nonsurgical sterilization.

' "Well established" is defined as registries that have had data included in both Volumes VI and VII of the IARC series.

Acknowledgements: The authors thank Dr Debra Novotny for assistance in reviewing the pathology slides and Melissa Hays and Carlos Henriquez for their statistical assistance

References

1. Sokal DC, Zipper J, Guzman-Serani R, Aldrich TE Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets 1977 to 1991 Fertil Steril 1995:64:325-34
2. Parkin DM, Whelan SL, Ferlay I. Raymond L, Young J Cancer incidence in live continents: volume VII Lyon: International Agency for Research on Cancer (IARC), 1997 (IARC Scientific Publications; no *143).*
3. Harlow BL, Weiss NS Lofton S The epidemiology of sarcoma of the uterus J Natl Cancer Inst 1986;76:399-402
4. Dabancens A, Pruyas M, Rivera M Zipper J Seguimento de canceres en una cohorte de mujeres esterilizadas con pellets de quinacrina Ginecol Reprod 1998;6:21-5

Advances in Contraception, 1999; 15: 175-178.

S.N. Bhuiyan, R. Begum, Department of Obstetrics and Gynecology, Chittagong Medical College, Chittagong, Bangladesh.
Contraception 2001 Nov;64(5):281-6. - (CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Quinacrine sterilization: experience among women at high risk for surgery

A.R. SARIN

Department of Obstetrics and Gynecology, Government Medical College, and Aastha Medical Center, Pa tiala, India

Abstract

A non-surgical method of female sterilization is needed because many women are at high risk of complications with standard surgical methods, especially in developing countries. Also, some women who desire sterilization refuse it for fear of surgery. To meet these special needs, we initiated a trial of quinacrine sterilization (QS), a non-surgical method involving transcervical insertion of 252 mg quinacrine as pellets by a modified IUD inserter. Diclofenac (50 mg) was inserted with the quinacrine pellets. This insertion was repeated a month later and a 150-mg injection of depo medroxyprogesterone was administered at the time of the first insertion. One hundred and thirty-four women of reproductive age entered the trial. Of these, 92 were considered to be at high risk for surgery, 27 had refused surgery, and 15 had had failed surgical sterilization. Mean follow-up was 3.46 years. No pregnancies or serious complications were experienced. The main side-effect was menstrual irregularity, due probably to the depo medroxyprogesterone injection. QS is a suitable option for women at high risk of surgical complications.

Introduction

Most female sterilization trial reports, including those for quinacrine sterilization (QS), are conducted among healthy women or at least women of average health in their area. To understand how we came to design a QS trial especially for high-risk women, the following aspects of our situation at a government medical school in a predominantly rural area of the Punjab in India must be considered. First, our government advises against surgical female sterilization for women with hemoglobin less than 7 g/dl, but 57% of women in our area are this anemic [1]. Second, since we are based at a referral center, we see women whose life would be endangered by another pregnancy but who are very poor risks for any surgery. Third, women

experiencing sterilization failures are frequently referred to us, but it is known that previous pelvic surgery increases the risk of serious complications of surgical sterilization by a factor of 2.7 [2]. Fourth, we find many women who desire no more children but who fear any surgery, despite their obvious need for sterilization. And, finally, our department has a leadership tradition of promoting choice among well-informed women. One must also consider the general situation of women and their children in the Punjab - 52% are illiterate, the mean number of years of schooling being 2.0. They have an average of 2.9 children, compared with 3.4 for all of India, but 46% of children under 4 years of age in the Punjab are underweight and 40% are stunted [3] Fewer than half of the women who say they want no more children are actually protected by sterilization.

It was in this context, and after reviewing published reports showing the safety and reasonable efficacy of QS [4-6], that we decided to make this method available in our department.

Materials and methods

From December 1993 through July 1999, we studied 134 women of reproductive age who had two transcervical insertions of 7 quinacrine pellets (252 mg; Sipharm, Sissein, Switzerland) with 2 diclofenac pellets (50 mg) a month apart during the proliferative phase of the menstrual cycle. A modified IUD inserter was used to perform the insertions that placed the pellets at the fundus following the standard protocol [7]. One 150-mg injection of depo medroxyprogesterone acetate (DMPA) was given with the first insertion as an additional contraceptive.

Of this group, 92 women were considered at high risk for surgery (having anemia, cardiovascular disease, bronchial asthma and a history of pelvic inflammatory disease); 27 had chosen a non-surgical procedure; and 15 had experienced earlier surgical sterilization failure or those for whom the operation was not technically feasible. All of these women gave their informed consent to undergo this procedure. Follow-up was scheduled for 1, 3, 6 and 12 months, and then annually, after the second insertion or whenever side-effects or complications were experienced. Home visits were made when the women did not report to the clinic. Three additional women were lost to follow-up and are not included in this analysis.

Results

No pregnancies or serious complications were reported. The mean follow-up was 3.46 years, with a minimum follow-up of 1 year. The main side-effect was transient menstrual irregularity, due probably to the DMPA injection. Other side-effects included transient lower abdominal pain, oligomenorrhea or amenorrhea and mild post-insertion bleeding.

Discussion

This is the first reported use of QS in women at high risk for surgery. The absence of major complications in this trial suggests that more experience is indicated in providing this option for such women. For normal women, QS experience exceeds 100 000 cases [8] and long-term concerns about the risks of ectopic pregnancy, birth defects and cancer appear to be similar to those for surgical sterilization [9]. Pregnancy failures are reported to be about twice those of surgical sterilization [9] but this may be acceptable to some well-informed women.

We conclude that QS is a reasonable option, especially for women who are at high risk with the surgical procedure.

Acknowledgements

The quinacrine pellets for this trial were provided by the International Federation for Family Health.

References

1. Sarin AR. Severe anemia of pregnancy: recent experience. Int J Gynecol Obstet. 1995;50(Suppl 2):545–9.
2. DeStefano F, Greenspan JR, Dicker RC, Peterson HB, Strauss LT, Rubin GL. Complications of interval laparoscopic tubal sterilization. Obstet Gynecol. 1983;61: 133–8.
3. Population Research Centre, Centre for Research in Rural and Industrial Development (PRC, CRRID) and International Institute for Population Sciences (HPS). 1993. National Family Health Survey (MCH and Family Planning) Punjab 1993. Bombay: PRC, CRRID and HPS.
4. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet. 1980;18:265–9.
5. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam. Lancet. 1993;342:213–17.
6. El-Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. Fertil Steril. 1993;59:301–4.
7. Institute for Development Training. Female voluntary non-surgical sterilization: the quinacrine method. Module 12 of Training Course in Women's Health. Institute for Development Training, Chapel Hill, 1996.
8. Kessel E. 100 000 quinacrine sterilizations. Adv Contracept. 1996; 12:69–76.
9. Kessel E. Quinacrine sterilization: an assessment of risks for ectopic pregnancy, birth defects and cancer. Adv Contracept. 1998;14:81–90.

Manuscript received 16 Nov. 99.
Acceptedforpuhlication 30 Nov. 99.

Resumé

Il est nécessaire de disposer d'une mtthode non chirurgicale de stérilisation parce que les méthodes chirurgicales courantes exposent de nombreuses femmes à des risques élevés de complications, surtout dans les pays en développement. Par ailleurs, certaines femmes qui souhaiteraient se faire stériliser, s'y refusent par crainte de l'intervention chirurgicale. Pour répondre à ces besoins spéciaux, nous avons mis en

S.N. Bhuiyan, R. Begum, Department of Obstetrics and Gynecology, Chittagong Medical College, Chittagong, Bangladesh.
Contraception 2001 Nov;64(5):281-6. - (CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

train un essai de stérilisation à la quinacrine (SQ), c'est-i-dire une méthode non chirurgicale par insertion transcervicale de 252 mg de quinacrine sous forme de pellets à l'aide d'un instrument d'insertion modifié. 50 mg de diclofenac ont été insérés en même temps que les pellets de quinacrine. Cette insertion a été répétée un mois plus tard et 150 mg de dépo-médroxyprogestérone ont été injectés au moment de la premiere insertion. Cent trente-quatre femmes en age de procreer ont été admises à participer à cet essai: 92 présentaient des risques chirurgicaux élevés, 27 avaient refuse toute intervention chirurgicale et chez 15, la méthode chirurgicale avait échoué. Le taux de suivi a été en moyenne de 3,46 ans. Aucune grossesse ou complication grave ne s'est produite. Des irrégularités menstruelles ont été l'effet secondaire principal, sans doute imputable à la dépo-médroxyprogestérone. La SQ est une option qui convient aux femmes presentant des risques élevés de complications d'ordre chirurgical.

Resumen

Se necesita un método no quirúrgico de esterilizacion femenina porque muchas mujeres corren alto riesgo de complicaciones ocasionadas por los mttodos quirúrgicos habituales, especialmente en paises en desarrollo. Además, algunas mujeres que desean esterilización la rechazan por temor a la cirugia. A fin de satisfacer estas necesidades especiales, iniciamos un ensayo de esterilizacibn con quinacrina (QS), método no quirúrgico que comprende la colocacion transcervical de 252 mg de quinacrina como pellets con un colocador DIU modificado. Con los pellets de quinacrina se insertaron 50 mg de diclofenac. Esta inserción se repitió al mes y se administrb una inyección de 150 mg de depo medroxiprogesterona en el momento de la primera inserción. Ciento treinta y cuatro mujeres de edad reproductiva participaron en este ensayo, de las cuales 92 eran consideradas de alto riesgo para la cirugia, 27 habian rechazado una intervención quirúrgica y 15 habian tenido una esterilización quirúrgica que había fracasado. El seguimiento medio fue 3,46 aiios. No se registrb ningún embarazo ni complicación grave. El principal efecto secundario fueron irregularidades menstruales, ocasionadas probablemente por la depo medroxiprogesterona. La QS es una opción apropiada para mujeres a alto riesgo de complicaciones quirúrgicas.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

P-121

Histologic Changes in the Fallopian Tubes after Lower Dose of Transcervical Quinacrine Insertion. A. R. Satin. A. Mohindroo. P. Chandra and S. S. Gill. Government Medical College, Patiala, Punjab, India.

Objectives: Quinacrine (Q) sterilization is usually done by two 252 mg monthly transcervical insertions. But there are concerns regarding its safety, We carried out this clinicopathologic study using single 180 mg Q pellet insertion.

Design: Histologic changes in fallopian tubes were studied after Q insertion in cases undergoing hysterectomy (Hx) for benign utero-cervical conditions in tertiary medical care setting.

Materials and Methods: Fifty women awaiting Hx consented for this study. Five Q (180 mg) and two diclofenac pellets (100 mg) were inserted transcervically with an IUCD inserter prior to Hx. Q-Hx interval Varied from 3 to 72 days. Microscopic changes after serial sections of fallopian tubes were studied using H&E stain and grouped as stage 0, 1,2 & 3. (Stage 0, no change; stage 1, acute inflammatory reaction and stage 2. chronic Inflammatory reaction in lamina propria; stage 3, fibrosis & complete tubal occlusion.) The extent of tubal involvement from comual end was also examined.

Results: All cases (10 tubes) with Q-Hx interval more than 36 days showed bilateral tubal occlusion at the comual end, while isthmus and fimbrial end showed changes only in two and one tube respectively. Stage 3 changes were observed in 20/82 tubes within 6 to 35 days & in none within 5 days.

Conclusions: 1) A single transcervical 180 mg insertion of Q causes total occlusion of all fallopian tubes after 36 days. 2) In contrast to our earlier study with 252 mg Q. the changes are less marked in the isthmus & fimbrial end which may be an advantage should the need for recanalization arise. 3) A lower single transcervical insertion of 180 mg may be safer than the presently recommended two insertions of 252 mg Q for sterilization.

Q & diclofenac pellets were supplied by International Federation of Family Health with no financial support.

Quinacrine Pellet Method of Non-Surgical female sterilization. A review of the method & analysis of 400 cases.

Pravin Kini . M. • Sita Bhateja • Rajgopal B.
Sita Bhateja Nursing Home, Langford Road, Bangalore
and Dept. of Obstetrics and Gyanecology, Kasturba Medical College, Mangalore.

Summary: **Female Sterilization is the most prevalent contraceptive method today, used by over 138 million married women of reproductive age compared to 95 million in 1984. Evidence suggests that demand for sterilization is a function of supply of Surgical Sterilization in India and other developing countries. At present only 31% of all married women of Reproductive age use sterilization. To achieve a mean sterilization prevalence of 47% of all maried women the number of sterilization would have to double the current projections of 1990's. Quinacrine pellet method for non-surgical female sterilization offers hope that this enormous shortfall in meeting the sterilization demand in the country can be met. The Quinacrine method of Non-Surgical Sterilization involves transcervical Intrauterine Insertion of 252 mg (36mg x 7 pellets) of Quinacrine pellets during proliferative phase of the Menstrual cycle with optional adjuvants. In over 100,000 cases of Q Method of non-surgical female sterilization world wide not a single fatality or a major complication has been reported. The failure rates are around 0.75 to 2%. We conducted a field study on 400 cases over a period of 2 years using the quinacrine pellet method of female sterilization with multiple insertions at Bangalore and Mangalore, Karnataka, India. Results of the trial showed a failure rates of 0.75% over a two year period. There were no mortality or any serious side effects. The trial is ongoing and patients are being recruited regularly. This method needs to be promoted as a safe and effective method for female sterilization as an alternative option to surgical method.**

Introduction

Voluntary female Sterilization is the most prevalent contraceptive method today, used by over 138 million married women of reproductive age compared to 95 million in 1984 (Robey et al 1992). Evidence suggests that demand for sterilization is a function of supply of Surgical Sterilization in India and other developing countries. Over 31% of all married women in the reproductive age groups have opted for sterilization in India in 1990 as against 23% in 1980 (Ross JA 1991). Increases in numbers have been as a result of improvement in surgical procedures, effective training programs and improved health care delivery systems. There has also been a concomitant increse in patient awareness regarding the need for sterilization.

In light of this major progress why promote a non-surgical method ? If availability of sterilization were greatly expanded the number of procedures would grow dramatically. In such circumstances of increasing demand we have contrasted the quinacrine method and the surgical method in terms of their relative efficacy, safety, cost and potential contribution to reducing maternal morbidity and mortality and rapid population growth. In addition we have also reviewed our ongoing study of a straight double insertion quinacrine pellet method of female sterilization that is being carried out at Bangalore & Mangalore Karnataka as a multicentric study.

Past and Future Demands for Female Sterilization

Based on the current trends in the growth of female sterilization in India it is estimated that there will be an additional 10 million sterilizations by the year 2000, thereby raising the prevalence from 31% to 36% of eligible cou-

ples (Ross JA 1991). This small increase is due to the fact that half the gains is being offset by the increase in numbers of married women of reproductive age. If we are to achieve prevalence of 47% as is now seen where sterilization is available without bariers of cost and availability, it is estimated there will be over 40 million additional sterilization's by the year 2000 (Ross JA 1991). It is unlikely that surgical sterilization's can meet this demand because of inherent limitations of surgical sterilization's. Even in heydays of camp sterilization's 5000 sterilization's were performed in a period of 3 months by a team from Baroda Medical College (The John Hopkins newsletter 1979). If doctors from all medical colleges were to match this feat approximately 0.5 million sterilization's required to achieve the prevalence of 47%. Also this does not take into account the present levels of sterilization's required to maintain the status quo.

Based on the sheer numbers involved it is highly unlikely that a surgical approach to sterilization's will succeed and what is needed is an non-surgical method of female sterilization. A recent review of ongoing research of non-surgical methods suggests the quinacrine pellet method of non surgical sterilization is the only one ready for large scale use (Bachicha JA 1991).

Table 1
Incidence of Minor side effects after QS sterilization

Sl. No.	Side Effects	Number of Women	Incidence %
1.	Lower abdominal pain	60	15%
2.	Headache & dizziness	40	10%
3.	Backache	4	1%
4.	Vaginal irritation	2	0.5%
5.	Fever	23	5.7%
6.	Menstrual disturbances	4	1%

Quinacrine Pellet Sterilization

This method developed by Zipper et al (Zipper J et al 1980), involves transcervical application of pellets of quinacrine in the proliferative phase 6th to 14th day of the menstrual cycle using a copper T intrauterine device like inserter. Seven pellets of 36 mg of quinacrine (252 mg) rapid dissolution time are inserted. The application technique is slightly different from that of an IUCD insertion, in that after the inserter has been introduced into the uterus after evaluation of uterine length, it is withdrawn from the uterus by 0.5 cm's and then the plunger is advanced after fixation of the inserter sleeve to expel all the pellets into the uterus. The procedure is performed twice at monthly intervals. The pellets do not need to be sterilized as quinacrine is a known antiseptic and the inserter can be reused after a alcohol sterilization (Kessel E et al 1993). The optional adjuvants that improve the efficacy & thus lower the failure rates are mentioned as under.

Adjuvant therapy

1. Medroxy-progesterone 150 mg IM given on the day of first insertion or Oral contraceptives started from the first day of the cycle till the third month after the first insertion.
2. Anti-prostaglandin such as 200mg Ibuprofen orally on the day of the first & second insertions.

Mode of action

Quinacrine acts by chelation of the DNA by formation of quinacrine-DNA complexes. This action is belived to result in fibrosis of the endothelial lining of the proximal areas of the fallopian tubes (Kessel E et al 1990). Endometrium is spared as it has a high levels of zinc which prevents DNA-quinacrine complexes. Anti-prostaglandin adjuvants such as ibuprofen and diclofenac sodium probably act by preventing disposal of quinacrine from the local area by inflammatory reaction (Kessel E et al 1990).

Medroxy-progesterone 150 mg IM or the progestins in the oral contraceptives acts by relaxing the tubal musculature, resulting in increase influx of quinacrine solution

into the fallopian tubes. In addition it acts as a temporary contraception, till fallopian tubes are fibrosed.

Efficacy

The quinacrine pellet method originally considered to have a lifetime failure rate of 5-6%, shows remarkable improvement with the increase in number of insertions and additions of antiprostaglandins (Kessel E et al 1993). Most ongoing studies have shown a failure rate from 1-2% at the end of one year and the largest study in Vietnam have shown a failure rate of 2% and this is without additions of antiprostaglandins (Hieu DT et al 1993). Further studies with additions of antiprostaglandins such as ibuprofen, and diclofenac sodium along with Medroxy-progesterone 150 mg IM have demonstrated failure rates between 1-4% when followed up for a period of two years (Mullick BC et al 1995). Latest unpublished reports show that timing the insertions on the 9th to 12th day of the menstrual cycle reduces the failure rates to almost nil. These reports have still to be replicated elsewhere, if replicated then this study would be an important landmark in the development of Quinacrine pellet method.

Surgical sterilization is highly effective and forms an effective benchmark of comparison. It has a low failure rate of less than 0.5% at the end of one year, however a 10 year follow up shows a failure rate of upto 2.5%.

The efficacy of newer protocols in the short term approaches that of surgical sterilization while on long term is still unknown. This marginal difference in efficacy is totally overshadowed by the excellent record on safety that quinacrine pellet method has over the surgical method.

Safety

In over 30,000 cases of quinacrine pellet sterilization's in Vietnam, 10,000 cases in India and 5000 cases in other regions not a sigle death has been reported (Sokal DC et al 1998). Whereas for surgical sterilization's carrying a case fatality rate of 21 per 100,000 in India (Bhatt RV 1991), we would have expected 10 deaths.

Morbidity is another important aspect of safety. All major reports of the quinacrine pellet method are unformly reassuring by their absence of any serious life threatening complications. In a large field trial at Vietnam there were common side effects such as lower abdominal pain, headache and mild fever which were easily treated with analgesics. Surgical sterilization carried a total major complication rate varying from 1.7 to 5.7% in various reviews (Bhiwandiwala PP et al 1982).

Long term sequelae of both methods have been a concern, but present evidence suggests that both procedures are free of the problem. There has been a worry that quinacrine pellet method may induce carcinogenesis but recent studies have shown no increased risk of abnormal cervical cytology or increased cancer risk from any other organ site. (Dabancens A et al 1995 & Sokal DC et al 1994). Thus from all available data at this time it appears that the quinacrine pellet method of female sterilization is far safer than surgical sterilization.

Reversibility

Since non-surgical method produces proximal tubal occlusion that does not extend beyond the muscularis layer the surgical approach for reversal involves reimplantation of the tube. This approach has a 50% intrauterine pregnancy rate. While reversal of surgical method of sterilisation involves excision of the scar and reanastomosis of the healthy ends and this has a intrauterine pregancy rate of 80%.

Role in Reduction of Maternal Mortality and Morbidity

The most potent argument for the Q method is that it is far easier to deliver in rural areas with high maternal mortality rates. It has always been difficult to deliver safe surgical sterilization in rural areas of India where it was required the most. It is in these areas where every sterilization can prevent two births. In these areas the maternal mortality is between 500 to 1000 per 100,000 live births.

At a cost of less than Rs. 1500, a maternal death can be prevented (a single sterilization by the Q method costs less than Rs. 30) (Kessel E et al 1990). It is estimated that to reach a complete coverage of sterilization in this country we will have to complete over 40 million sterilization's by the end of this decade. Only quinacrine pellet method can meet this demand and thus prevent over 80 million births and around 800,000 maternal deaths.

Maternal morbidity which is unfortunately unmeasured, is a factor that has to be accounted in weighing the role of quinacrine method in its role in reducing maternal morbidity.

Role in Slowing Rapid Population Growth

In India where 38% of births are of the fourth parity and above especially in rural India, this method can have a tremendous impact. It is in group of older high parity women not wanting further children, where this method will make a major contribution. These populations have a poor access to surgical sterilization's and continue to miss the opportunity to contracept leading on to an ever-growing parity status. Q method due its ubiquitous delivery is an ideal candidate for these populations.

In younger women the situation is slightly different. By the age of 29 nearly 80% of the married women would have had their child (Anonymous Govt. of Karnataka 1994). So by the time the health provider has got to them the demographic damage is already done. In most cases women would have avoided permanent sterilization after their second child as the risk to benefit analysis done by them does not favor immediate sterilization or there is no easily accessible point of sterilization. By the time the women decide to sterilize they have had another child or may be more. Q method again due to its easy availability and delivery which may be handled by the local nurse can alleviate this problem.

The quinacrine pellet method requires technical skills similar to that for an IUCD insertion. In large trials conducted world over the procedures have been increasingly carried out by nurses and paramedical personnel quite efficiently (Hieu et al 1993). Thus the potential access for this method is very large and with a minimal levels of training large number of operators can be recurited. This improves the delivery of sterilization services to the most remote areas of the country thereby meeting the enormous demand for sterilization that exists in the country thereby increasing the prevalence of sterilization closer to the 47% mark.

Patients & Methods

400 women who approached the centers of Sita Bhateja Nursing Home, Bangalore & Kasturba Medical College, Mangalore for permanent sterilisation of women were offerred Quinacrine Pellet method of female sterilisation as an option instead of surgical sterilization. Details such as age, number of living children, age of the last child, breast feeding or not & their LMP were all recorded. Patients with gross cervicitis & pelvic inflammatory disease were treated before accepting them into the trial. All patients were asked to report to the clinic between the 6th to 14th day of their cycle. The patient was again councelled on the method & made to fully understand that this was permanent method & normally was not reversed. The pellet inserter was sterilised by a rinse with absolute alcohol followed by air drying of the inserter. The inserter was loaded with seven pellets of quinacrine. Since quinacrine is an antiseptic there was no need for its sterilisation.

At the time all patients received an injection of Medroxyprogesterone Acetate 150mg IM followed by an oral tablet of ibuprofen 400mg. A bimanual examination was conducted and uterus sounded with 4mm karmen cannula. If the uterine length was greater than 7 cms the procedure was abandoned & pregnancy test done. The stopper on the inserter was placed 0.5 cms less than the length of the uterus in order to make sure the tip of the inserter is about 0.5 cms away from the uterine fundus. This ensures that there is space for all the pellets to be expelled out into the uterus.

Inserter was introduced into the uterus after correction of the uterine version upto the stopper mark. Then unlike IUCD insertion, the sleeve of the inserter was held still & the plunger pushed till all the pellets were expelled. Patients were then asked to remain in a supine position for about 15 to 30 minutes. They were warned about possibilities of having yellowish discharge due to leakage of the quinacrine solution into the vagina from cervix. In case of a bloody insertion where more than 0.5 ml of blood was seen then a third insertion was planned.

Same procedure was repeated after one month or on the 6th to 14th day of the next cycle except for Medroxyprogesterone injection which was not given. All other procedures were followed. After the procedure patient was asked to maintain a record of her symtoms which included details of menstrual disturbances, pelvic pain, dysuria, etc which were recorded & if severe, therapy was given. Patients were followed up for 2 years for failure in terms of pregnancy, both intrauterine & ectopic gestations and for any long term side effects.

Results

Out of the 400 women who underwent sterilization after two years of follow-up, 3 women were found to be pregnant & all had intrauterine pregnancies with a failure rate of 0.75% at the end of 2 years of folow-up. All failures were terminated & none of the patients carried the pregnancies to term. There was no mortality or major morbidity with this procedure. The incidence of minor side effects are given in the table below. Most side effects were self limiting and required no therapy. 40 (6.1%) women required analgesics or antibiotics due to the severity of symtoms. Amenorhoea was observed in 1 woman which resolved after 4 months after the first insertion. Oligomenhorrea was noted in 3 women which took between 4 to 8 months to resolve. Most of these menstrual symtoms may be due the minimal action of quinacrine on the uterine endometrium.

Patient response to the procedure was positive & all patients were sufficiently motivated to come for second insertion & for regular follow up. There was no loss to follow up or protocol deviation in this study as these were closely monitored & well selected group of patients.

Discussion

Quinacrine pellet method is a safe & effective method of female sterilisation especially when provided with adjuvant drugs. Our series shows no deaths or incidence of any major morbidity both in our hands & in various studies done worldwide. In contrast surgical sterilisations in developing nations report 19 to 99 deaths per 100,000 cases & a serious complication rate of 1.7% with laparoscopy & a 5.7% serious complication rate with laparotomy (Bhiwandiwala PP et al 1982). All side-effects have been minor & of a short duration as noted in other studies.

The failure rates of 0.75% compares favourably with surgical method which has a failure rate of 0.5%. The improvement of our failure rate when compared to other studies is probably due to the better insertion technique. Most of the other trials where done on a large scale field trial basis where insertions were done by non-medical personnel & non-gynecologists. This probably skewed the results to give higher failure rates.

The greatest advantage of this method over surgical method is that it has the possibility of raising the contraceptive prevalence with ease of delivery which no surgical method can match while at the same time providing an efficacious contraception. The cost of quinacrine for two insertions is less than Rs 35 & when combined with long acting progestins the cost is around Rs 100 & if combined with oral contraceptives then it would cost only Rs 60 (includes the cost of quinacrine insertion & the OC cost). There is at this time no other cost effective & safe sterilization method available which can match the quinacrine pellet method.

Acknowledgements

Quinacrine pellets and the inserters were provided by International federation of Family health, Oregon, USA with informational resource by CHIP project, 3004, 12A main HAL 2nd stage, Bangalore 560008, India.

We thank Dr. Elton Kessel for his guidance in this program and Dr. Sita Bhatija Nursing Home and Kasturba Medical College in providing the necessary infrastructure to conduct the trials.

References

1. Anonymous: Govt. of Karnataka. Family Planning statistics for the State of Karnataka - 1993 (Bangalore Department of Health and Family Welfare 1994.
2. Bachicha J.A.: Female Patient 1991; 16: 49-56, 1991
3. Bhatt RV. Asia Oceania J Obstet Gynaecol 17:297-301.1991
4. Bhiwandiwala, P.P., Mumford, S.D. and Feldblum, P.J: Am.J.Obstet.Gynecol, 14, 319-31. 1982.
5. Dabancens, A., Pruyas, M., Rivera, M. and Zipper, J. Fertil, Steril, 64; 444-446. 1995
6. Hieu, D.T., Tan, T.T., Tan. D. N., Nguyet, P.T., Than, P. and Vinh, D.O. Lanct, 342, 213-17. 1993.
7. Kessel, E., Zipper, J. and Mumford, S.D (Eds.) The Quinacrine pellet method for non-surgical female sterilization : a collection of background materials. (Research Triangle Park, NC: Center for Research on Population and Security). 1990.
8. Kessel. E., Zipper J., Hieu D.T., Mullick B., and Mumford S.D. Proc. of VIIIth World congress on human reproduction, Bali, Indonesia, April 1993.
9. Mullick, B.C., Kessel, E., and Mumford, S.D. Adv. Contracept 1995; 11.239-44.
10. Robey, B., Rutstein S.O., Morris. L., and Blackburn, R. The reproductive revolution: new survey findings, Popul. Rep. [M] No. 11. (Baltimore, MD: Population Informtion program) 1992.
11. Ross. J.A. (New York: Population Council Working paper No. 29) 1991.
12. Sokal, D.C., Kessel E., Zipper. J., and King T. Quinacrine: Clinical experience. A background paper for the WHO consultation on the development of new technologies for female sterilization. 1994.
13. Sokal DC., Zipper J., Guyman-Serani R., Aldrich TE. Fertil. Steril, 64:325-334. 1995.
14. The John Hopkins Program for International Education in Gynaecology and obstetrics: Dr. Rohit Bhatt of India Relates Experiences. JHPIEGO Newsletter, Vol IV, No. 3, October 1979, p 1.
15. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M: Int J Gynaecol Obstet;18:275-90.1980.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

P72.76 QUINACRINE PELLET NON-SURGICAL FEMALE STERILIZATION. A TWO YEAR OF REVIEW OF CASES IN SOUTH INDIA

S. Bhateja, P. Kini, Rajgopal. K.
Dr. Sita Bateja Nursing Home, Langford Garden, Bangalore - 560 025. INDIA.
Chip Trust, 3004, 12 'A' Main, HAL II Stage, Bangalore - 560 008. INDIA.
Dept. of OB/GYN, Kasturba Medical College, Mangalore - 575 001. INDIA.

Female sterilization is the most prevalent contraceptive used in India.there remains, however, considerable unmet need for this popular method, especially in rural and urban slum areas where surgical services are difficult to provide. The quinacrine pellet method has potential for satisfying this need. We, therefore, conducted a clinical trial of the method in several well equipped urban clinics in Karnataka State for well informed women desiring this permanent method rather than surgical sterilization. Our protocol involved transcervical insertion of 7 quinacrine pellets containing 36 mg of quinacrine (252 mg) using a modified IUCD inserter between the 6th and 12th day of the patient's menstrual cycle. The procedure was repeated a month later. We completed 600 cases in 1995-1996. Quinacrine causes an inflammatory reaction and occlusive scar in each fallopian tube but has only a transient effect on the endometrium. All cases were evaluated for complications, side effects and pregnancy failures during a one year follow - up period. There were 7 (1.2%) intrauterine pregnancies by one year and no mortality or life threatening complications. Minor self-limiting side effects, similar to those reported early after IUCD insertions, ranged from 25% to 40% in our clinics. The women responded well to symptomatic therapy. We conclude that the quinacrine pellet method of non-surgical female sterilization is safe in terms of complications and side effects and is acceptably effective considering its ease of delivery and low cost. We recommend it is an additional permanent contraceptive option for our women.

P72.80 NON SURGICAL FEMALE STERILIZATION WITH QUINACRINE VIS-A-VIS LAPAROSCOPIC IN RURAL TNDTA. A COMPARATTVE EVALUATION. A.K.GHOSH AND A.HAZRA, DEPT. OB/GYNAE,NATIONAL MEDICAL COLLEGE, INDIA. The unmet need and dismal trend of population control in developing countries call for a highly acceptable, safe and efficient method.The current study, an ongoing one, a part of International Family Health Project, examines the relative value of single transcervical intra-uterine instillation of Quinacrine pellets (250 mg) by copper T IUCD introducer in the early proliferative phase. The resultant inflammatory fibrosis of the proximal part of the tube takes 12 weeks. During this period a concurrent use of Combined OC or Intramascular Depo rrovera (Meciroxy Progesterone) helps to avoid unplanned pregnancy. A canparative evaluation with Laparoscopic sterilization over 5 years in 46863 women indicated a significant superiority of the method over Laparoscopy. The maternal mortality varied from 0 to 19.3 per 100,000 by different Laparoscopist, including the first author. In contrast, there was no major complication, neither any death following Quinacrine sterilization (N = 251). Menstrual upset eg, scanty loss, and short spell of amenorrhaea was found in 11 per cent. There were 7 pregnancies, less than 3 per 100 women user/year, of which one ended in Spontaneous abortion, the rest had had suction evacuation. The success of this method is in conformity with the large Vietnam trial on 31,781 cases with no maternal death (Du Trong et al, Lancet, 1993, 342, 213-217). In conclusion, the Quinacrine method seems appropriate for the developing world to increase the contraceptive prevalance.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

SP76.5 QUINACRINE STERILIZATION: RISK OF ECTOPIC PREGNANCY.

DT Hieu
Department of MCH and Family Planning,
Ministry of Health, Hanoi, Vietnam

Ectopic pregnancy carries a high risk of maternal death in developing countries. It is therefore important to know the effect of contraceptive methods on the risk of ectopic pregnancy. It is known that all contraceptive methods reduce the risk of ectopic pregnancy by reducing the risk of pregnancy. A comparison of ectopic pregnancy risk is still needed between new and commonly used contraceptives. As this risk may be low, only large well monitored trials will provide evidence that is statistically significant. The large field trial of quinacrine sterilization in Vietnam provided an opportunity to measure ectopic pregnancy risk for this method and for IUDs, the most prevalent contraceptive method in Vietnam. We analyzed collected data for three quinacrine sterilization studies in Namha Province (N = 4511) where there were 6 ectopic pregnancies (0.13%) and from a survey of 18,000 IUD users who experienced 25 ectopic pregnancies (0.14%). Of the pregnancies after quinacrine sterilization in Namha Province, less than 3% were ectopic. The ectopic pregnancy incidence per 1000 women-years of quinacrine sterilization use in the Namha studies was 0.89. A large trial reported by the Centers for Disease Control and Prevention for surgical sterilization in the United States showed 32.9% of their pregnancy failures were ectopic. Even though the quinacrine sterilization failure rate in Namha Province was six times that reported for surgical sterilization in the US, the risk of ectopic pregnancies of the quinacrine sterilization method is lower.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

SP76.1 100 000 QUINACRINE STERILIZATIONS

E Kessel
Department of Public Health and Preventive Medicine
Oregon Health Sciences University, Portland, Oregon
97201, USA

100 000 quinacrine nonsurgical female sterilizations have been completed over the past decade involving transcervical insertion of quinacrine (252 mg) as pellets by one, two or three monthly insertions. No deaths have been reported and serious complications are far fewer than for surgical sterilization. Side-effects are mild and transient. Efficacy has improved from 3 pregnancy failures per 100 women at one year to approximately 1 by improved insertion technique and use of an additional contraceptive for 3 months. Efficacy is increased by repeat insertions or higher dose, which however extends damage to the tube beyond the intramural segment. Long-term follow-up of early cases in Chile shows no increased risk of cancer for this method. It is decreased by presence of blood in the uterine cavity. The main advantage of quinacrine sterilization is its ability to raise contraceptive prevalence and thereby reduce maternal mortality and morbidity, especially in rural and urban slum areas of developing countries. It should be made available as an option to well informed women everywhere as an economical and safe permanent family planning method.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

SP76.6 QUINACRINE STERILIZATION: MEDROXYPROGESTERONE AS ADJUVANT

B C Mullick, N R Bairagi
Indian Rural Medical Association
Calcutta, India

Our initial comparison of depot medroxyprogesterone (DMPA) 150 mg IM and 3 cycles of oral contraceptives (OCs) as adjuvants to quinacrine nonsurgical female sterilization was a before-after trial of single transcervical insertion of quinacrine 252 mg. The OC component was conducted in 1992-1993 and the DMPA component in 1993-1994. An important and statistically significant decline in pregnancy failures from 8.2 (SE 3.69)' per 100 women at 18 months to 0.55 (SE 0.55) was noted in favor of DMPA. We had also noted in a separate before/after trial that insertion technique can influence efficacy. In this 900 case trial the insertion technique was changed after 495 cases from midlevel uterine placement of quinacrine pellets to fundal placement. A statistically significant decline in pregnancy failures from 4.4 (SE 0.92) to zero occurred per 100 women at 24 months. In order to separate the effects of **DMPA** and insertion technique a systematic allocation of OCs for three months or DMPA injection was administered for every other case among 635 women in 1995-1996. All but 89 cases were additionally restricted by having insertions made on days 9-12 of **the** menstrual cycle. With this restriction there were no pregnancy failures at 18 months of use with 55 cases still at risk. Without this restriction the pregnancy failures showed no statistically significant difference between the DMPA and OC groups. We conclude that a single insertion of quinacrine with either DMPA or OCs as additional contraception for 3 months provides acceptable efficacy if fundal insertions of quinacrine pellets are consistently made. Randomized trials of insertion technique and of early and late insertions in the proliferative phase of the menstrual cycle are needed.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

SP76.4 QUINACRINE STERILIZATIONS: EXPERIENCE AMONG HIGH RISK WOMEN

SR Sarin
Department of Obstetrics and Gynecology, Government Medical College, Patiala 14700 1, India

A nonsurgical method of female sterilization is needed because many women are unfit for standard surgical methods, especially in developing countries. An alternative technique also seems desirable where surgical technique has failed or when women do not wish to undergo surgery. In such cases a novel approach by intrauterine insertion of quinacrine has been tried. During an ongoing trial we have studied until now 98 women of reproductive age who had a transcervical insertion, by a modified IUCD inserter, of seven quinacrine pellets (252 mg) and two diclofenac sodium pellets (50 mg), both supplied by the International Federation for Family Health. There were two insertions at monthly intervals, along with one 150 mg injection of depot medroxyprogesterone acetate (DMPA) with the first one as an additional contraceptive. Seventy-five cases were considered at high risk for surgery (mainly severe anemia, cardio-vascular disease and sepsis); 14 had voluntarily chosen a nonoperative procedure; and nine were cases of earlier laparoligation failure. No serious side effects were encountered and these were mainly menstrual irregularities due to simultaneous DMPA administration. The mean follow-up period was 17.6 months. There have been no pregnancy failures to date. We conclude that quinacrine sterilization is a promising alternative to surgery for women at high risk of associated complications and for those desiring sterilization, but fearful of surgery.

FERTILITY AND STERILITY®
Copyright © 1997 American Society for Reproductive Medicine
Published by Elsevier Science Inc

Vol. 67, No 5, May 1997
Printed on acid-free paper in U.S.A.

Quinacrine pellet nonsurgical female sterilization in Wonosobo, Indonesia*

Agung Suhadi, M.D.†
Ariawan Soejoenoes, M.D.‡§

Regency Hospital, Wonosobo, and Diponegoro University, Dr. Kariadi Hospital, Semarang, Indonesia

Objective: To evaluate the efficacy, safety, and acceptability of two monthly transcervical applications of quinacrine, 252 mg, and ibuprofen, 55.5 mg, as pellets for sterilization.
Design: Prospective clinical study.
Setting: Family planning clinic of a referral hospital.
Patient(s): Two hundred normal women who requested sterilization and volunteered for this method.
Intervention(s): Each woman received quinacrine, 252 mg, and ibuprofen, 55.5 mg, transcervically as pellets in the proliferative phase of two consecutive menstrual cycles from August 1992 to October 1993.
Main Outcome Measure(s): Life-table pregnancy failure rates and incidence of complications and side effects.
Result(s): The pregnancy failure rate was 2.0 per 100 women at 24 months. There were no serious complications, and side effects were transient.
Conclusion(s): Intrauterine insertion of quinacrine pellets is a safe and acceptably effective method of nonsurgical female sterilization. (Fertil Steril® 1997;67:966–8. © 1997 by American Society for Reproductive Medicine.)

Key Words: Quinacrine pellet sterilization, nonsurgical female sterilization, female sterilization

Surgical female sterilization, the most prevalent and. effective method of contraception for women who desire no more children, requires trained personnel, adequate medical care facilities, and acquisition and maintenance of sophisticated equipment. For three decades investigators have been trying to develop a safe, effective nonsurgical method to satisfy the unmet need for voluntary sterilization. It is projected that some 328 million women will avail themselves of such services in the next 10 years if they become available (1). Transcervical insertion of quinacrine pellets using a modified intrauterine device (IUD) inserter, as developed by Zipper and co-workers (2), is the leading candidate to accomplish this goal. Clinical experience with the method has been reviewed recently (3), including some evidence that addition of an antiprostaglandin may improve its efficacy and relieve mild side effects. Quinacrine promotes inflammation and fibrosis in contact with certain tissues, including the fallopian tube.

This method is of particular interest to a developing country such as Indonesia, which has a very low prevalence of female sterilization (2.9%) and an unacceptably high maternal mortality of 390 per 100,000 live births. The method could raise contraceptive prevalence, thereby slowing population growth and reducing maternal mortality by prevention of unwanted pregnancies, especially for high parity women.

The aim of this study was to evaluate the efficacy, safety, and acceptability of two transcervical applications of 252 mg quinacrine and 55.5 mg ibuprofen as pellets for nonsurgical female sterilization. The study was approved by the National Family Plan-

Received June 7, 1996; revised and accepted January 27, 1997.
* *Presented* at the XVth Asian and Oceanic Congress of Obstetrics and Gynecology, Bali, Indonesia, October *15* to *20, 1995.*
† Department of Obstetrics and Gynecology, Regency Hospital.
‡ Department of Obstetrics and Gynecology, Diponegoro University, Dr. Kariadi Hospital
§ Reprint requests: Ariawan Soejoenoes, M.D., R.S.B. Bunda, Jalan Mojopabit No. 8, Semarang *50125,* Indonesia (FAX: *62-24-416037).*

0015-0282/97/$17.00

ning Coordination Board of Wonosobo Regency, Central Java Province, which served as the institutional review board.

MATERIALS AND METHODS

A prospective clinical study of quinacrine nonsurgical female sterilization was conducted at the Wonosobo Regency Hospital, Central Java Province, Indonesia. From August 1992 through October 1993, 200 women, who gave informed consent, received 252 mg of quinacrine hydrochloride in the form of seven cylindrical pellets (Sipharm, Sissein, Switzerland) followed by 55.5 mg ibuprofen in three pellets transcervically during the proliferative phase of the menstrual cycle. All insertions were made by the senior author (A.S.). The pellets were inserted again in the next menstrual cycle. Dilatation was required in <5% of cases. The procedure is essentially the same as inserting a Copper T IUD (Kimia Farma, Bandung, Indonesia).

Follow-up was scheduled at 6, 12, 24, and 48 months after the last insertion and at any time when complications or complaints occurred. Women were admitted to the study if they requested sterilization for family planning reasons and preferred this method over surgical sterilization. Excluded were women (<2%) who had pathologic pelvic conditions (except cervicitis), such as upper tract infection, or gross distortion of the uterine cavity or who appeared unusually nervous. Those women who had to be excluded were offered a choice of surgical sterilization or other methods of contraception.

Data were collected on standardized forms developed by the International Federation for Family Health. Life-table analysis was used to calculate efficacy.

RESULTS

All 200 women completed the first insertion but 3 declined the second and were offered an alternative method; 2 additional women were lost to follow-up during the second year because they moved from the area.

Most of the women (178, 89.0%) came from rural areas; they were provided transportation to the hospital in small groups. There were 22 (11.0%) urban dwellers. The mean age was 33.2 ± 9.75 (SD) years, and age ranged from 24 to 40 years. The mean number of live births for the population was 3.5 ± 0.50, with a range of two to eight live births. Contraceptive use reported for the 3 months before the first insertion approximated the pattern for Indonesia as a whole. A total of 43% of the subjects had used an effective contraceptive method compared with 47% for all of Indonesia.

Complications and complaints reported between insertions and up to 1 year and 2 years after the second insertion are shown in Table 1. The main side effect after the first insertion was lower abdominal pain (116 cases, 60.1%). Two women' reported severe abdominal pain and required antibiotic and analgesic treatment. Fever occurred in 26 cases (13.5%) and leukorrhea in 15 (7.8%) up to 1 month after first insertion. These symptoms lasted from a few hours to a few days. Symptoms were generally milder after the second insertion. In two women, temporary amenorrhea that occurred (1.0%) during the first year lasted up to 4 months but required no treatment.

Four women became pregnant after the second insertion during the 2-year follow-up period. Pregnancies occurred 4, 5, 14, and 18 months after the second insertion. The pregnancy rates are shown in Table 2. The diagnosis of pregnancy was made by pelvic examination and confirmed by pregnancy test. One of the pregnancies was terminated by vacuum aspiration. The other three ended in spontaneous delivery of a term infant, and no major malformation was noted, although one delivery was complicated by postpartum bleeding because of retained placenta.

DISCUSSION

Our results in terms of complications and pregnancy failures are consistent with those reported by others (3). In more than 100,000 quinacrine sterilizations to date, there has been no reported case fatality and serious complications are rare (3).

Hieu and coworkers (4) suspect that the insertion technique may affect efficacy and recommend a revised technique to ensure that all pellets are placed at the fundus. We used the traditional technique, as with a Copper T IUD (Kimia Farma) insertion, resulting in a vertical column of pellets starting at

Table 1 Complications and Complaints Reported Within 1 Month of First Insertion and Within First and Second Years After Second Insertion (Wonosobo, Indonesia, 1992 to 1994)*

Complication/ complaint†	One month after first insertion (n = 200)	One year after second insertion (n = 197)	Two years after second insertion (n = 193)
Amenorrhea	2 (1.0)	2 (1.0)	4 (2.1)
Menorrhagia	7 (3.5)	3 (1.5)	3 (1.6)
Leukorrhea	15 (7.5)	4 (2.0)	3 (1.6)
Lower abdominal pain	116 (58.0)	1 (0.5)	1 (0.5)
Fever	26 (13.5)	4 (2.0)	— —

* Values are number of subjects with percentage in parentheses.

† Women could have multiple complications or complaints.

Table 2 Cumulative Pregnancy Rate per 100 Women After Second Insertion of 252 mg Quinacrine and 55.5 mg Ibuprofen as Pellets (Wonosobo, Indonesia, 1992 to 1994)

Months after insertion	No. at risk	No. of pregnancies	No. of withdrawals	Pregnancy rate	Cumulative pregnancy rate
				%	%
				1.0	
0 to 6	197	2	0	0.0	1.00
6 to 12	195	0	0		1.00
12 to 24	195	2	2	1.0	2.00

the fundus. It could be that if we had used the technique of Hieu et al. (4), our pregnancy failure rate might have been lower, as suggested by Bairagi et al. (5). Only a randomized study of these insertion techniques will provide an answer.

There is considerable evidence that at least a second insertion is needed for high efficacy (3). However, Mullick and colleagues (6) have achieved efficacy rates of >99% at 18 months by providing medroxyprogesterone, 150 mg IM, at the time of a single insertion of quinacrine. We await a confirming report.

Concerns have been expressed regarding possible carcinogenicity of intrauterine administration of quinacrine because it is a known mutagen. However, there are no reports of cancer with use of quinacrine for treatment or prophylaxis for malaria at much higher doses orally (36,000 to 52,000 mg/y) than needed for sterilization by intrauterine application. Also, a recent 2- to 14-year follow-up study in Chile (3) showed no evidence of increased risk of cancer by intrauterine administration of quinacrine.

From present knowledge of this method of nonsurgical sterilization we believe that the benefits of the method outweigh known risks for a developing nation such as Indonesia. There also may be some advantages for an industrialized country.

Acknowledgments. We thank Elton Kessel, M.D., Secretary General of the International Federation for Family Health, Leasburg, North Carolina. The quinacrine and ibuprofen pellets were provided by the Center for Research on Population and Security, Research Triangle Park, North Carolina. Also, sincere thanks to Mochamad Anwar, M.D, Department of Biostatistics and Clinical Epidemiology, School of Medicine, Gadjah Mada University, Yogyakarta, Indonesia, for statistical data analysis.

REFERENCES

1. Mumford SD, Kessel E. Sterilization needs in the 1990s: the case for quinacrine nonsurgical female sterilization. Am J Obstet Gynecol 1992;167:1203–7.
2. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivers M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 1980; 18:275–9.
3. Sokal DC, Zipper J, King T. Transcervical quinacrine sterilization: clinical experiences. Int J Gynaecol Obstet 1995; 51(suppl):S59–S69.
4. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of nonsurgical female sterilization with quinacrine pellets in Vietnam. Lancet 1993;352:213–7.
5. Bairagi NR, Mullick BC, Kessel E, Mumford SD. Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization. Adv Contracept 1995; 11:303–8.
6. Mullick BC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet non-surgical female sterilization. Adv Contracept 1995; 11:239–44.

Fertility and Sterility 2001;75:830-31.

ORIGINAL RESEARCH ARTICLE

96 39

ELSEVIER

Phase I Prehysterectomy Studies of the Transcervical Administration of Quinacrine Pellets

Leonard E. Laufe,* David C. Sokal,† Lynda P. Cole,† Donna Shoupe,‡ and Robert S. Schenken§

To determine the safety of transcervical administration of quinacrine pellets as a method of voluntary female sterilization, three noncomparative Phase I clinical trials of the administration of 250 mg quinacrine were carried out in 21 women who were scheduled to undergo hysterectomy 24 h or one month later.

Detailed results are presented for one of the trials using IO-min pellets. Six of 10 women had minor transitory complaints during the postinsertion 24-h follow-up period. Five women reported pelvic/abdominal cramping, one experienced headache, and one experienced dizziness. Blood chemistry values were not adversely influenced by the quinacrine. The average plasma level of quinacrine peaked at 3 h, 36.1 ng/ml, slightly lower than the value observed 4 h after oral administration of 200 mg in a previous study. An average of 27% of the administered dose was recovered in tampons. Quinacrine was detected in the plasma of two women at the four/six-week visit. Selected results are presented from two other trials that were halted because of slow recruitment.

The transcervical administration of 250 mg of 10-min quinacrine pellets was well tolerated. However, based on recent mutagenicity testing and meetings with regulatory officials, it appears unlikely that the use of quinacrine for nonsurgical sterilization could be approved in the United States or Europe. CONTRACEPTION 1996;54: 18 1-1 86

KEY WORDS: quinacrine, clinical trials Phase I, tubal sterilization, pharmacokinetics

Introduction

Since the mid-1960s, researchers have been working toward the development of inexpensive nonsurgical methods of female sterilization that involve simple delivery methods and are associated with minimum morbidity. The transcervical insertion of pellets of quinacrine hydrochloride with the use of a modified IUD inserter has been proposed as one such method. The quinacrine pellet method was developed by Dr. Jaime Zipper of Santiago, Chile, in collaboration with Family Health International (FHI).[1]

In the mid 1980s, FHI conducted three Phase I studies of quinacrine pellets in the United States under an Investigational Exemption for a New Drug (IND) that had been granted to FHI by the U.S. Food and Drug Administration (FDA) in 198 1. One of the studies was a 24-h prehysterectomy study using "lo-minute" quinacrine pellets formulated to have a dissolution half-life of about 10 min. The other two were one-month prehysterectomy studies, one with 10-min quinacrine pellets and the other with specially prepared, slow-dissolving, or "100-minute", pellets. The 100-min pellets were composed of a mixture of quinacrine and cholesterol. It was hypothesized that slow release of the quinacrine might increase exposure of the tubes to quinacrine. Due to slow recruitment, both of the one-month prehysterectomy studies were closed before completion.

FHI canceled its IND in 1990 due to various factors, including lack of funding and concerns about long-term safety and service delivery issues. However, a number of other researchers in various countries have continued to explore the use of quinacrine pellets.[2–5] Due to recently increased interest and controversy regarding the use of quinacrine pellets,[6–8] we are presenting the data from our Phase I studies.

We will present the methodology and results from the 24-h prehysterectomy study in detail. For the two, one-month prehysterectomy studies we will only present certain results: the data on adverse events, some

*Formerly at the University of Texas Health Science Center at San Antonio, Texas, USA, presently retired; †Family Health International, Research Triangle Park, North Carolina USA, *Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles, CA USA, and §Department of Obstetrics and Gynecology, University of Texas Health Science Center, San Antonio, TX USA

Name and address for correspondence: David C. Sokal, M.D , Associate Medical Director,Clinical Trials Division, Family Health International, P.O. Box 13950, Research Triangle Park, NC 27709, USA. Tel: 919-544-7040; Fax: 919-544-7261

Submitted for publication September 12, 1995
Revised June 28, 1996
Accepted for publication June 28, 1996

ISSN 0010-7824/96/$15 00
PII SO01 O-7824(96)001 74-6

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

limited pathology data, and the data on the blood levels attained with the 100-min pellets.

Methods: 24-h Prehysterectomy Trial

Design

This study was designed to evaluate the safety and pharmacokinetic profile of quinacrine over a 24-h interval between the transcervical intrauterine administration of quinacrine hydrochloride pellets, 250 mg, and hysterectomy.

This noncomparative Phase I clinical trial was performed at a single clinical site in San Antonio, Texas, in 1983-84. Plasma, saliva, urine, and tissue collections were made as described below. The study protocol was reviewed and approved by the Institutional Review Boards of the University of Texas Health Science Center at San Antonio and Family Health International. All subjects gave written informed consent before entering the study. Women were observed for abdominal pain, headache, dizziness, or other adverse effects over the 24-h postinsertion interval.

Drug, Dosage, and Administration

Quinacrine hydrochloride pellets, with a dissolution half-life of about 10 min, were prepared by the University of North Carolina School of Pharmacy, packaged in modified IUD inserters, and sterilized. A total dose of 250 mg of quinacrine in pellets was transcervically administered into the uterus of each participant approximately 24 h before a scheduled hysterectomy. The insertion technique was similar to the insertion of a copper-T IUD. After measuring the depth of the fundus, the investigator introduced the IUD inserter into the fundus up to the indicated depth. The investigator then retracted the outer inserter tube while holding the plunger completely still, thus releasing the quinacrine pellets.

Blood and Saliva Specimens

Samples of venous blood and saliva were obtained at nine points over a 48-h interval, ranging from 24 h before to 24 h after hysterectomy (preinsertion and at ½, 1, **2,3, 4,** 10, **24,** and 48 h postinsertion; total blood volume did not exceed 150 ml). Additional samples of blood, saliva and urine were to be obtained just before hospital discharge and at the four/six-week follow-up visit.

Urine and Tampon Collection

Total urine was collected from O-48 h after quinacrine administration. Tampons were inserted in the vagina during the 24-h period from quinacrine insertion to hysterectomy in order torecover any unabsorbed drug.

Tissue Samples

Following each hysterectomy, five uterine tissue specimens of about 500 mg each were taken, one from each cornua, one each from the posterior and anterior myometrium, including the endometrium, and one from the cervix, including the mucosa.

Assays

Clinical Chemistry Clinical chemistries of blood samples were determined by sequential multiple analyzer (SMA) for the following tests: cholesterol, triglycerides, glucose, blood urea nitrogen (BUN) , creatinine, uric acid, sodium, potassium, chloride, CO,, calcium, inorganic phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Quinacrine Assays Frozen urine, saliva, plasma, and tissue specimens were shipped to Johns Hopkins University, Baltimore, Maryland, where quinacrine was measured spectrophotometrically.[9,10]

Subject selection

The following inclusion and exclusion criteria were used for subject selection. For inclusion, the criteria were: (1) menstruating women, 2 l-50 years of age with a normal pelvic examination aside from the condition leading to hysterectomy; (2) >42 days since last pregnancy ended; (3) written informed consent; and (4) the procedure was able to be scheduled 6-12 days post-onset of menses.

Women were excluded if they had any of the following: (1) D&C within the previous six months; (2) use of an IUD in the past 30 days; (3) invasive cancer; (4) positive pregnancy test; (5) previous surgical sterilization; (6) history or evidence of pelvic inflammatory disease; or (7) history of significant disease of the cardiovascular, renal, hepatic, or central nervous system.

Results: 24-h Prehysterectomy Trial

Participants

The average age of the women was 26.6, with a range of 20-40. The average number of total live births that each woman had prior to the study was 2.6, with a range of O-4. One subject's age constituted a protocol violation because she was only 20 years of age rather than 21. The reasons for hysterectomy included uter-

Contraception
1996;54:181–186

ine prolapse, dysfunctional uterine bleeding, and cervical carcinoma in-situ.

Adverse events

All 10 women completed the study. Six women reported minor transitory complaints during the 24 h following quinacrine administration. These complaints included pelvic/abdominal cramping or low back pain reported by five women, similar to the pain usually associated with menses. The duration of the pain ranged from 10 min to 3 h. The timing of the pain in relation to the quinacrine insertion procedure was variable, beginning as early as 2 h to as late as 18 h after the procedure. No medication was required by any of the women.

Two women had minor side effects relative to the central nervous system. One of the women who experienced cramping also had a brief episode of dizziness that occurred about 4 h after the procedure. While she attributed the dizziness to hunger, mild dizziness is commonly associated with orally administered quinacrine. She required no medication. A sixth woman complained of a headache, which started about 3 h after the procedure and lasted for about 2 h; she was given oral acetaminophen.

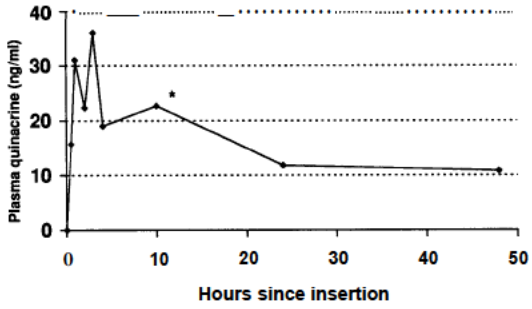
Clinical Chemistries

Although values for a few parameters fell outside the normal range, the abnormalities were generally minimal, sporadic, and transitory and were not considered clinically important or related to quinacrine administration. Of the abnormalities that were seen, most occurred in women who had had abnormal or borderline baseline results.

Pharmacokinetic Results

Of 110 planned blood samples, there were two missing, one each at the l-h and 48-h sampling points. Plasma, saliva, urine, and tissue concentrations of quinacrine and tampon quinacrine content are presented below.

The mean plasma quinacrine concentration at each sampling time is shown in Figure 1. Blood plasma quinacrine concentrations peaked within the first 4 h after insertion. Six women had their highest levels 1 h after insertion (**11.8-99.1** ng/ml), and four women at 2/4 h postinsertion *(8.7-137.5* ng/ml). By 48 h postinsertion, the levels had decreased to about one-third of the peak values. Two of 10 women had detectable plasma quinacrine concentrations at the four/six-week follow-up visit; levels were low, 8.9 and 4.0 ng/ml. The highest average plasma level was 36.1 ng/ml at 3 h after intrauterine administration, while the average of the individual peak values, independent of time, was 46.3 ng/ml.



. **The 10-hour value may be falsely elevated** due to hemolysis.

Figure 1. Mean plasma quinacrine concentration by time since insertion (n= 10).

Saliva concentrations of quinacrine usually peaked later than blood plasma concentrations. However, the values were highly variable and were not correlated with plasma levels. Four women had their highest levels at 0.25 h after insertion (43.1-220.5 ng/ml); five women had their highest levels at 24 h or later after insertion (30.4-860.0 ng/ml); and quinacrine was not detectable at any time in the saliva samples of one woman.

Over the first 48 h, a mean of 2.3 mg of quinacrine was excreted in the urine (0.6-8.7 mg). This represents about 1% of total dose and is consistent with the well-known slow elimination of quinacrine and other related compounds following oral administration.

Table 1 shows quinacrine concentrations in the uterine tissues. No solid remnants of the quinacrine pellets were found, i.e., the pellets had completely dissolved. Mean tissue quinacrine concentrations

Table 1. Tissue quinacrine concentrations ng/mg net weight)

Patient	Anterior	Posterior	Left Tube	Right Tube	Cervix
1	51.3	9.7	51.3	70.5	19.0
2	28.6	9.5	28.5	14.8	52.1
3	11.4	54.9	17.1	32.2	39.4
4	72.7	130.8	41.3	5.2	24.1
5*	62.6	50.5	48.3	170.9	61.9
6*	39.9	5.1	23.2	12.8	6.7
7	5.0	4.0	28.7	23.2	20.9
8	12.0	5.2	61.5	26.1	5.1
9	59.9	9.9	7.8	76.2	-t
10	10.9	8.8	12.5	20.9	-t
Averages	**36.2**	28.8	32.0	45.3	28.7

. Specimen arrived thawed
t – = Missing values

ranged from 28.7 ng/mg in the cervical tissue sections to 45.3 ng/mg in the right cornual sections. Tissue quinacrine concentrations varied greatly within and among subjects. The mean concentrations in the five tissue segments studied did not differ significantly.

Tampons, which had been worn for 24 h after quinacrine insertion, were analyzed for nine of the 10 women. The mean quinacrine content of tampons was 68.0 mg (27% of dose), with a range of **13.5-111.8** mg (5% to **45%).**

Results: One-Month Prehysterectomy Trials

Adverse Events

Subsequent one-month prehysterectomy Phase I clinical trials were begun in 1985 and 1986 with 10-min pellets and 100-min pellets, respectively. Recruitment was difficult and only five and six patients were recruited in the two trials before they were discontinued. In the trial of the 10-min pellets, two of the five women reported adverse events.

Patient number 4 reported heavy vaginal bleeding that started approximately 24 h after insertion and lasted for two days, at which time a heavy brown discharge was noted, which had stopped by day 14. On day 21, the same woman complained of a thick, yellow discharge.

Patient number 5 complained of severe cramping pains and a spotty discharge which began about 2 h after the insertion. The pain decreased with oral acetaminophen, but occasional cramping pains similar to menses lasted for about two weeks. The same woman complained of headaches about a week later. None of these complaints were judged to be serious by the investigator and none required treatment other than oral analgesics.

In the trial of the 100-min pellets, five of the six women reported adverse events as follows: Patient number 2 reported copious clear, yellow vaginal discharge on day seven which was resolved by day 14.

Patient number 3 had low-abdominal pain and watery, blood-tinged vaginal discharge starting at 12 h postinsertion; the abdominal pain resolved by 24 h postinsertion and the discharge resolved by day seven.

Patient number 4 reported vaginal bleeding starting at 2 h postinsertion which was resolved by day 14. This patient also experienced an achy feeling and a low-grade fever and chills beginning 2-4 h after quinacrine insertion. In addition, soreness of the left shoulder and right leg, palpitations, and a shaky feeling were reported at 12 h postinsertion; chills, fever, neck pain, shortness of breath, and buzzing in the ears were reportted at 24 h postinsertion. The patient reported that taking alcohol baths and eating garlic relieved the shortness of breath. The patient was followed closely on an outpatient basis, and did not require hospitalization or specific therapy.

The investigator summarized this episode as having lasted five days, with the worst symptoms lasting for about the first 24 h. The event was judged to be of moderate severity.

Patient number 5 experienced vaginal bleeding starting at 2 h postinsertion which resolved by day seven. She reported low-abdominal cramping at 12 h postinsertion, which was followed by intermittent pain in the right lower quadrant lasting about two weeks. At one-day postinsertion she reported labial irritation with burning, and also said that she had chills and fever the previous evening. Her temperature had returned to normal at the time of the one-day follow-up visit.

Patient number 6 experienced cramping and vaginal bleeding from 2 h postinsertion until day seven; on day seven the patient complained about leg numbness from the knees down and ankle edema, neither of which were present at the physical examination.

Pathology and Blood Levels from the One-Month Trials

Gross examinations of the removed uteri from the one-month trials did not show any evidence of intrauterine adhesions, synechia, or extra-uterine adhesions. However, in one woman who had received the 100-min pellets, the surgeon reported the presence of filmy adhesions from the cornu and top of the uterus to the omentum. It was not possible to determine whether those adhesions were due to quinacrine or whether they were pre-existing.

Histologic examination of removed segments of the Fallopian tube, mostly the interstitial segments, showed mixed results. Data were missing for five tubes. Of available data on 17 tubes, there was absence of the epithelium or obliteration of the lumen in nine tubes, while eight tubes showed normal epithelium, or only mild inflammatory changes.

Histological examination of endometrial sections showed either normal secretory or proliferative pictures, depending on the woman, and four minor abnormalities. Two women had findings of adenomyosis; these probably predated their quinacrine insertions. One woman had evidence of chronic endometritis and one woman had a report of "focal cystic change, " which is sometimes seen in cases of atrophic endometrium. These two findings may have been related to quinacrine.

The blood levels measured in the trial of the 100-min pellets were, as expected, significantly lower than the levels seen after the 10-min pellets. No con-

centration of quinacrine could be found in any of the baseline samples or in any sample collected at day 14 or later; the mean standard deviation (SD) quinacrine serum concentration was 7.23 (2.9) ng/mL at 2 h, 7.01 (2.8) ng/mL at 12 h, 3.51 (0.7) ng/mL at day one, and 0.29 (0.3) ng/mL at day seven.

Discussion and Conclusions

Adverse Events

No serious adverse events were reported among the 15 women who received the lo-min pellets. This number of women is too small to make any generalizations about adverse events; however, reports of larger, more recent clinical studies also suggest that the procedure is well tolerated.[2–5]

More adverse events were reported from the study of the 100-min pellets, including one which was judged to be of moderate severity by the investigator. A larger trial of 100-min pellets conducted by Dr. Zipper in Chile" reported two cases of pelvic inflammatory disease among 112 women following the first insertion of the 100-min pellets. It is possible that those cases of pelvic inflammatory disease were actually cases of chemical peritonitis resulting from spillage of some quinacrine through the tubes into the peritoneal cavity. Three cases of hematometra were also reported among the 103 women in that study who received two insertions.

Cases with signs of peritoneal irritation, or hematometra, have been much less commonly reported following the use of lo-min pellets.[2–5] In a recent study of quinacrine pellet insertions, 10% of 100 women complained of fever after the first insertion. However, none of these women were judged to have had a serious reaction.[2]

It is possible that the 100-min pellets caused local toxicity due to their prolonged presence in the uterus. One could speculate that as the uterus tried to expel the slow-dissolving pellets, occasionally a still-solid pellet might physically obstruct the cervical canal. If that occurred, continuing uterine contractions might result in the expulsion of some dissolved quinacrine out into the peritoneal cavity through the Fallopian tubes.

Little additional data are available concerning the 100-min pellets. Difficulties in formulating pellets with uniform dissolution time led to the abandonment of their development. Given the small sample sizes involved in the studies of the 100-min pellets and the absence of any randomized trials comparing the 10-min with the 100-min pellets, it is not possible to conclude whether the adverse events observed in the trial of the 100-min pellets were related to their slow dissolution time or to the presence of cholesterol, or were just a reflection of better reporting. A randomized, blinded study comparing lo-min versus 100-min pellets was never done.

Pathology

An unpublished manuscript by Alegria et al. reports the presence of necrotic endometrial tissue after 48 h, and regeneration of normal endometrium after one month. While we do not have pathology data on the uteri removed after 24 h, the uteri removed after one month showed grossly normal endometrial tissues. Two women had endometrial abnormalities on histological examination that may have been due to quinacrine, but their clinical significance is unclear.

A paper by El Sahwi[3] reported hysteroscopic observations after one, two, and three insertions. He reported no endometrial abnormalities after a single insertion, but increased abnormalities after two and three insertions. He noted mainly atrophic and polypoid reactions; in addition, three of 20 women had fine adhesions after three insertions. In the absence of symptomatic hematometra, most authors have not attributed any clinical importance to intrauterine lesions caused by quinacrine, but this issue may merit additional study.

On histologic examination, only about 50% of the Fallopian tubes had appeared to be obstructed. This does not seem consistent with the clinical observations of pregnancy rates following one or two quinacrine insertions. There are at least two hypotheses which could be considered as explanations for this apparent discrepancy. First, based on Merchant's suggestion that Fallopian tube closure takes up to six weeks, one might hypothesize that some of the apparently normal tubes would have closed if given more time.[12]

The second hypothesis takes into account El Sahwi's observations, described above, regarding endometrial changes. While it has been generally considered that quinacrine acts only by occluding the Fallopian tube, it is possible that some of quinacrine's effectiveness is due to its ablative effect on the endometrium. Endometrial ablation procedures generally result in subsequent infertility, and quinacrine may act partially through a similar mechanism.

Pharmacokinetics

The lo-min pellets of quinacrine used in the 24-h hysterectomy study produced plasma levels of quinacrine that were similar to levels found after oral administration of 200 mg. Using the same spectrophotometric assay method,[10] Shannon reported an average level of 59.9 ng/ml 4 h after an oral dose of 200 mg, compared with an average level of 36.1 ng/ml

3 h after intrauterine administration in the current study.[13] The average of the peak values from the present study is 46.3, still below the level reported from oral administration. Shannon's study also showed a wide range of values, from **19** to **124** ng/ml. While both investigators used the same method,' it should be noted that these two studies were done in different laboratories, and about 40 years apart, so there may be some unknown limitations in the comparability of the results.

Plasma levels of quinacrine after administration of the 100-min pellets were considerably lower, with values of only around 7 ng/ml at 2 and 12 h, compared to about 30 and 20 ng/ml, respectively, for the 10-min pellets.

There was only a weak correlation (r = 0.47) between peak plasma levels and the absorbed dose, which was calculated as 250 mg minus the amount of quinacrine found on tampons. The wide variation in tampon content could be an artifact due to leakage of some quinacrine around the tampons.

As is the case with other anti-malarials such as chloroquin, quinacrine has a long elimination half-life in humans. Two women still had low, but detectable, plasma levels of quinacrine at four/six weeks after the insertion.

In conclusion, the transcervical administration of 250 mg of 10-min quinacrine pellets was well tolerated. The peak plasma levels were similar to those observed following oral administration. The use of 100-min pellets was associated with more side effects, but because of the small sample sizes, the reasons and significance of this difference cannot be determined.

Future Prospects

WHO has recommended that appropriate toxicology testing be completed on quinacrine prior to further human studies of quinacrine pellets. In response to this recommendation, FHI sponsored a Toxicology Experts Meeting held April 24, 1994, in Arlington, VA. FHI then sponsored the conduct of four genetic toxicology tests by Microbiologic Associates in late 1994. These tests confirmed quinacrine's mutagenicity. Based on the results of these tests and consultation with representatives of regulatory agencies, it is unlikely that the transcervical use of quinacrine pellets could be approved in the U.S. or Europe.

While FHI is involved in long-term safety studies of women who have received quinacrine, FHI is not conducting or planning any clinical studies with quinacrine. Pre-clinical studies could be planned to evaluate potential non-mutagenic substitutes for quinacrine, if funding were available.

Acknowledgment

Partial support for this study was provided by Family Health International under a Cooperative Agreement with the U.S. Agency for International Development (USAID). FHI is an international not-for-profit organization which conducts research and provides technical assistance in health, family planning, sexually transmitted diseases, and AIDS. It is based in Research Triangle Park, North Carolina, U.S.A. The views expressed in this article do not necessarily reflect those of FHI or USAID.

References

1. Zipper J, Cole Ll?, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 1980; 18:275-9.
2 Agoestina T, Kusma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. Adv Contracept 1992;8:141-51.
3 El Sahwi S, Kamel M, Haiba N, Osman M. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of nonsurgical sterilization. Adv Cont Deliv Syst 1992;8:151-9.
4. El-Kady AA. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. Fertil Steril 1993;59:301-4.
5. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than I?, Vinh DQ. 31,781 cases of nonsurgical female sterilisation with quinacrine pellets in Vietnam. Lancet 1993;342: 2 13-7.
6. Benagiano G. Sterilisation by quinacrine. Lancet 1994; 344:689.
7. Kessel E. Quinacrine sterilisation revisited. Commentary. Lancet 1994;344:698-9.
8. Berer M. The quinacrine controversy one year on. Reprod Health Matters 1994;4:99-106.
9. Dubin NH, Blake DA, DiBlasi MC, Parmley TH, King TM. Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. Fertil Steril 1982;38:735-40.
10. Brodie BB, Udenfriend S. The estimation of atabrine in biological fluids and tissues. J Biol Chem 1943; 15 1:299.
11. Zipper J, Cole LP, Rivera M, Brown E, Wheeler RG. Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for nonsurgical female sterilization. Adv Contracep 1987;3:255-61.
12. Merchant RN, Prabhu SR. Clinicopathologic study of Fallopian tube closure after single transcervical insertion of quinacrine pellets. Int J Fertil 1995;40:47-54.
13. Shannon JA, Earle DP Jr, Brodie BB, Taggart JV, Berliner RW. The pharmacological basis for the rational use of atabrine in the treatment of malaria. J Pharmacol Exp Ther 1944;8 1:307-30.

RESEARCH NOTE

Quinacrine Pellet Method of Nonsurgical Female Sterilization in Iran: Preliminary Report on a Clinical Trial

By Sheitaneh Soroodi-Moghaddam

For a study of the safety, efficacy and acceptability of female sterilization with quinacrine pellets in a private-practice setting, data on 160 women who obtained the procedure in Tehran between September 7990 and April 1994 were evaluated. Three-fourths of the women were monitored for at least one year, and more than ha/f were monitored for more than two years. By the end of the study period, two women had become pregnant, for a gross pregnancy rate of 7.2%; neither pregnancy was ectopic. Within the first two months after the procedure, about half of the women reported complications or side effects, which were minor and easily treatable; after the first two months, the only side effect reported was delayed menses. The cost of sterilization with quinacrine pellets is one- 70th that of surgical sterilization. However, knowledge about the method is not widespread within the medical community in Iran.

(International Family Planning Perspectives, 22:122-l 23 & 127, 1996)

After the *1979* Islamic Revolution in Iran, the new government altered the 1967 fertility control policy, and the pace of population growth accelerated rapidly. In 1986, the population growth rate was 3.8% (3.4% when refugees from Afghanistan are excluded)—substantially higher than the 1976 rate of 2.7%, and one of the highest rates in the world.' More recently, in response to social and economic pressures, the government has once again become very concerned with the issue of population growth. The Ministry of Health has taken various steps to promote family planning, from erecting billboards with messages discouraging people from having large families, to providing free oral contraceptives.

Modern contraceptives are available in Iran and are used by roughly half of women in both urban and rural areas. Among urban women, 19% use the pill, 11% each have undergone voluntary sterilization and use the IUD, 8% rely on the condom and 2% are protected by their husband's vasectomy; in rural areas, 27% use the pill, 11% have had a tubal occlusion, 4–5% use the IUD or condom and 1% have a husband who has had a vasectomy.[2] Given the prevalence of tubal occlusion, the cost of hospitalization for sterilization and the risks associated with any surgical procedure, nonsurgical female sterilization is an alternative worth studying.

The only nonsurgical technique for tubal occlusion that is ready for clinical trials is the quinacrine pellet method, developed by Jaime Zipper and colleagues." The method involves the transcervical intrauterine administration of quinacrine hydrochloride to nonpregnant women during the proliferative phase of the menstrual cycle (days 5-12).

This research note describes the first four years of an ongoing trial undertaken in a private-practice setting to determine whether this method is applicable in Iran. The goal of the study is to assess the safety, efficacy, acceptability and ease of delivery of quinacrine.

Study Population

Study participants were carefully selected from among women seeking voluntary sterilization at a single private clinic between September 1990 and April 1994; women were included only if they lived close enough to the clinic to be able to return for long-term follow-up. In all, 168 women underwent sterilization with quinacrine during this period; the analyses are based on the 160 women who returned to the clinic for all scheduled follow-up visits through August 1994. Thus, all of the women were monitored for at least four months; three-fourths were monitored for one year or more, and slightly more than half for more than two years.

Participants were almost evenly divided between those aged 26-35 and those aged 36-45 (52% and 47%, respectively). Two younger women also underwent the procedure: a 19-year-old for whom another pregnancy was medically contraindicated and a 21-year-old who had six children. The women had between one and 11 children: Some 24% had l-3 children, 56% had 4–6, 18% had 7-9 and 3% had 10 or 11.

Procedure and Results

To ensure informed consent, all prospective acceptors and their husbands were counseled by a family planning specialist prior to the procedure. Counseling included a detailed description of the method and its administration, possible complications and side effects, and the risk of failure. The counselor explained that the effect of the procedure is intended to be permanent and not reversible. Both the wife and the husband signed an informed-consent form.

The International Federation for Family Health quinacrine study protocol,[4] based on the work of Zipper and his colleagues, was applied throughout the study. Originally, Zipper recommended that quinacrine be administered in three doses of 252 mg (seven pellets of 36 mg each) at one-month intervals;[5] this regimen was used for the first 62 procedures. At that point in the study, however, the provider learned that Zipper had changed his recommendation to two monthly doses, each consisting of 252 mg of

Sheitaneh Soroodi-Moghaddam is a family planning specialist in private practice in Tehran, Iran.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

quinacrine plus 50 mg of an antiprostaglandin to lessen spasm and thereby reduce the failure rate and the incidence of minor side effects.[6] These changes were adopted for the last 98 procedures. (Ibuprofen was available only in pellets of 18.5 mg, so the actual dose of antiprostaglandin used was 55.5 mg, administered in three pellets.)

A modified Copper T IUD inserter was used to administer the quinacrine, according to the following procedure: After preparing the cervix and sounding the uterus, the clinician set the blue depth marker on the inserter sleeve, removed the plastic cap and advanced the inserter to the fundus. She then withdrew the inserter 0.5 cm, fixed the inserter sleeve and slowly advanced the plunger to expel all pellets at the fundus. The inserter was then withdrawn. After each insertion, the woman was given a five-day course of antibiotics.

Women returned to the facility for follow-up one, two and 15 days after each insertion; one, two, three and six months after the last insertion; and then annually for three years. There was no charge for these visits. A cycle of oral contraceptives was provided at the time of the last insertion and at the one- and two-month follow-up visits.

By the end of the study period, two women had become pregnant (one who had undergone the three-dose method and one who had had two doses), for a gross pregnancy rate of 1.2%; neither pregnancy was ectopic. Approximately half of the women experienced complications or side effects within the first two months after the procedure (see Table 1). Only two women complained of multiple complications (two each). All complications and side effects were of a minor nature-predominantly lower abdominal pain, local itching and fever-and were easily remedied. No complications were reported after the two-month follow-up visit except for delayed menses.

Discussion

In several respects, sterilization with quinacrine appears to be superior to other contraceptive methods available in Iran. The failure rate of 1.2% observed in this study is quite acceptable. Furthermore, the complications and side effects reported by the study participants were minor when compared with those associated with surgical sterilization. The method also proved to be very easy to deliver in a private-practice setting, and its cost was only one-10th that of surgical sterilization. Although the study did not measure women's satisfaction with the method, it appears to be very high in some instances. For example, on the advice of one study participant, 18 of her extended family members obtained quinacrine sterilization.

Despite the potential advantages of quinacrine sterilization, the method is not widely known in the medical community. Anecdotal evidence suggests that as a result, some Iranian women have been dissuaded by their family doctors from undergoing the procedure, even though it would have been appropriate to the woman's needs.

Similarly, women who have undergone the procedure have subsequently encountered physicians whose lack of knowledge about it became an obstacle to appropriate care. For example, one woman visited a doctor several months after undergoing sterilization with quinacrine to obtain confirmation of its effectiveness. The doctor told her that a few pellets could not possibly make one infertile, but he referred her to a radiologist for a hysterosalpingography. The test, which involves x-raying the uterus and fallopian tubes after injecting a dye, showed that both tubes were indeed occluded-a result that surprised both the radiologist and the doctor who made the referral. However, this test was a poor choice because the pressure it creates in the tubes could have dislodged the plug of scar tissue and reopened a tube; fortunately, this did not happen in this instance.

In another case, a woman who had obtained a nonsurgical sterilization and perineoplasty went to another obstetrician-gynecologist about a year later because she had a slight discharge. When the doctor asked her what method of birth control she was using, she replied that she had undergone tubal occlusion using pellets. Dismissing this answer, the doctor insisted that the woman had likely been the victim of a scam and that her previous physician had probably inserted a contraceptive implant without her knowledge. Only when the doctor examined the woman and commented on how well the perineoplasty had been done did he believe the woman's account.

Thus, dissemination of information about tubal occlusion with quinacrine pellets is critical for the proper introduction and steady proliferation of this simple, low-cost method.

Table 1. Complications and side effects reported following nonsurgical female sterilization with quinacrine pellets, and prescribed treatment, Iran, 1990-I 994

Complication	No. of women	Treatment
Lower abdominal pain	18	Analgesic (2-3 days)
Itching (local)	16	Cortisone cream
Fever 25 days	14	Antibiotic (4 days)
Backache	8	Analgesic (2-3 days)
Vaginal discharge	8	Antifungal, antibiotic vaginal suppository (6 days)
Spotting	8	None
Decreased menses		None
Cervical adhesion		Surgical correction
Bleeding		Vasoconstrictor

References

1. A Aghajanian, "Population Change in Iran, 1966-86: A Stalled Demographic Transition?" Population and Development Review, 17:703–715, 1991.

2 United Nations Population Fund, *Family Planning in Islamic Republic of Iran,* Tehran, 1994

3 J Zipper et al, "Efficacy of Two Insertions of 100-Minute Releasing Quinacrine Hydrochloride Pellets for Non-Surgical Female Sterilization," *Advances in Contraception,* 3:255–261, 1987.

4. International Federation for Family Health (IFFH), "Protocol for Straight and Comparative Studies of Nonsurgical Female Sterilization by Quinacrine Pellets and Quinacrine Pellets Plus Adjuvants," Leasburg, N C, USA, 1992

5 J Zipper et al, "Quinacrine Hydrochloride Pellets: Preliminary Data on a Nonsurgical Method of Female Sterilization," *International Journal of Gynaecology and Obstetrics,* 18:275–279, 1980.

6. E Kessel, IFFH, personal communication, 1992; and J. Zipper, M Rivera and A Dabancens, "Stérilisation Féminine Non-Chirurgicale: Utilisation de Pellets Endo-Utérins de Quinacrine et Betamethasone Revision du Sujet: Bases Expérimentales-Pharmacologie-Toxicologie-Efficacite" (Non-Surgical Female Sterilization: Use of Endo-Uterine Pellets of Quinacrine and Betamethasone Review of Question: Experimental Basis, Pharmacology, Toxicology, Efficacy), *Revue Français de Gynecologie et d'Obstetrique,* 88:185–190, 1993.

Resumen

En *un estudio sobre la seguridad, eficacia y aceptabilidad de la esterilizacion femenina en base a grageas de quinacrina en un medio de consulta médica privada, se evaluaron los datos de* 160 *mujeres que se sometieron a este procedimiento en Teheran, entre septiembre de 1990 y abril de 1994. Se control6 al 75% de las mujeres por un período mínimo de un año, y ma's de la mitad por ma's de dos años. Al final del estudio, dos mujeres quedaron embarazadas, lo cual significó una tasa bruta de embarazos del 1,2%; ninguno de los em barazosfue ectópico. Dentro de los primeros dos meses de realizado el procedimiento, aproximadamente la mitad de las mujeres registraron complicaciones o efectos secundarios, los cuales fueron pequeños y de fácil tratamiento; luego de los dos primeros meses, el único efecto secundario fue el retraso de la menstruacibn. La esterilización en base a grageas de quinacrina cuesta la décima parte del valor de una esterilización quirúrgica. Sin embargo, no se ha di-*

(continued on page 127)

Quinacrine Pellet Method. ..

(continued from page 123)

seminado ampliamente el conocimiento de este método en tre la comunidad médica de Iran.

Résumé

Auxfins d'une etude sur la sécurité, l'efficacite' et l'acceptabilité de la stérilisation feminine par pastilles de quinacrine en pratique de clientele, les données relatives à 1 60 femmes ayant obtenu la procedure à Teheran entre les mois de septembre 2990 et d'avril 1994 ont été évaluées. Soixante-quinze pour cent des femmes ont été surveillées pendant au moins un an, et plus de la moitie, pendant plus de deux ans. Au terme de la période d'étude, deux femmes s'étaient retrouvées enceintes, soit un taux de grossesse brut de 1,2%; aucune de ces deux grossesses ne s'était avérée extra-uterine. Au cours des deux premiers mois qui avaient suivi la procedure, la moitié des femmes environ s'étaient plaintes de complications ou d'effets secondaires, toutefois mineurs et faciles à traiter. Au terme des deux premiers mois, le seul effet secondaire signalé0 était celui de règles tardives. Le coût de la stérilisation par pastilles de quinacrine est 10 fois inférieur à celui de la procedure chirurgicale. La mtthode est cependant peu connue dans les milieux médicaux iraniens.

One year experience using quinacrine pellets for non-surgical female sterilization

AGUNG SUHADI*
ARIAWAN SOEJOENOES**

**Department of Obstetrics and Gynecology Wonosobo Regency Hospital, Central Java Province, Indonesia*
***Department of Obstetrics and Gynecology Faculty of Medicine Diponegoro University, Dr. Kariadi Hospital, Semarang, Central Java Province, Indonesia*

Tujuan: Untuk mengevaluasi kemanjuran, keamanan don penerimaan penggunaan transservikal dua kali pellet quinacrine 250 mg dan ibuproven 55,5 mg sebagai sterilisasi wanita non-bedah.

Rancangan/rumusan data: Kajian klinis dikerjakan dengan mengambil ibu-ibu yang menginginkan sterilisasi sebagai suatu cara keluarga berencnna. Setiap wanita menerimn quinacrine hydrocloride dengan dosis 250 mg dalam bentuk pellet silindris 7 buah diikuti dengan ibuproven 55.5 mg tmnsservikal. Pellet dimasukkan dua kali dalam periode dua bulan selama fase proliferasi dari siklus menstruasi. Pengamatan lanjut dikerjakan dalam 6, 12, 24 dnn 48 bulan setelah pemberian pellet terakhir. data dikumpulkan menggunakan formulir bsku yang dikembangkan oleh *The International Federation for Family Health* (IFFH).

Tcmpat: Klinik Keluarga Berencnno, Bagian Obstetri dan Ginekologi KSU Wonosobo, Propinsi Jawa Tengnh. Indonesia.

Subjck, **pasien, peserta**: 200 wanita diteliti selama periode Agustus 1992 sampai Oktober 1993. Semua memenuhi kritcria penerimaan dan penolakan.

Ukuran luaran utama: Komplikasi, keluhan, angka kehamilan dan angka kelangsungan.

Hasil: Umur dan anak hidup rata-rata adalah 33,2 ± 9,75 (SD) dan 3,5 ± 0.50 (SD). Efek samping utama setelah insersi pertama adalah sakit perut bawah pada 116 kasus (60,1 %). Dua kasus mengalami sakit perut bawah berat yang memerlukan pengobatan antibiotika dun analgetika. Keluhan lain yang dilaporkan antara lain panas menggigil (13,5 %) dan leukorea (7.8 %) yang hilang tanpa pengobatan khusus. angka kelangsungan kumulatip per 100 wanita dalam 12 bulan setelah insersi terakhir pellet quinacrine adalah 0.97 ± 0.01 (SE). Angka kehamilan adalah 0.0 l.

Kesimpulan: Hasil penelitinn ini menunjukkan bahwa penggunaan pellet quinacrine perlu dikembangkan lebih lanjut sebagai metoda yang memberikan harapan, aman dun efektif pada sterilisasi wanita non-be&h dengan pertimbangan kemudahan dari metodanya.

[Maj Obstet Ginekol Indones 1996; 20: 39-43]

Kata kunci: Pellet quinacrine transservikal, kemanjuran, keamanan, angka kelangsungan, cara sterilisasi non-be&h.

Objective: To evaluate the safety und acceptability of two transcervicul application of250 mg of quinucrine and 55.5 mg ibuproven pellets us non-surgical female sterilization.

Design/data identification: A descriptive study was done by recruiting women seeking sterilization for family planning reason. Each women received a250 mg dose of quinucrine hydrocloride in the form of seven cylindrical pellets. The pellets was inserted twice with the period of two months during the proliferative phase of menstrual cycle. Follow-up was conducted in 6, 12, 24 and 48 months after the last administration. Data were collected using standarized forms developed by the International Federation for Family Health (IFFH).

Setting: Family planning clinic, Department of Obstetrics and Gynecology Wonosobo Regency Hospital. Central Juvu Province, Indonesia.

Subject, patients, participants: Two hundred women were studied during the period of from August 1992 to October 1993. All of them fulfilled the inclusion und exclusion criteria.

Main outcome measures Complications, complains, pregnancy rate and continuation rate.

Results: Mean age and number of live births of women was 33.2 ± 9.75 (SD) and 3.5 ± 0.50 (SD). The main side effects after the first insertion were lower abdominal pain in 116 cares (60.1 %). there were two cases who experienced severe lower abdominal pain and required antibiotic and analgesic treatment. Other complications reported were chilling (13.5 %) und leucorrhea (7.8 %) which subsided without my specific treatment. The cummulutive continuation rates per 100 women at 12 months after the lust quinucrine pellet insertions was 0.97 ± 0.01 (SE). The pregnancy rate was 0.01.

Conclusions: The result of the study indicated that the use of quinucrine pellets diserves to be further developed as a promising, safe and effective method of non-surgical female sterilization, considering the ease of the method.

[Indones J Obstet Gynecol 19%; 20: 39-43]

Keywords: Transcervicul Quinucrine pellet, efficacy, safety, continuation rate, non-surgical ste rilization method.

INTRODUCTION

The estimated number of couples controlling their fertility through sterilization has increased dramatically over the past two decades, from 15 million in 1970 to 100 million in 1980.1 In developing countries, the demand for sterilization far exceedes the supply of services. the approximated half of the fe-

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

cund women want no more children, but fewer than half of these women use effective methods of fertility control, due to among them the lack of funds, professional personal and the organization to mount such programs in the crowded urban or scattered rural areas, This is an estimate of unmet need for sterilization. Many of the women countinue to use effective reversible methods of contraception for long periods after the desire of no-more-children.[2,3]

Extensive research has been performed to develop a simple method of non surgical female sterilization. Zipper and associates identified quinacrine hydrocloride as a drug likely to produce tubal occlusion when placed into the uterus.[4] Several clinical trials have been done to evaluate various doses, concentrations, solvents for the suspensions and instillation schedules of quinacrine. Zipper's quinacrine solution schedule of three instillations of a solution of 1.5 mg of quinacrine powder suspended in 5 ml of 2 % xylocaine has a high pregnancy rate and produced occasional transient toxic psychosis.[5,6]

In an effort to overcome these difficulties, quinacrine hydrochloride pellets have been developed to produce a delivery system that would bring the chemical into prolonged contact with the tubal ostia through delayed uterine retention, and this increase the probability of successful occlusion. Because the quinacrine pellet dissolves relatively slow within the uterine cavity, the risk of rapid intravascular absorption presented with the solution may be reduced.7

The aim of the study was to evaluate the efficacy, safety and acceptability of two tran'scervical applications of 250 mg quinacrine and 55.5 mg ibuproven pellets as non-surgical female sterilization.

MATERIALS AND METHODS

A descriptive study was conducted at the Wonosobo Regency Hospital, Central Java Province, Indonesia. From August 1992 through October 1993 two hundred women who gave informed consent received a 250 mg dose of quinacrine hydrochloride on the form of seven cylendrical pellets followed by 55.5 mg ibuproven transcervically. The pellets was in-. serted with the period of two months during the proliferative phase of menstrual cycle. Insertion is accomplished by placing seven quinacrine pellets followed by 55.5 mg ibuproven pellets in a plastic tube with a push rod positioned behind them. The tube is then passed through the cervical canal until the fundus is reached. Dilatation is infrequent. The push rod is then held stationary, and the tube is pulled back after it espelled the pellets into the upper segment of the uterine cavity. After the pellets have been discharged, the inserter is removed.

The procedure is essentially the same as inserting an IUD. Insertions were performed during the proliferative phase of two consecutive menstrual cycles.7

Follow-up was scheduled at six, 12, 24 and 48 months after the last administration and at any time when complications or complaints occured. Women were admitted to the study if they requested sterilization for family planning reason and if they did not have a history of medical or psychiatric problems. Excluded were women who had pathologic pelvic conditions (except cervisitis) or those who appeared unusually nervous. Those women who had to be excluded were offered a choice of surgical sterilization or other methods of contraception.

Data were collected using standarized forms developcd by the International Federation for Family Health (IFFH). Descriptive and life table analysis using Kaplan Meier Survival curve to draw the continuation rate conducted in this study.*

RESULTS

All 200 women completed the first insertions the report analysis, include 197 of the cases: three cases were excluded from the analysis due to discontinuing the second insertion.

Table 1 Number of quinacrine pellet insertions

Quinacrinc pellets	n	%
First insertion	200	100.0
Second insertion	197	98.5

Table 2 Area of origin for women

Area of origin	n	%
Urban	22	11.0
Rural	178	89.0
Total	200	100.0

The majority of the women 178 (89.0 %) came from rural areas, whereas 22 (11 .0 %) were urban people. Areas of origin for these women are shown in Table 2.

Mean age and number of live births of women entering the study are provided in Table 3. The mean age was 33.2 ± 9.75 (SD), ranging from 24 to 40 years. The mean number of live births for the popu-

lation was *3.5 ± 0.50* (SD), with a range of 2 to 8 live births.

Table 3 Age and live births for women entering quinacrine pellets study

	Quinacrine pellets
Mean Age (years)	33.2 ± 9.75
Mean number of live births	3.5 ± 0.50

Table 4 Distribution of contraceptive methods before quinacrine pellet insertions

Contraceptive methods	n	%
None	69	34.5
IUD	25	12.5
Orals	40	20.0
Injectable	61	30.5
Condom	4	2.0
Withdrawl/rythm	1	0.5
Total	200	100.0

Most women 69 (34.5 %) had never used a contraceptive, while 43 % had used an effective method 3 months prior to this procedure (Table 4).

Complications and complaints reported are shown in Table 5. The main side effects after the first insertion were lower abdominal pain in 116 cases (60.1 %). Two women reported severe abdominal pain and required antibiotic and analgesic treatment. Chilling in 26 cases (13.5 %), leukorrhea in 15 cases (7.8 %). These symptoms lasted a few hours to a few days. Symptoms were generally milder after the second insertion. Temporary amenorrhea occured in two women (1 .O %), that lasted to 4 months but required no treatment.

The cumulative continuation rates in this study per 100 women at one year were 0.97 ± 0.01 (SE) (Table 6). Pregnancies occured within one and two months after the second insertion. The pregnancy rate was 0.01 or 1%.

Table 6 Cumulative continuation rate at 12 months after the second administrations

Months after administration	Continuation rate	S E
6	0.97	0.01
12	0.97	0.01

The diagnosis of pregnancy was made by pelvic examination or a combination of pregnancy test and pelvic examination. One of the pregnancies was terminated by menstrual regulation and the other pregnancy ended in a spontaneous delivery with term a female baby, and no major malformation was noted.

DISCUSSIONS

Surgical female sterilization, the most effective method of contraception for women who desire no additional children, requires trained personal, adequate medical care facilities and the acquisition and maintenance of sophisticated equipment.7

For about three decades investigators around the world have been trying to develop a safe, 95 percent effective method of non-surgical female sterilization that could be performed under local anesthesia or on an outpatient basis by non physicians, preferably after only a brief training period. Such a method has been called vital for meeting the worldwide demand for voluntary sterilization, since it is projected that around180 million peoples will be seeking sterilization over the next 10 years.9

Researchers have experimented with various

Table 5 Complications and complaints reported within one year after second administration of quinacrine pellets

Complications/Complaints	First insertion (n = 200)		Second Insertion (n = 197)	
	n	%	n	%
Amenorrhea	2	1.0	2	1.0
Menorrhagia	7	3.6	3	1.5
Leukorrhea	15	7.8	4	2.0
Pain in lower abdomen	116	60.1	1	0.5
Chilling	26	13.5	4	2.0

* More *than one complication/complaint may occur for each women*

chemical sterilants to produce tubal occlusion. Drugs such as ethanol, formaldehyde and silver nitrate cause tubal occlusion but cannot be used because of their toxicity. Methylcyanoacrylate (MCA), phenol atebrine (Quinacrine)-biligraphin paste (PAP) act by causing tissue adhesiveness. They are highly effective but the process of application has not so far been established for these chemicals, The Erb method used liquid silicon rubber to plug the oviducts, but its application required both a skilled surgeon and complex equipment.[1,3,9,10,11,12,13,14]

Since 1968, Zipper and associates in Santiago, Chile, evaluated various doses, concentrations, solvents for the suspension and instillation schedules of quinacrine and caused 69-94 % tubal occlusion.[1,7]

Zipper has also found that two transcervical applications of 250 mg. quinacrine pellets followed by intramuscular or intrauterine administration of antiprostaglandins both lowers the incidence of mild side effects and the failure rates.[3,4,14]

Since August 1992 through October 1993 Non-surgical female sterilization using two transcervical applications of quinacrine pellets were conducted on 200 females in the Family Planning Clinic, Wonosobo Regency Hospital, Central Java Province, Indonesia. Three cases were excluded due to discontinuing the second insertion. The majority of the women (89.0 %) in the study was from rural areas. Bhatt and Waszak in Baroda, India reported the majority of the study (77.4 %) was from urban areas.[11]

The mean age of the women was 33.2 ± 9.75 (SD), the youngest was 24 years and the oldest was 40 years, whereas the mean number of live births was 3.5 ± 0.50 (SD), ranging from 2 to 8. These figures were 31.3 years for the mean age and 3.5 for the mean number of live births in the study of Bhatt and Waszak in Baroda, India (1985).[11] The figures in the studies of Zipper and associates in Santiago, Chile, were 3 1.4 years and 3.6.4

About 34.5 percent of women used no contraception before quinacrine insertion and this was comparable with another similar study in Baroda, India.[11]

There were no major complication during the procedure. There were two cases who experienced severe lower abdominal pain and, required antibiotic and analgesic treatment. Zipper reported that one case in his study was treated with penicillin.[15] Other complications reported were chilling (13.5 %) and leukorrhea (7.8 %) which subsided without any specific treatment. Hieu and associates in Namha, Vietnam, showed that these symptoms lasted for a few hours to a few days. Symptoms were generally milder after the second insertion.16

The cumulaive continuation rate per 100 women at 12 months after the last quinacrine pellets insertions was 0.97 ± 0.01 (SE). Pregnancies occured in one and two months after the second insertion resulting the pregnancy rate of 0.01 or 1% due to incomplete tubal occlusion. The one year pregnancy failure rate in the Vietnam trial was 2.63 per 100 women for those receiving two monthly transcervical insertions of 252 mg quinacrine as pellets and 5.15 for those receiving single insertion. Failure rate (pregnancies) was strongly affected by the skill of the operator. The amount of experience the operator had was of little importance compared with his or her skill.[16] There are other possibilities for lowering the failure rate. For example, prehysterectomy studies showed that completion of tubal occlusion takes at least 6 weeks in some women. The use of contraception for during this period would be advisable.16 The dose of quinacrine to be used in a single insertion should probably not be less than 2 16 mg or more than 324 mg. Merchant's prehysterectomy data suggest that a 100 mg dose of quinacrine is too low, and that more than 324 mg would be superfluous. Recent data from Bairagi showed low failure rates with a dose of 2 16 mg of quinacrine plus ibuproven or diclofenac and three cycles of oral contraceptives.17

There were no deaths in this study. Up till now, no death have been reported using this method anywhere in the world. The 'use of quinacrine pellets appears to have reduced the incidence of transient toxic psychosis or cortical excitation, a side effect that has been observed in studies using intrauterine solution. No women in the Indonesia studies developed transient psychosis. But in the Zipper studies using solution 2 % developed transient psychosis.[15]

Eventhough mortality related to surgical sterilization is low, there are still some risks associated with the surgical procedure. These risks as well as the unmet demand for sterilization, are reason for the urgent need for development of non-surgical female sterilizat ion procedures.

CONCLUSIONS

1. The use of quinacrine pellets is a promising method because of its safe, acceptability and effectiveness for non-surgical female sterilization.
2. The use of quinacrine pellets should be extended to the general practitioner and midwifery personnel, seen from the ease of the method.
3. More data are needed on the long-term safety of the method and on other factors, including the insertion technique, the number of insertions, and whether antiprostaglandins increase efficacy.

ACKNOWLEDGEMENT

We would like to thank Dr. Elton Kessel, General Secretary of the International Federation for Family Health, Oregon, USA, for his contribution to this study in providing quinacrine and ibuproven pellets.

Also sincere thanks are due to Dr. Mochammad Anwar M Med Sc. Clinical Epidemiology Department, School of Medicine, Gadjah Mada University, Yogyakarta, Indonesia, for statistical data analysis.

The study was endorsed by the National Family Planning Coordination Board (BKKBN) of Wonosobo Regency, Central Java Province, Indonesia.

REFERENCES

1. Kessel E, Mumford SD. Potential demand for voluntary female sterilization in the 1980s: The compelling need for a non-surgical method. Fertil Steril 1982; 37: 725-33
2. Kessel E. Prospects for non-surgical female sterilization, Int J Gynaecol Obstet 1989; 29: I-4
3. Kessel E, Zipper J, Mumford SD. Introduction. The quinacrine pellet method for non-surgical female sterilization, a collection of background materials. Center for Research on Population and Security, Research Triangle Park, North Carolina, USA, 1990;1-11
4. Zipper J, Riven M, Cole LP, Brown E, Wheeler RG. Efficacy of two insertions of 100 minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization. Adv Contracept 1987; 3: 255-61
5. Zipper J, Stacchetti E, Medel M. Human Fertility control by transvaginal applications of quinacrine on the fallopian tube. Fertil Steril 1970; 21: 58 I-9
6. Zipper J, Stacchetti E, Medel M. Transvaginal chemical sterilization: clinical use of quinacrine plus potentiating adjuvants. Contraception 1975;12:11-21
7. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivers M. Quinacrine hydrochloride pellets: preliminary. data on a non-surgical method of female sterilization. Int J Gynecol Obstet 1980; 18: 275-9
8. Matthews DE, Farewell VT. Using and understanding medical statistics. Basel New York Karger 1985; 67-75
9. Klitsch M. Sterilization without surgery. Int Fam Plann Perspect 1982; 8: 101-4
10. Kang XP, Wan HZ, Wang P, Wang SX, Chow LP. Effectiveness of phenol-atabrine-paste (PAP) instillation for female sterilization. Int J Gynecol Obstet 1990; 33: 4 9 - 5 7
11. Bhatt R, Waszak CS. Four year follow-up insertion of quinacrine hydrochloride pellets as a means of non-surgical female sterilization. Fertil Steril 1985; 44: 303-6
12. Zipper J, Medel M, Goldsmith A, Edelman D, Pastene L, Rivera M. The Clinical efficacy of the repeated transcervical instilation of quinacrine for female sterilization. Int J Gynecol Obstet 1976; 14: 499-502
13. Laufe LE, Cole LP. Non-surgical female sterilization. Int J Gynecol Obstet 1980; 18: 333-9
14. Mehtaji S, Jadwani K, Goyal V. Chemical sterilization with quinacrine. In: Pachawu, eds. Fourth transaction of scientific papers of the India FRP Contributors conference, India Fertility Research Programme 1977; 167-70
15. Zipper J, Edelman D, Cole LP, Rivera M. Overview of clinical trials with quinacrine. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ,eds. Female transcervical sterilization. Philadelphia, Harper and Row, 1983; 172
16. Hieu DT, Tan TT, Tan DN, Nguyen PT, Vinh DQ. 3 1781 cases of non-surgical female sterilization with quinacrine pellets in Vietnam. Lancet 1993; 342: 213-7
17. Sokal DC, Kessel E, Zipper J, King T. Quinacrine: Clinical Experience. A Background Paper for the World Health Organization Consultation on the Development of New Technologies for Female Sterilization. WHO, Geneva, July 25-27, 1994

A RETROSPECTIVE STUDY OF QUINACRINE STERILIZATION IN VIETNAM

Conducted by

The Ministry of Health
Hanoi, Vietnam

Dr. Tran Thi Trung Chien
Vice Minister of Health

Dr. Do Trong Hieu
Director, MCH & FP Department
Principal Investigator

Family Health International
Research Triangle Park, NC USA

Dr. Theodore M. King
President

Dr. Cynthia Waszak
Senior Research Associate
Technical Monitor

For presentation at the Quinacrine Sterilization Dissemination Meeting in Hanoi, Vietnam, February 1995

Report prepared by

Dr. Do Trong Hieu
Dr. Dao Quang Vinh
Dr. Nguyen Kim Tong
Dr. Cynthia Waszak
Ms. Karen Katz
Dr. Robert Hanenberg
Dr. David Sokal

Acknowledgements

Funding for the study described in this report was provided by the Buffett Foundation and Family Health International. The views expressed in this report are those of the authors and do not necessarily reflect those of the Buffett Foundation or of Family Health International.

The authors wish to thank the following people for their assistance with this study and the production of this report:

(in alphabetical order)

At FHI
Barbara Bamett
Catrina Best
Ward Cates
Carol Connell
Rachael DiSantostefano
Rosalie Dominik
Lucinda Glover
Barbara Janowitz
JoAnn Lewis
James McMahan
Arlene McKay
Ellen Montgomery
Nancy Williamson

In Vietnam
Nguyen van Tuong
Pham Thi Minh Duc
Pham Trinh
Ton That Bach
Staffs of the MCH/FP Centers in
Nam Ha, Hai Hung and Thai Binh

Family Health International

Family Health International (FHI) is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning and prevention of STDs and AIDS.

TABLE OF CONTENTS

LIST OF TABLES

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

LIST OF FIGURES

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

A RETROSPECTIVE STUDY OF QUINACRINE STERILIZATION IN VIETNAM

INTRODUCTION

Quinacrine has been used on a limited basis as a method of nonsurgical female sterilization since the 1970s. In a number of developing countries quinacrine represents an effective, simple and inexpensive way to provide sterilization services to large segments of the population.

Quinacrine has been used in 13 countries by an estimated 80,000 women (Contraceptive Technology Update, 1994). In the 1970s and 1980s, clinical trials with quinacrine were conducted in several countries including Chile (Zipper et al., 1980), Egypt (El Kady et al., 1993), India (Bhatt & Waszak, 1985), Pakistan (Bashir, 1993), Malaysia (Arshat et al., 1987) and Indonesia (Agoestina & Kusuma, 1992). In 1989, the Ministry of Health in Vietnam conducted two preliminary clinical trials of quinacrine on 200 women in two provinces. With promising results in these two sites, quinacrine services were expanded to include 24 provinces, though only those providers who agreed to client follow-up to monitor method failure and complications were allowed to participate in this introduction. By the end of 1992 nearly 32,000 Vietnamese women had undergone a quinacrine sterilization. A paper describing the clinical experience of these women was published in ***The Lancet*** in 1993 (Hieu et al., 1993).

Most previous research on quinacrine users has involved relatively small data sets and has focused on issues of safety and efficacy. No published studies have described the acceptability of quinacrine to women or their satisfaction with the method and service delivery. The large number of participants in the Vietnam program presented an opportunity to gather information from a sizeable number of users and to fully examine women's perspectives on the method. With funding provided by the U.S.-based Buffett Foundation, Family Health International conducted a retrospective survey of quinacrine users in conjunction with the Vietnamese Ministry of Health.

Family Planning in Vietnam

The results of the 1988 National Demographic and Health Survey (DHS) suggested that Vietnamese women's contraceptive needs were not being met. At that time, nearly 60% of the women of reproductive age indicated that they did not want any more children. There are no published statistics on the numbers of women who do not want children and who are not using contraception. However, in the DHS report it was estimated that for the five years preceding the survey the total wanted fertility rate for women between the ages of 15 and 44 was 2.5 children while the actual total fertility rate of this group was 4.5 (National Committee for Population and Family Planning (NCPFP), 1990).

Contraceptive prevalence in 1988 was estimated at 53% (39% modem methods), and the IUD was found to be the method most commonly used and most widely available. However, reports suggest that there is dissatisfaction with the IUD and that failure rates are high (Allman et al., 1991). In addition, other reports indicate a reluctance on the part of providers to distribute pills because of a lack of confidence in women's ability to take them properly and a preference

for IUDs (UNFPA, 1993). Almost 45% of contraceptive users were supplied at the commune health centers and 37% at a district hospital. WhileIUDs are usually inserted at the commune health centers, pills and condoms are generally not available at the commune level and must be obtained from the district hospital (NCPFP, 1990) making access to resupply of these methods more difficult than for the IUD. Abortions and menstrual regulations(MRs) are very common, and apparently many women perceive pregnancy termination as a means of fertility control (Hieu et al., 1994). The government however, does not recognize abortion and MR as methods of family planning, but rather as a means of addressing method failures.

At the time the quinacrine trials were initiated in Vietnam, quinacrine sterilization was viewed as a possible way to fill the gap in demand for permanent contraceptive services. According to the quinacrine program's administrator, the demandfrom women themselves for this permanent method of contraception motivated a number of providers to request training and supplies so that the method could be introduced within their own district's family planning programs. Unfortunately, the demand outweighed the resources available; officials acknowledge that the training for insertors was done in an informal way and often was inadequate. Furthermore, supervision of insertors was minimal.

Policy required that women who received quinacrine were to be at least 30 years old and have at least two children; the youngest of these should have been at least three years old (though a third child could be younger than three years) prior to insertion. Variations in this policy allowed younger women with a greater number of children to be eligible for quinacrine sterilization. There were no incentives for quinacrine sterilization from the central level of the Ministry of Health, but a number of officials at the district and commune level did provide women undergoing quinacrine sterilization with food or money. This was viewed by officials as a means of compensating time or lost wages rather than as incentives. This kind of compensation was not limited to quinacrine sterilization and was given for other methods as well, such as the IUD and surgical sterilization.

History of Quinacrine Sterilization[1]

The use of quinacrine as a method of nonsurgical sterilization was first proposed by Dr. Jaime Zipper in Chile (Zipper et al., 1968). Different methods of administration were tried, but the procedure most commonly used now involves the transcervical insertion of seven pellets of quinacrine into the uterus using a modified IUD inserter. The pellets dissolve within about 30 minutes. Most commonly, two insertions given one month apart are performed during the proliferative phase of the menstrual cycle (days five to 12). As the pellets dissolve they produce necrosis of the endometrial lining of the uterus and inflammation of the intramural portion of the fallopian tubes. Although the endometrium regenerates itself, the fallopian tubes are permanently fibrosed and closed in a high percentage of women.

In the 1970's, quinacrine suspensions or slurries were studied; however, these studies were discontinued due to concerns about toxicity, cases of serious central nervous system (CNS)

'For a more complete review of the history of quinacrine sterilization, see Sokal, et al., in press.

excitation and three deaths which were reported to the U.S. Food and Drug Administration (USFDA). There have been no reports of similar severe complications following the use of quinacrine pellets and, in fact, major complications from the use of quinacrine pellets are rare (Sokal et al., in press). In The ***Lance?*** paper on the clinical experience of over 30,000 women in Vietnam, eight cases of major complications were reported (Hieu et al., **1993). This** is a rate of 0.03% or one in 4000 women. There were no cases of uterine perforation reported in Vietnam although three cases in other trials have been reported (Zipper et al., 1983; El Kady et al., 1993). No investigators have reported a case of acute CNS excitation with the use of quinacrine pellets, and no deaths have been reported immediately following quinacrine pellet insertions. However, following multiple (but not single) insertions of quinacrine pellets, abnormal endometrial lesions may occur (El Sahwi, 1992; Merchant et al., 1986). Also, occasional cases of uterine synechia (adhesions within the uterus), including one in Vietnam, and hematometra (an accumulation of blood in the uterus) have been reported (Zipper, 1987 & Hieu, 1993).

Although few major complications have been associated with quinacrine pellets, minor side effects or complaints have been documented in the various clinical trials. From 9 to 25% of women who have participated in various trials of this method have reported cramping or lower abdominal pain following the insertion, similar to that often experienced during an IUD insertion. Other transient complaints include backache, bleeding, headaches and dizziness. The leakage of quinacrine into the vagina causes vaginal pruritus (itching) in some women. Amenorrhea and irregular menstruation of several months' duration have been reported in 1 to 20% of women undergoing this procedure and may be more frequent in women who have had multiple insertions (Sokal, in press).

Currently available human data on the possible risk of cancerfrom the intrauterine use of quinacrine are not sufficient to draw any firm conclusions. A cluster of eight cancers of different types, including a uterine leiomyosarcoma, was detected during long-term follow-up of 572 women in Chile, but the results of a retrospective cohort study suggest that the cluster was probably a random occurrence, not causally related to quinacrine. This cohort is being followed up for at least an additional five years, through 1996 (Sokal et al., in press).

Despite the many trials that have been conducted, there is still no standard regimen for administering quinacrine, and studies have varied in terms of number of doses, insertion technique and the use of adjuvants (a supplemental drug given to increase effectiveness). In Vietnam, the standard protocol required two insertions, though at least one provider implemented a one-insertion protocol for older women. In some districts, treatment included the use of an intrauterine insertion of ampicillin as an adjuvant. The use of different adjuvants has been studied by Dr. Zipper, who found a low failure rate after three years (one pregnancy in 114 women), using a combination of quinacrine, betamethasone and copper sulfate (Zipper et al., 1993).

Because of the differences in these studies and the lack of controlled clinical trials, it is difficult to estimate the efficacy of quinacrine, although pregnancy rates are higher than those seen after surgical sterilization. Examples of pregnancy rates found in studies without the use of adjuvants include: 5% at one year after one insertion (Hieu et al., 1993), 3.7% at four years after three insertions (Bhatt & Waszak, 1985) and 8% at 10 years after three insertions (Mullick, manuscript in preparation). A recent study which used adjuvants and supplementary

contraception for the first few months after quinacrine insertion, however, found a pregnancy rate of 0.7% at 18 months following one insertion (Mullick, manuscript in preparation).

The available data suggest that the risk of ectopic pregnancies after quinacrine sterilization is less than among noncontraceptors. Data from women in Vietnam indicate that in the short term, the risk of ectopic pregnancy is similar to the risk in IUD users. More recent data from Chile show that ectopic pregnancies can occur up to 10 years after quinacrine sterilization (Sokal et al., manuscript in preparation).

The Quinacrine **Controversy**

The introduction of quinacrine in Vietnam on such a large scale has sparked a debate among the world's reproductive health providers, researchers, donors and women's health advocates. Quinacrine has been studied since the 1970s, and its short-term safety has been documented. In approximately 80,000 quinacrine sterilizations, no deaths have been reported immediately following quinacrine pellet insertion yet three to eight deaths would be expected based on the same number of surgical sterilizations in the developing world (Khairullah et al., 1992). This method is inexpensive and easy to administer, which means that health workers who are not physicians can be trained to perform the insertions. Overall, it has the potential to greatly increase access to sterilization services at a price (about US $1.00/insertion that is affordable to most family planning programs.

However, many fear that not enough is known about the safety and efficacy of the method. Quinacrine has not been approved by the USFDA for intrauterine use. Questions have been raised about toxicity and the possibility of a link to cancer. Furthermore, quinacrine has not been proven to be as effective at preventing pregnancy as surgical sterilization, and method failure has led to concerns about an increased risk of ectopic pregnancies. The possibility of coercion is an issue that has also been raised. In response to these concerns, the government of Vietnam suspended the quinacrine program in December 1993, pending additional information on the method. There were also concerns that women would worry about their quinacrine sterilizations when, as a result of the suspension and reports coming from international meetings on quinacrine, articles were published in Vietnamese newspapers and magazines, which claimed that quinacrine was unsafe and could cause cancer.

The Retrospective Study

The retrospective study described in this report was developed prior to the suspension of Vietnam's quinacrine program, but the results may answer some of the questions defining the controversy. The study was designed to evaluate the strengths and wealmesses of the quinacrine sterilization program from the users' perspectives, and thus, provides information about how the method has been experienced by the women themselves. Of primary interest are women's perspectives on how they made the decision to use the method, the method itself, the care received, the impact method use has made on their health and personal lives, and their satisfaction with quinacrine. In order to place the results of the survey of quinacrine users into the overall context of family planning in Vietnam, interviews were also conducted with a comparison group of IUD users. IUDs are the most widely used method of contraception in

Vietnam and would have been the most likely alternative used if quinacrine were not available. Surgical sterilization was relatively unavailable during the same time period; though it seems logical to compare quinacrine with another permanent method, not enough acceptors of surgical sterilization were available to permit comparison.

This study addresses many of the issues of interest to the medical community, such as side effects and complications, pregnancy, and informed consent as reported by users. When this study was being developed, it also had been hoped that some additional analyses could explore factors related to method failure using the logbook data on the original 30,000 women; unfortunately, the logbooks often lacked data on last menstrual period and previous contraceptive use, and this plan had to be changed.

Questions about toxicity, teratogenicity, potential carcinogenicity, and the best insertion technique for quinacrine sterilization are beyond the scope of this project, however, and cannot be answered in this report. These issues will only be resolved with further research, such as pre-clinical toxicology studies and additional well-controlled clinical trials (Phase I/II) to better assess the most effective regimen of quinacrine. Favorable results from the Phase I/II trials could be the basis for initiation of larger Phase III clinical studies (Sokal, personal correspondence 10/15/94).

METHODOLOGY

Objectives

The purpose of this study was to evaluate the quinacrine sterilization program from the users' perspectives. The specific objectives were to answer the following research questions, which were asked in the context of the family planning program in Vietnam at the time of the initiation of the quinacrine program:

1. What factors influenced acceptance of quinacrine sterilization?
2. What were women's experiences with quinacrine sterilization services?
3. What were women's experiences with the method itself in terms of side effects, complications and illness, method failure and its effects on their daily lives?
4. What were the levels of satisfaction and regret among quinacrine acceptors?

Study Design

The study was designed to retrospectively obtain information from women who had undergone the quinacrine sterilization procedure during its introduction in Vietnam from 1989 through 1993. A sample of IUD users was also interviewed to get comparative data on the outcomes of interest. The sample populations were drawn from three provinces: Nam Ha, Thai Binh and Hai Hung (Figure 1). These provinces are located near Hanoi and were selected because they were the first provinces in which quinacrine sterilization was provided and had the greatest numbers of quinacrine insertions from 1989 through 1993. The four districts in each of

these provinces with the greatest number of quinacrine acceptors were chosen for the study. The comparison sample of IUD users was drawn from the same 12 districts.

Selection of participants. The sampling frame was developed by using logbooks which recorded data on quinacrine insertions at all service delivery sites within the chosen districts. A database was created which included the logbook information on all 6535 quinacrine insertions in these districts between April 1989 and December 1993. A random sample of women to be interviewed was drawn from this database using a SAS program, which stratified the population according to province, district, and five-year age intervals. The probability of being selected was equal across strata.

The sample of IUD acceptors. in these districts was drawn from a sampling frame constructed using logbooks kept at the district hospitals. The logbooks listed women who had IUDs inserted at the hospital itself and at commune health facilities visited by mobile team personnel from the district hospitals. A total of 6446 IUD insertions, performed from January 1989 to December **1993** in the same 12 districts, comprised the sampling frame for randomly choosing IUD acceptors to be interviewed. The IUD sample was frequency matched to the quinacrine sample on the same three stratification variables in the quinacrine sample: province, district and age. As a result, these factors are not expected to be confounders in comparisons of characteristics at insertion, complications experienced, satisfaction or other variables between IUD and quinacrine acceptors.

Sample size. The sample size chosen for the quinacrine users was 1815. Assuming 25% non-response, a planned sample of 1800 subjects per group would yield sufficient power (greater than 80%) to detect a 5% difference in any dichotomous outcome variable. For outcomes that occur in less than 10% of the population, the sample size would allow sufficient power to detect absolute differences of 3% or less. A total of 1679 of 1815 quinacrine users selected and 1511 of 1685 IUDs users selected were interviewed. The IUD sample was smaller because some strata had fewer IUD users available in the sampling frame. The number responding in each group was greater than the number needed (1350 per group) to achieve the planned power.

The **Questionnaires**

Two questionnaires were developed for this study: one for the quinacrine acceptors and one for the IUD acceptors (Appendix A). The two questionnaires were similar, and both were designed to provide information on sociodemographic characteristics; contraceptive knowledge, attitudes and practices; the decision to accept a particular method; service delivery characteristics, such as care and counseling received; complications and side effects associated with the method, including pregnancies; other clinical and non-clinical outcomes associated with the method; and user satisfaction. In addition, for quinacrine acceptors, questions on regret were included. The questionnaires contained both pre-coded and open-ended questions.

The questionnaires were originally developed in English and were translated into Vietnamese by research staff at the Hanoi Medical College in Hanoi. Independent translators in the U.S. backtranslated the questionnaires to English. Questionnaires were pretested prior to and

during the interviewer training. Revisions after the backtranslations were made on the basis of these pretests.

Data Collection

Interviews for the quinacrine acceptors took place between March and April 1994 and for IUD acceptors between July and August 1994. The implementation of the survey was coordinated by the Hanoi Medical College. The study coordinator and interviewer supervisors were staff members at the College. They were responsible for managing logistics related to implementation as well as the verification of questionnaires. Personnel from the Maternal and Child Health/Family Planning Centers (MCH/FP) in each of the study provinces also facilitated the interviews and verified the addresses of the respondents.

Primary and secondary school teachers from each study district were recruited and trained to serve as interviewers. One supervisor was responsible for the interviewers in each district. Local teachers were chosen over health workers to reduce participants' reluctance to be critical about the method or the services they received and to increase their comfort during the interview.

Potential respondents were informed of their right not to participate in the study. Every respondent who agreed to participate signed an informed consent form, which explained her rights to terminate the interview at any time or to refuse to respond to any particular question she did not want to answer. Respondents were paid the equivalent of $1 .OO (US) to compensate for the time spent answering questions.

The interviewers were able to locate and interview 1679 women (93%) of the quinacrine sample and 15 11 women (90%) of the IUD sample. The reasons interviews were not conducted with the remainder of the samples are given in Appendix B. The data presented in Table 1 show that the groups of respondents for each method had similar geographic distributions. All quinacrine users who reported a pregnancy were reinterviewed by health workers from the provincial MCH/FP centers with a second questionnaire to verify the pregnancy and its outcome.

Data Processing and Analysis

Data were entered into a personal computer by the staff of the Hanoi Medical College and the Ministry of Health in Hanoi using the Epi Info data entry program (Dean et al., 1990). The Ministry of Health was responsible for coding open-ended questions. The data were cleaned in Hanoi with the assistance of an FHI staff member and were jointly analyzed by the MOH and FHI in Hanoi and North Carolina using Epi Info (Dean, A. et al., 1990), SPSS-PC (Norusis, 1990) and SUDAAN (Shah, B. et al., 1991).

Results presented in this report are descriptive comparisons of answers to interview questions given by quinacrine and IUD acceptors. Weights were calculated to account for both non-response among quinacrine and IUD acceptors selected and insufficient numbers of IUD users in the sampling frame for some strata. The Ns reported in the tables are the unweighted Ns, but the percentages, means and standard deviations reported in the text and tables are the weighted results. Likelihood chi square and t-tests of significance were performed to compare most outcomes as they were related to the two methods. SUDAAN was used to conduct these

comparisons. SUDAAN incorporates the correlation within a stratum (province-district-age) and the increased variability due to the weights when calculating error terms for these statistics.

Age at insertion and insertion dates were obtained from logbook data. There was no way to identify women who were supposed to get only one insertion from those who did not return for an intended second insertion. The number of quinacrine insertions were &fined as the number of insertions prior to a method failure if there was one. A few women obtained two or three insertions but may have had the last insertion after a method failure. For example, a woman who got pregnant after one insertion, but then had two more insertions after the pregnancy was terminated was counted in the one insertion group. Method failures were confirmed for the women in the quinacrine group on the basis of a second interview, conducted with the women who indicated during the first interview that they had gotten pregnant after the quinacrine insertion.

To calculate failure rates for quinacrine users and to examine the relationship between method failure for quinacrine users and several other factors, lifetable analyses were conducted using the SPSSPC "survival" program. Failure rates were compared on the following variables: age at insertion (< 35 years vs. 35 or more years); number of insertions (one insertion vs. more than one insertion (before pregnancy diagnosed)); age by number of insertions; prior IUD use (women who had been using an IUD immediately prior to quinacrine insertion vs. those who had not); prior IUD use by age; and district (as a proxy for service delivery differences). These subgroups were compared using Cox's proportional hazards regression procedure in SUDAAN. Failure rates for the IUD acceptors could not be calculated because the question about the date of the pregnancy was inadvertently omitted from the IUD questionnaire.

Although questions posed to IUD acceptors regarding IUD failures, results of the pregnancy, menstrual patterns, etc., were intended to refer to the reference IUD (i.e., the IUD inserted on the date given in the IUD logbooks), this was not always the case. For a few women, the reference IUD was removed and another was later reinserted. In these cases, answers given refer to the most recent IUD, not the reference IUD.

The analyses presented in this paper were designed to address the questions set forth in the objectives. Subsequent papers will address additional questions and hypotheses generated by the results presented in this report. Secondary data analysis appropriate for addressing any follow-up questions will be performed at that time. All data analyses were verified by FHI's Division of Biostatistics.

Human Subjects Review

Prior to implementation of the study, the protocol and questionnaires were reviewed and approved by Vietnam's Ministry of Health and FHI's Protection of Human Subjects Committee, an institutional review board conforming to U.S. Public Health Service Regulations.

RESULTS AND DISCUSSION

1. What factors influenced women's decisions to obtain a quinacrine sterilization?

Contraceptive decisions are made based on knowledge, experience, individual and family needs, personal preferences and availability. Specifically, factors which may influence a woman's decision to accept a contraceptive method include sociodemographic characteristics (age and parity); contraceptive history; information about the method; social influences; and perceptions of availability and advantages of a method. Concerns have been raised about the possibility of coercive measures taken to pressure women to accept quinacrine in Vietnam and its role was investigated.

So&demographic characteristics. At the time of insertion, the quinacrine respondents were on average 34.9 years old and the IUD users were 34.3 years old (Table 2) indicating that the frequency matching and weighting led to quinacrine and IUD samples which were quite comparable on age, as desired.

The quinacrine respondents had a mean of 3.6 children while the IUD group had 2.9 children ($p<.001$). These results are consistent with the expectation that controlling for age, women with more children would be more inclined to accept apermanent method.

Most women met the age and parity criteria for receiving quinacrine sterilization services, though the results indicate that some respondents were younger or had fewer or younger children than stated policy. Ten percent of the women were under age 30 at the time of insertion, and all had at least two children. Only six women had one child, and all of these women except one were over 30 years old.

Contraceptive history. The majority of women in both groups had experience with contraceptive methods before their quinacrine or IUD insertion (Table 3). Not surprisingly, the IUD was the predominant method used. Other modem methods, such as condoms, oral contraceptives and injectables, had been used by a much smaller percentage of women (less than 15% for any of these methods).

Over 40% of the quinacrine users and 15% of the IUD users had experienced at least one method failure ($p<.001$), and the IUD was the method which had failed for the majority of these respondents. The average number of abortions and MRs was greater for quinacrine users as compared to IUD acceptors ($p<.001$).

Sources **of information. The** first source of information for the majority of women in both groups were service providers (Table 4). A larger percentage of IUD acceptors than quinacrine acceptors knew someone who had used the method (88% vs. 60%, respectively; $p<.001$) —not surprising since quinacrine was a new method at the time many of them underwent the procedure.

Social influences. The data indicate that women felt themselves to be in control of the decision to obtain their chosen method of contraception though it is clear that women also discussed their methods with people within their personal realm —husbands, neighbors and

relatives. An overwhelming majority of women in each group identified themselves as the person who most influenced their decision to get the method (Table 4). The percentage of IUD users who discussed the method with their husbands was slightly higher than that of quinacrine acceptors. A higher percentage of quinacrine users (17%) than IUD users (8%) did not discuss the method with anyone else ($p<.001$). A higher percentage of IUD users (91%) compared to quinacrine users (77%) reported that their husbands approved of their method before insertion; 20% of the quinacrine acceptors compared to 8% of the IUD acceptors did not tell their husbands they had gotten the method $p<.001$) (Table 5).

Most quinacrine users were offered food or money as compensation for time lost or transportation costs or even as an incentive to accept the method (Table 6). This practice is not unique to the quinacrine program in Vietnam and has been used for IUD and surgical sterilization services (Hieu et al., in press). Eighty percent of the quinacrine acceptors and 54% of the IUD acceptors said that they received something when they obtained their method. Over 50% of the quinacrine acceptors received food (usually rice) compared to 16% of the IUD acceptors. Thirty-four percent of the IUD acceptors said they received medicine (usually ampicillin). Close to 100% of the women in both groups said that they felt no pressure to accept the method that they chose (Table 7).

Ninety-seven percent of the quinacrine acceptors said that they signed a consent form before obtaining the method, and 84% said that the risks and benefits were explained to them prior to getting the method (Table 8). Since no consent form is required for IUD use in Vietnam, these two questions were not asked of IUD users.

Perceptions. To provide insight into their perceptions of the advantages of the method chosen, respondents were asked to identify reasons why they preferred the method they had chosen over other methods (Table 9). The most commonly given reason for women using both methods was that their chosen method was "more convenient;" 65% of the quinacrine users and 73% of the IUD users responded in this way. "Convenience" as the primary reason for method choice is expected for methods that are not user- or coitus-dependent. Quinacrine users were more likely than IUD users to say they chose the method because it was reliable or because it did not require surgery; reliability as a motivating factor makes sense in light of the high percentage of quinacrine users who had experienced a method failure prior to their quinacrine insertion. A higher percentage of quinacrine users than IUD users citing "no surgery required" perhaps indicates that they had been considering quinacrine as an alternative to surgical sterilization. No one spontaneously cited incentives as one of the reasons for undergoing the sterilization.

In order to further understand reasons for their contraceptive choices, women were asked which method they would have chosen if their current method were not available (Figure**2).** Over half the quinacrine acceptors answered "IUDs," and 17% answered "tubectomy." Four percent of the quinacrine users said "no method" while in contrast, 29% of the IUD acceptors responded that they would be using no method if IUDs were not available ($p<.001$). Over 20% said they would be using a permanent method such as tubectomy or quinacrine, and 40% said they would be using user-dependent methods: condoms, abstinence or withdrawal. Although some quinacrine and IUD users indicated that they would have had a tubectomy, this may not

have been a realistic alternative since surgical sterilization services were not readily available at this time.

Women in Vietnam had little variety in contraceptive choice during this time period. IUDs were the most widely available method, yet many of the quinacrine users had already experienced an IUD failure, which would probably motivate them to try another method. Furthermore, the results as a whole provide no evidence of coercion and indicate that women who obtained a quinacrine sterilization were highly motivated to seek a permanent method of fertility control.

2. **What were women's experiences with quinacrine sterilization services?**

The results of this study indicate that service delivery for quinacrine sterilization in Vietnam was comparable to that received by IUD acceptors of comparable ages. Generally, access to these two services was good and waiting time, with a few exceptions, was reasonable. However, certain weaknesses were identified, primarily with respect to client counseling, provider training and supervision, and client follow-up. While quinacrine respondents were asked about their experiences at each insertion visit, only the experience at the first visit is reported since there was a high level of correlation in responses between the first and second insertions.

Access and waiting time. According to the respondents in this survey, access to quinacrine services was not more or less convenient than access to IUD services (Table 10). The majority of quinactine and IUD acceptors received their services at a commune health center (74% and 69%, respectively). For the remainder, quinacrine users were more likely to get their insertion at a district maternity hospital while the IUD users went to a district hospital or polyclinic.

About90% of both groups received services at a site which was three kilometers or less from their home. Service sites were reached by walking or by riding bicycles, the most common methods of transportation in Vietnam. Nearly all the women in both groups reported that it took one hour or less to reach the clinic. The total time spent at the clinic was two hours or less for about 90% of the women with a range of less than one hour to six hours; 6% of the quinacrine users and 3% of the IUD users felt that they had waited too long.

Counseling. Counseling was evaluated in terms of important information which should have been explained to the client about their chosen method, primarily with regard to side effects. A slightly higher percentage of quinacrine acceptors (88% vs. 82%; $p=.014$) reported that they receive family planning counseling before receiving their method although the IUD acceptors were more likely to have received written materials with information about their method (27% vs. 10%; $p<.001$). As reported by respondents, two-thirds of the IUD counseling and over three-fourths of the quinacrine counseling was done by physicians with the remainder by nurses or midwives. For nearly three-fourths of women in both groups, the person who provided counseling was the same person who performed the insertion (Table 11).

Quinacrine users were asked if they had been told about common side effects associated with quinacrine insertions such as lower abdominal pain, mild fever, headache, menstrual irregularity, and yellow vaginal discharge. While over two-thirds of the quinacrine users were

told about the possibility of yellow discharge, less than half were told about possible abdominal pain and one-third about bleeding. Only 18% of the respondents reported that they were told about the possibility of menstrual irregularities.

IUD users were asked whether they had been counseled about the primary side effects related to IUD use: irregular or excessive menstrual bleeding, discharge due to infection and pain. Two-thirds of the respondents reported that they were told about the possibility of excessive bleeding and over one-half were told about pain. Only one-fourth mentioned menstrual irregularity and one-third mentioned discharge.

Women were asked if there was any important information which they wish they had been told before receiving their method. Only six percent of the quinacrine acceptors said "yes;" most of these women wished they had more information on side effects, the effectiveness of quinacrine and the effect it could have on their health. There were seven women (.004%) who reported that they had not understood that quinacrine sterilization was a permanent method. The IUD acceptors who wanted more information (4%) had similar questions; most wanted more details on side effects, and information on the effect of the IUD on their health and on its effectiveness.

The majority of quinacrine users were not aware of the most common side effects associated with its use. While the IUD counseling was somewhat better, there was still a large percent of women who did not receive sufficient information. Since the persons who counseled the women were often the same ones who performed the procedures, it is likely that they did not have enough time to do adequate counseling. Yet, good counseling is crucial to providing quality services, and this is one area of service delivery which can be strengthened.

The procedure. While most women were supposed to receive two insertions of quinacrine, some women never returned for the second insertion. Furthermore, one investigator in Nam Ha implemented a one-insertion protocol. Nearly three-fourths of the respondents received two insertions one month apart, nearly one-fourth received only one insertion and a few received three insertions (Table 12). According to investigators, third insertions were sometimes performed in women who had a method failure or who requested a third insertion after hearing about the method failure of a friend or neighbor. For the purposes of this analysis, however, only those women who received three insertions without an intervening method failure were counted as having three insertions. According to the respondents, most of the health care providers inserting the quinacrine and theIUDs were physicians.

3. What were women's experiences with quinacrine sterilization as a method of family planning?

Method use affects more than just fertility outcomes and can have an impact on day-to-day experience. It is important to understand what beneficial and negative physical effects are associated with the method and how these effects relate to other activities and relationships. Physical aspects that were evaluated included side effects, illnesses, hospitalizations, other health outcomes, pregnancies and menstrual pattern changes. The "clinical" results reported here were based solely on women's reports. While women may have interpreted certain outcomes, such as illnesses and hospitalization, as being caused by method use, these are not clinical judgments.

These reports are important because they can affect women's evaluations of satisfaction and acceptability of the method.

Side effects. The side effects reported by quinacrine and IUD users were similar to those reported in other studies (El Kady et al., 1993; Agoestina et al., 1992; Arshat et al., 1987). While most quinacrine acceptors reported some type of complaints associated with their method, most of these complaints were for minor problems. Table 13 shows that 67% of quinacrine users said they experienced at least one side effect after their insertion(s). The most common complaints among the respondents were yellow discharge (42%) and pain (22%). Nineteen percent of the quinacrine acceptors went to a health facility because of a problem. Yellow discharge and pain were the main reasons for returning. Although fewer women experienced itching, menstrual irregularities and headache, the ones who did were more likely to return (45%, 41% and 34%, respectively; not shown in table) than women who reported other side effects.

Fewer IUD users (44%) reported side effects, and only 11% returned to a clinic because of a problem. The most common complaints were bleeding and pain although they occurred in only about 15% of the respondents. Bleeding and pain were also the most common reasons for returning to a health facility, although the women who complained of cervicitis or backache and abdominal pain had the highest percentages returning to the clinic (55% and 30%, respectively; not shown in table).

Overall, there was a significant difference between the percentages of quinacrine users and IUD users returning to a health facility because of complaints ($p<.001$). Furthermore, within individual categories of side effects, the quinacrine users were always more likely to return for pain or irregular menses (Figure 3). This might signify that the problems experienced were more severe, or it could indicate women's awareness of quinacrine's more experimental status. It may also reflect the need for more adequate counseling because they may not have not that they were experiencing common side effects.

Illnesses since insertion. Respondents were asked to report any illnesses they had since their insertion (Table 14). Fifty-seven percent of quinacrine users and 43% of IUD users reported having an illness, and the types of illnesses varied. The primary complaint among the quinacrine users who had an illness was fever (64%) and, to a much lesser extent, gynecological problems (11%). While fever was also the most common illness among IUD acceptors, it was only experienced by 32% of the group; an additional 25% reported problems due to arthritic disease.

Hospitalizations. The percentages of hospitalizations were roughly similar for both groups, and fewer than half of these were gynecological in nature. Less than 10% of women interviewed reported that they had been hospitalized (either on an inpatient or outpatient basis) since their insertion (9% of quinacrine acceptors and 6% of IUD acceptors; $p=.015$) (Table 14). Though this difference is statistically significant, the absolute difference is small and can perhaps be explained by the greater number of quinacrine users who were hospitalized as a result of a method failure. Of the women hospitalized, approximately 40% in each group reported a hospitalization that was due to a gynecological or obstetrical problem. In the quinacrine group, half of these hospitalizations were pregnancy-related reasons: MR or abortion, a tubal ligation and, in six cases, an ectopic pregnancy. Most of the remainder were hospitalized for menstrual

difficulties, such as menorrhagia and dysmenorrhea. The majority of the IUD hospitalizations in this category were menstrual-related or due to endometritis. Three women using an IUD reported they were hospitalized because of an ectopic pregnancy. The second most frequently cited reason for hospitalization in both groups was a fever or infectious disease.

One percent of respondents in each group reported that they had been diagnosed with a cervical or uterine tumor. The period of time from insertion to interviews did not permit any determination of either method's possible association with malignancy. Most of the quinacrine users had less than five years experience with the method and studies attempting to establish a causal relationship with cancer frequently discount the first four to five years of follow-up data. Assessing the risk of carcinogenesis in humans requires longer follow-up, usually on the or&r of 10-20 years.

Other health outcomes. Women were asked to describe other changes in their health since their quinacrine or IUD insertions (Table 15). Among the quinacrine users, the five most frequently cited changes included: lightheadedness (24%); weight loss (19%); weakness (16%); weight gain (14%); and headaches (10%). Among IUD users, the greatest percentages of women said they had experienced lightheadedness (20%); weight loss (16%) and headaches (14%).

Pregnancy among quinacrine users. Two-hundred and twenty-two quinacrine acceptors (13%) reported a pregnancy or a suspected pregnancy after one or more quinacrine insertions (Table 16). Among these, 78% had a menstrual regulation or an abortion. Since no pregnancy tests were done and no pathology reports were available, it is not possible to know with complete accuracy how many of the women who had MRs were truly pregnant. The percentages and rates estimated here are thus the upper bounds of the true pregnancy rates.

Pregnancies resulted in live births for 11% of the women reporting pregnancies. Nearly 3% of these women were still pregnant at the time of the interview. Ectopic pregnancies were reported by six women who had experienced method failures or 0.34% of the total sample.

Pregnancy rates were calculated using the lifetable method and compared on factors thought to be related to failure rates: number of insertions; age at insertion; district as a proxy or indicator variable for variations in service delivery characteristics; and IUD use immediately prior to quinacrine insertion. Because of the large difference between the pregnancy rates for one- vs. two or more insertions ($p<.001$), all rates were disaggregated by number of insertions. The one-year pregnancy rate for women with two insertions was .05 compared to .17 for women with only one insertion. At three years these rates were .11 for women with two or more insertions and .28 for women with one (Table 17).

When the rates were further disaggregated by age categories (< 35 years vs. 35 or older), it was found that there also was a significant main effect for age. Women in the older categories had lower failure rates than those in the younger categories for each insertion group ($p<.001$) (Table 18). Among all the women receiving two or more insertions, those under 35 had a 12-month pregnancy rate of .06 compared to .04 for those in the over 35 group. Among those in the one insertion group, the 12-month pregnancy rate was .25 for the younger women and .11 for the older ones (Table 18).

Noticeable differences were seen in the pregnancy rates calculated by district for women receiving two or more insertions but not for those receiving one insertion because of the low

numbers in many of the individual districts (Table 19). One year rates ranged from .01 in the Nghia Hung and Nam Thanh districts to .07 in Quynh Phu and Ly Nhan. Thi xa TB was dropped from this analysis because of the small number of women in this district.

The variability in effectiveness rates in different districts may indicate differences in the skills of the insertors. Hieu and his colleagues have acknowledged the difficulty of providing adequate training in insertion techniques and the need for a standardized technique emphasizing high fundal placement of the quinacrine pellets, taught under close supervision of skilled clinicians. Hieu reported that by the end of 1992, 1307 physicians and midwives were performing quinacrine insertions (Hieu et al., 1993). The fact that so many physicians and midwives began participating in the quinacrine services program made quality control difficult and may have lead to higher rates of method failure than was found in small scale clinical trials in other countries.

Parallels are found in the research literature on postpartum IUD insertion. In areas where the method was widely introduced to a large number of providers without adequate supervision of training the results showed very high expulsion rates (Chi, 1994). This situation has been reversed, however. Newer studies of postpartum IUD insertion demonstrate very low expulsion rates where training and insertor competence are emphasized (Mate et al., 1994).

Although only providers who agreed to client follow-up were supposed to be trained for the introductory trial, the majority of women who had only one insertion were supposed to have two insertions. In view of the much higher pregnancy rates for one as compared to two insertions, mechanisms to ensure follow-up for those who do not return for the second insertion need to be established. During counseling women need to be aware of the higher risk of failure associated with one insertion. Also, better counseling on side effects could minimize the number who fail to return after one insertion because of problems they experienced.

A further analysis was conducted to determine if IUD use prior to quinacrine insertion might increase a woman's risk of method failure (Table 20). Researchers questioned whether the possibility of blood in the uterus after IUD removal might interfere with the action of quinacrine. When pregnancy rates were compared for women who did and did not have an IUD removed prior to quinacrine insertion, no difference was found. When rates were calculated for age and prior IUD use, no interaction was found. A main effect for age continued (higher rates for younger women), but no effect for IUD use occurred within either of the two age categories (not shown in tables).

A complicating factor in determining pregnancy rates in this survey is that the calculations were based solely on women's reports of pregnancy. In a majority of these cases, however, the "pregnancy" ended in an MR but was never confirmed. Pregnancy tests are not done routinely (pregnancy test kits are not generally available in Vietnam). Furthermore, a woman in Vietnam will typically have an MR even if she is only a few days late with her period (Gorbach, 1994). While one cannot actually estimate the "true" pregnancy rate from these data, one small survey done by the Thai Binh MCH/FP Center found that up to one-third of the MRs performed in their study were unnecessary (Ministry of Health, Vietnam, unpublished report). Therefore, it is likely that the pregnancy rates estimated from these data are higher than the true pregnancy rates.

Ectopic pregnancies. There were six ectopic pregnancies, four in women with two insertions and two in women with one insertion. Both one-insertion ectopic

pregnancies were among women over 35 years old; two-insertion ectopic pregnancies occurred in three women less than 35 and one woman over 35. Two ectopic pregnancies occurred in the first year of quinacrine use; two occurred in the second and two occurred in the third year. The rates per 1000 woman years are 1.33 for women with two insertions and 2.83 for women with one insertion. The rate after one insertion is higher, but the difference is not statistically significant, p=0.3. Women with only one insertion might be at higher risk for ectopic pregnancy, but this study is too small to address that issue.

The overall rate of ectopic pregnancies per 1000 person years is 1.62. This rate is difficult to interpret for several reasons: (1) the study was not designed to look at rates of ectopic pregnancy; (2) the number of ectopic pregnancies is small, only 6 cases; and (3) the rates of ectopic pregnancy per 1000 women years in other populations of Vietnamese women, such as non-contracepting women, women using IUD's, or women who have been surgically sterilized, are not available for comparison.

Comparisons with data from other populations is difficult because of different standards of diagnosis, and because of the wide temporal, ethnic and geographic variations in rates of ectopic pregnancy. For example, the rate of ectopic pregnancy in the US has been steadily increasing over the past 20 years. In the US, rates of ectopic pregnancy are generally higher in non-white women and in older women.

Sivin (199 1) estimated that among cohabitating, non-contracepting women in the US during the period 1970-78, that the rate of ectopic pregnancy per 1000 women of all races was about 4 to 5 per 1000 woman years among women aged 25 to 44. In the same report, Sivin gives the following ectopic pregnancy rates per 1000 person years among women that were observed during studies of the two USFDA-approved IUDs currently available in the US: for the TCu380A, a rate of 0.2 per 1000 women years; and for the Progestasert, a rate of 5.4 to 7.5 per 1000 woman years. (The relatively high proportion of ectopic pregnancies seen with some types of IUDs probably are not caused by the IUD, but rather result because the IUD is very effective in preventing intrauterine pregnancies but not tubal pregnancies.) The rate of ectopic pregnancy observed in this study following one or two insertions of quinacrine pellets, therefore, is within the range seen with the use of FDA approved IUDs.

Pregnancy among IUD acceptors. Eighteen percent of IUD acceptors reported a failure of their most recent IUD use (Table 21). Over half of the most recent method failures terminated in abortions or menstrual regulations. Over one-third of them ended in live births. Most women who reported having an IUD method failure for their most recent IUD, were using a method of contraception at the time of the interview, and most of these women were using an IUD. After the IUD, tubectomy and quinacrine were the methods most often used, though by a much lower percentage. Pregnancy rates were not calculated for IUD acceptors because the date of pregnancy was not collected.

IUD removals. Seventy-six percent of the IUD acceptors had an IUD at the time of the interview (Table 22). IUDs had been removed in nearly a quarter of the sample due to method failures, medical reasons and personal reasons. Medical reasons for termination included: expulsion (19%); bleeding and pain (22%); method failure with no reinsertion (10%); and infection (7%). Nearly one-fourth of those who had a removal said they wanted another method, primarily sterilization, and 6% had their IUDs removed for a planned pregnancy.

Menstrual **pattern changes.** Women were asked questions about their menstrual and intermenstrual bleeding and pain. During the three months prior to the interview, current users in the IUD group reported heavier menstrual flow compared to the women in the quinacrine group (Figure 4). Consistent with this, when asked to compare menstrual flow before and after method insertion, quinacrine acceptors were more likely to say that flow was lighter afterwards, and current IUD users were more likely to say that it was heavier than before they received the method (Figure 5). This is also consistent with the results concerning the number of bleeding days. Quinacrine users were more likely to report a shorter than average number of days of bleeding compared to IUD users (3.9 for IUD users and 3.0 for quinacrine users) (Figure 6). Intermenstrual bleeding was reported in equally small percentages (<6%) for both quinacrine and IUD users (not shown). Dysmenorrhea (painful menstruation) was more likely to be experienced by IUD users than by quinacrine acceptors during the three months prior to the survey (Figure 7), though equal percentages of women in each group reported dysmenorrhea prior to quinacrine or IUD insertion (not shown).

The data are consistent with previous studies of both methods. Quinacrine acceptors reported less menstrual and intermenstrual bleeding and pain associated with their method use than did the IUD acceptors. The increase in bleeding and pain associated with IUD use is thoroughly documented (Rybo & Andersson, 1994). Clinical trials of quinacrine sterilization also have demonstrated a decrease in menstrual bleeding and pain (El Kady et al., 1993; Arshat et al., 1987). The comparison of menstrual pain and bleeding between quinacrine and IUD users may seem somewhat biased due to the increased pain and bleeding usually associated with IUDs. However, quinacrine's effect on the endometrium is probably similar to an endometrial curettage, which is often used to treat dysfunctional uterine bleeding in older women in developed countries (Mattingly & Thompson, 1985). Thus the perceived decrease in menstrual bleeding and pain is probably real. Prospective studies where baseline and follow-up data can be collected will be needed to further consider this matter.

Daily life experiences. The use of contraceptive methods has varying effects on the daily lives of their users. These effects result from both the physical experience of method use (side effects, menstrual pattern changes, complications, and method failures) and the social experience (support of partner, family and friends for limiting fertility and/or using a method and the ability to fulfill important roles despite physical side effects). The effects of certain methods on these daily life experiences have received little attention in the research literature until recently, and much needs to be learned about what the effects are and how to measure them. They are of extreme importance in the ways in which women make decisions about whether and which method they use. The questions asked in this survey have no precedent and should be considered a first step in thinking about what to ask. Resource constraints limited our ability to do more

qualitative work prior to questionnaire development, though the need for further work of this type is suggested by the current findings. Because questions like this are so infrequently asked of women in this context, the range of possible responses could not always be anticipated; thus, a mixture of open-ended questions and pre-coded multiple choice questions was used. The response categories used in the multiple choice questions were based on answers to pretest questions before the study was initiated.

Forty percent of women in both samples responded that they did feel differently about themselves after the use of their method. The wide variety of responses is listed in Table 23. Most of these answers were related to their physical well-being and included: health was worse or better, fatigue, headaches, backaches, dizziness, or weight gain or loss.

It is clear that some women felt that method use was related to feelings about themselves, their relationships with others and their ability to carry out various roles and duties. There were also apparent differences between the groups of women. Twenty-three percent of IUD users said that it had affected their ability to do farm work compared to 18% of quinacrine users (p=.004). Twice the percentage of IUD users (15%) than quinacrine users (7%) reported that it affected their ability to do housework. Though we have no way to know for sure, this is likely to be related to increased menstrual bleeding and pain.

Women were also asked whether their contraceptive method use affected various aspects of their lives such as their family relationships or their ability to carry out specific roles (Table 24). Only very small percentages of women in each group said that method use had affected their relationships with their husbands, other family members or ability to care for children. When women were asked how method use had affected these aspects of their lives, most of the small percentage of women described the negative ways it had done so: It had made it harder to do work or caused fatigue. Among quinacrine users, these explanatory answers, however, were from less than half of those who cited some effect.

In order to examine one further indication of the effect of method use on their lives, women were asked whether their sex lives were better, worse or the same as before the insertion (Table 25). More of the IUD acceptors reported "no change" as compare with quinacrine acceptors (93% vs. 83%, respectively), with more quinacrine users than IUD users reporting less satisfaction with their sex life (15% vs 7%; p<.001). This finding is supported by other responses in Tables 23 and 24.

At least one study of the relationship between surgical sterilization and sexuality has shown a decrease in excitement in sexual life, though a review of the literature in the same paper indicates that most other research has found improved or unchanged libido, coital frequency or sexual satisfaction (Kjer, **1990)** However, focus group discussions conducted for another study in Vietnam found that fears of surgical sterilization were partly due to expectations of a decrease in sex drive (Hieu et al., 1994). Therefore, the reports of a worse sex life could be a consequence of the expectation of lower sex drive after any type of sterilization. This issue deserves further analysis and study.

4. **What were the levels of satisfaction or regret among quinacrine sterilization acceptors?**

Answers to global questions about satisfaction (e.g., "How satisfied were you with...?") usually are unsatisfactory to researchers because respondents tend to provide favorable answers,

and there is little variance in the responses to these questions despite variations in other aspects of experience with the method. In an attempt to avoid this, a number of questions were asked to tap several dimensions of satisfaction, such as whether the method was a good choice, fears about pregnancy, and the best and worst things about the method. Satisfaction was also evaluated in terms of support or disapproval of family member and friends.

Satisfaction. Eighty-six percent of the quinacrine acceptors and 80% of the IUD acceptors interviewed felt their method was a good choice of contraception for them (Table 26). Nine percent of the quinacrine acceptors and 5% of the IUD acceptors, however, felt that it was not a good method because they had gotten pregnant. Three percent of the respondents in the quinacrine group cited health problems as the reason it was not a good method compared to 6% in the IUD group. Less than one percent (0.02%) said they had wanted more children.

Since the purpose of contraception is to prevent pregnancy, it was expected that method use would alleviate fear of pregnancy. In response to questions about fear of pregnancy, 61% of the quinacrine group and 57% in the IUD group said they never felt worried about getting pregnant, while lower percentages of women in the two groups (8% and 7%, respectively) worried frequently about this (Table 27). Though this was more than half the women in each group, the percentage who say they never worry about pregnancy was far less than expected.

To see how having a method failure affected the responses to questions about fear of pregnancy and whether or not the method was a good choice, results to these questions were examined separately for women with and without method failure (Table 28). Women in both method groups were much more likely to say that the method had been a good choice for them if they had not had a failure than if they had ($p < .001$ for each method group comparison). Women who were using either method and who experienced a failure were more likely to sometimes or frequently worry about a pregnancy than were women who had never had a failure ($p < .001$ for each method group comparison).

Women were asked in open-ended questions to identify the best and worst things about the method (Table 29). The most common responses from quinacrine users with regard to the best thing was that it "prevents pregnancy/reduces the need for abortion" **(23%);** it is a "permanent method" (23%); it is "safe" (14%); it "improves health" (11%); and it is "convenient" (9%).

A larger percentage of IUD acceptors said that the best thing was that it "prevents pregnancy" (59%), while the next most common responses were "convenience" (12%) and "improves health" (8%). The majority of both the quinacrine and IUD acceptors either said that they could not think of anything bad about the method or gave no response to the question on the worst thing about their method. Among those who could identify the worst thing, the responses from the two groups were similar, with respondents most often citing worsening health, method failures and side effects.

Quinacrine and IUD acceptors reported support from friends and family for their method use. Eighty-eight percent of quinacrine users and 93% of IUD users had been told by friends or family of their approval for their method use. Seventy-six percent of quinacrine users and 93% of IUD users had heard no disapproval spoken by friends or family members (Table 30). The higher percentage of disapproval expressed to quinacrine users compared to IUD users can

perhaps be attributed to less familiarity with quinacrine because of its more recent introduction as a contraceptive method in Vietnam.

Women in the study were asked whether they had ever recommended the method to anyone else. Eighty-eight percent of the quinacrine and IUD acceptors had recommended it to someone else (Table 31). Those who had not done so and who responded to the question of why they had not said that they either wanted to keep their use a secret or had not had an occasion to do so. Only 1% of the IUD group cited dissatisfaction (side effects) as a reason for not recommending the method.

Regret

Regret is a concern related to methods that cannot be reversed.' High levels of regret may indicate inappropriate pressure or inadequate counseling and screening of clients. Regret was measured in this study by asking if and why quinacrine users felt regret and whether they wished they could change their mind about their sterilization. Conversely, lack of regret was measured by asking if a woman wishes she could have had the procedure earlier. Published studies on surgical sterilization have reported rates of regret from 1% to 25%. Regret cannot be completely eliminated because it often is a response to changes in women's lives, though it can be reduced through effective counseling and screening of sterilization candidates. (Bartfai and Kaali, 1989; Bertrand, et al., 1991; Islam and Rahman, 1993; Kjer, 1990a; Grubb et al., 1985; Hapugalle, Janowitz et al., 1989; McGonigle and Huggins, 1990; Pitaktepsombati and Janowitz, 1991; and Wilcox, et al., 1991).

Only 2% of quinacrine users said that they regretted having done something that would prevent them from having more children (Table 32). However, further examination of their reasons for regret showed that less than half of these women specifically said that they wanted more children. The most common other reason stated was "method failure," which should be considered a measure of dissatisfaction rather than of regret. The low percentage of women reporting regret because they want more children can be interpreted as providing evidence that women were appropriately informed about the permanent nature of this procedure and not pressured or coerced. This is consistent with other findings which were already presented. None of the seven women who reported that they did not understand that quinacrine was a permanent method before acceptance expressed regret when this question was asked (not shown). **As expected,** when this measure of regret was stratified by method failure, there was little relationship between failure and regret (Table 32).

When women were asked if they could change their minds about getting the method, however, a greater percentage -- 11 —said "yes." The reason most women gave was method failure (Table 32). Forty-one percent of those who had a method failure compared to 5% of those who had not said that they wished they could change their minds($p<.001$).

Sixty-two percent of the quinacrine acceptors said that they wished they had the procedure done earlier indicating a need felt by women for greater availability of permanent methods ($p<.001$) (Table 32). Consistent with the above results, the percentage of women wishing they had had the procedure earlier was nearly twice as high (66%) for those with no failure as for those with a method failure (35%).

Nearly 6% of the women said that their husbands had expressed regret over the sterilization; on the other hand, 70% of the women, said that their husbands had told them they

were glad about the sterilization (Table 33). Of the women who reported regret, 45% had husbands who had expressed regret about the quinacrine sterilization (not shown).

Fear **of** cancer

When respondents were asked if they had heard anything in the news about quinacrine, 87% said they had not, 8% said they had heard that the method was effective and 1% had heard that it had no side effects (Table 34). Only 1% had heard that it caused cancer and an additional 1% heard it was unsafe. A fear of cancer or a more generalized concern for safety was found by a similarly small percentage of women in responses to open-ended questions such as "reasons why the method was not a good choice" and "worst things about the method." For the first question, 1% said they felt the method was not safe, and less than 1% mentioned a fear of cancer specifically (Table 26). To the second question, 3% answered that fear of disease was the worst thing, and another 1% answered that feeling that the method was not safe was the worst thing (Table 29).

5. Data **limitations**

A limitation to any retrospective survey is that the quality of the data collected is dependent on the respondents' memories. In this study, women were interviewed who had their insertions up to five years before the survey. Conversely, there were also women interviewed who had less than six months experience with their method, which may not be enough time to adequately assess satisfaction and regret. However, the outcomes of interest are perceptions related to use and these are necessarily influenced by the passage of time. While they may not represent "objective" truth, these perceptions are the truth that women use to make judgments about future use and the information that they pass along to other women. The possibility exists that the user of a newer method of contraception might remember the negative aspects of the method because of its more "experimental" status; on the other hand, quinacrine users may have dismissed some of the side effects to justify their use of a permanent method.

Another concern is a "courtesy bias" influencing respondents to give more favorable responses that they think the interviewer wants to hear. This bias may have been especially strong because respondents were interviewed in their homes, which often are crowded. While this bias may be stronger in Asia than in other parts of the world, it is found within all research. Also, we do not expect that this demand bias would affect the responses of the quinacrine group differently than those of the IUD group. Also, investigators were concerned that perceptions of quinacrine users might be negatively biased by the media coverage of the quinacrine controversy just months prior to the survey, but there is no evidence that this occurred.

Unfortunately, due to logistical issues, the surveys of quinacrine and IUD acceptors were conducted sequentially rather than simultaneously. This could have led to some differences in the ways the questions were posed by the interviewers, as well as different responses concerning recent events. For example, the high level of reported fevers among the quinacrine acceptors might reflect the occurrence of an epidemic of infectious disease (e.g. influenza) in the months immediately preceding the quinacrine interviews.

Another possible limitation of the data results from the use of the district hospital logbooks for the IUD sampling frame. In Hai Hung province, most of the names of the women

in these logbooks actually had their IUDs inserted in the hospital, whereas in the other two provinces, these logbooks contained the names of women who hadIUDs inserted by teams of doctors in mobile units who went to the commune health centers to deliver services. It also was necessary to drop 10% of the women from the sampling frame due to insufficient addresses. It is possible that women with difficult to find addresses may differ from other women in some way.

CONCLUSIONS AND RECOMMENDATIONS

A The results demonstrate that, overall, the respondents in this study were satisfied with their use of quinacrine and did not regret their decision to get sterilized. Furthermore, the decision to use quinacrine was typically made by the woman herself, usually in consultation with her husband. The results do not provide any evidence of undue pressure or coercion. However, the findings do point to certainweaknesses in the service delivery structure, which affected the quality of care the women received. Finally, questions remain about the optimal means of administering quinacrine. While this uncertainty is not specific to Vietnam, it is an issue which, nonetheless, must be resolved.

The issues related to quinacrine services are both clinical and programmatic. From a clinical standpoint, this study validates other research findings, which have found quinacrine to be a safe method of contraception in the short-term. It does not appear to be as effective as surgical sterilization, but effectiveness can be improved by (1) requiring a two-insertion procedure and (2) limiting use to women 35 years or older.

Controlled clinical trials need to be conducted in order to determine the most effective means of quinacrine administration. While the data from Vietnam demonstrated clinically significantly lower pregnancy rates with two insertions, other data have suggested that one or two insertions, with the use of an adjuvant such as ibuprofen, can result in low pregnancy rates. Also, particular insertion techniques may improve effectiveness.

The evaluation of long-term safety and effectiveness was not within the scope of this study and can only be assessed through longitudinal data collection. Family Health International plans to continue to follow this cohort of women to provide the information necessary to address concerns such as ectopic pregnancy, cancers, and hospitalizations and illnesses that may have been related to quinacrine.

Programmatically, several elements of service delivery need to be improved for both quinacrine and IUD services to improve quality of care: counseling (information to users), provider training and supervision (technical competence), and client follow-up (continuity of care). While most quinacrine users received family planning counseling, the majority were not aware of the most common side effects associated with quinacrine. Improved counseling and information about expected side effects could improve levels of satisfaction with the method and may also decrease the number of women who fail to return for their second insertion. Counseling would also alleviate fears that may result from rumors or misconceptions. Counselor training workshops should be conducted to give providers comprehensive family planning information and improve their communication skills.

The clinical training for quinacrine service providers was often inadequate, and follow-up and supervision of providers was minimal. These results emphasize that future training would have to be more rigorous and providers would have to be monitored to ensure they are using the proper techniques. The lack of adequate training may have resulted in higher pregnancy rates and subsequently led to dissatisfaction in those women who experienced a method failure. Follow-up of clients to ensure that they return for their second insertion also needs to be an integral part of quinacrine services. This is especially important in view of the higher pregnancy rates seen with one insertion. Also, women should be monitored more closely because quinacrine is a relatively new method of contraception.

The retrospective survey is a first step in a developing area of research: the effect of family planning on women's lives. Further multivariate analyses will be done to determine the relationships between satisfaction and regret regarding women's experiences with the method and their personal characteristics. Method acceptance and satisfaction among those who wish to limit their fertility might be improved by additional qualitative research on the use of quinacrine. This could provide information relevant to how women make decisions about method use and could describe more clearly how the use of this method affects their day-today lives. Research on women's perspectives also can provide insights into how quality of care could be improved.

Should the quinacrine sterilization program be restarted in Vietnam? To answer this question, it is important to consider the place of quinacrine within the context of a changing family planning program. While the introduction of quinacrine was a logical response to existing conditions in Vietnam at that time, current circumstances necessitate a rethinking of the program.

As the presence of international donors increases in **Vietnam,** more funding has become available, which should assist in the training of family planning providers as well as in the provision of other family planning methods. In practical terms, this means that method choice is expanding as oral contraceptives, injectables and surgical sterilization become more widely available. Also, **clinical traigin** and newer IUDs can make this method a more attractive choice. Furthermore, the TCu380 IUDs are now recommended for up to 10 years of use and may be a reasonable alternative, especially for many women who are under 35 years of age. Women who experience unacceptable pain and bleeding associated with the IUD, however, may want to have the option of quinacrine sterilization available. Further research into the acceptability of IUD use, especially with newer longer lasting IUDs, should be conducted to make this determination.

While quinacrine seems promising as a contraceptive choice, this paper has noted many issues which still remain, including efficacy, safety and appropriate service delivery mechanisms.

BIBLIOGRAPHY

Agoestina T and I Kusuma (1992). Clinical evaluation of quinacrine pellets for chemical female sterilization. Advances in 8, 14 1-15 1.

Allman J, Nhan VQ, Thang NM, San PB & VD Man (1991). Fertility and family planning in Vietnam. Studies in Family Planning, 22,5 308-317.

Arshat H, Suan AE, & KS Kim (1987). Nonsurgical female sterilization with quinacrine pellets: Malaysian experience. Malaysian Journal of Reproductive Health, 5(2) 61-69.

Bartfai G & S Kaali (1989). Late sequalae following laparoscopic female sterilization. International Journal of Fertility, 34, 67 - 70.

Bashir A (1993). Quinacrine: nonsurgical female sterilization. Advances in Contraceptive Delivery Systems, 9, 37 -42.

Berer M (1994). The quinacrine controversy: one year on. Reproductive Health Matters, 4, 99-107.

Bertrand J, Kashwantale C, Balowa D, Baughman N & C Chirwisa **(1991)** Social and psychological aspects of tubal ligation in Zaire: a follow-up study of acceptors. International Family Planning Perspectives 17, 100 - 107.

Bhatt R & C Waszak (1985). Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. Fertility and Sterility, 44, 303-306.

Chi I-cheng (1994). Postpartum IUD insertion: timing, route, laceration, and uterine perforation in Proceedings from the Fourth International Conference on IUDs Bardin **W** and Mishell D (eds) Boston: Butterworth-Heinemann, pp. 219-228.

Contraceptive Technology Update, April 1994.

Dean AG, Dean JA, Burton AH, Dicker RC. (1990). Epi Info, Version 5: a word processing, database, and statistics program for epidemiology on microcomputers. USD, Incorporated, Stone Mountain, GA.

El-Kady A, Nagib H & E Kessel(1993). Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization, Fertility and Sterility, 59, 301-304.

El-Sawhi S (1992). Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for nonsurgical sterilization. Advances in Contraception, 2, 79-90.

Goodkind D (1994). Abortion in Vietnam: measurements, puzzles, and concerns. Studies in Family Planning, 25, 342-352.

Gorbach P. Personal communication. November 8, 1994.

Grubb G, Peterson H, Layde P & G Rubin (1985). Regret after the decision to have a tubal sterilization. Fertility and Sterility, 44, 248-253.

Guzman-Serani R, Bernales A & L Cole (1984). Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. Contracentive Deliver-v Svstems, 5, 131-135.

Hapugalle D, Janowitz B, Weir S, Covington D, Wilkens L & C Aluvihare (1989). Sterilization regret in Sri Lanka: a retrospective study. International Family Planning Perspectives, 15, 22-28.

Hieu D, Van H, Donaldson P & Q Nga. The pattern of IUD use in Vietnam. International Family Planning Perspectives, in press.

Hieu D, Stoeckel J & NV Tien (1994). Pregnancy termination and contraceptive failure in Vietnam. Asia-Pacific Ponulation Journal, 8,4 3-18.

Hieu D, Tan T, Tan D, Nguyet P, Than P & D Vinh (1993). Thirty-one thousand seven hundred eightyone cases of nonsurgical female sterilization with quinacrine pellets in Vietnam, The Lancet 342, 213 - 217.

Islam M & M Rahman (1993). Client satisfaction with sterilization procedure in Bangladesh. Asia-Pacific Ponulation Journal, 8, 39 - 52.

Khairullah Z, Huber D & B Gonzales (1992). Declining mortality in international sterilization services. Advances in Contracentive Delivery Systems, 8, 151 - 159.

Kjer JJ (1990a). Regret of laparoscopic sterilization. European Journal of Obstetrics and Gynecology and Reproductive Biology, 35, 205-210.

Kjer JJ (1990b). Sexual adjustment to tubal sterilization. European Journal of Obstetrics and Gynecology and Reproductive Biology, 35, 211 -214.

Kjer J & L Knudsen (1989). Ectopic pregnancy subsequent to laparoscopic sterilization. American Journal of Obstetrics and Gynecology, **160**,1202 - 1204.

Lee E and M Desu (1972). A computer program for comparing ***k*** samples with right-censored data. Computer Programs in Biomedicine, 2,3 15-321.

Mate EM, Ndegwa J, Waszak C, Katz K, Hubacher D & K Jesencky (1994). Evaluation of introductory program of postpartum IUCD insertions in Nyeri, Kenya. Family Health International. Research Triangle Park, NC.

Mattingly RF & Thompson JD (1985). Operative Gynecology. JB Lippincott Company, Philadelphia. Sixth edition; 499-501.

McGonigle K & G Huggins (1990). Tubal sterilization: epidemiology of regret. Contemporary Ob/Gyn, October, 15 - 24.

Merchant R, Doctor V, Thaku S, Sinha M, Jhaveri C, Kessel E & S Mumford (1986). Clinicopathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets, Advances in Contraception, 2, 79 -90.

Miller W, Shain R & D Pasta (1990). The nature and dynamics of post-sterilization regret in married women. Journal of Applied Social Psychology, 20, 506 - 530.

Ministry of Health, Vietnam. Calculation of unnecessary MRs. unpublished report.

Mullick, B et al. Manuscript in preparation.

Mumford S & E Kessel (1992). Sterilization needs in the 1990s: the case for quinacrine nonsurgical female sterilization. American Journal of Obstetrics and Gynecology, 167, 1203-1207.

National Committee for Population and Family Planning (1990). Vietnam: Demographic and Health Survey 1988. Hanoi.

Norusis, M (1990). SPSSPC+ Advanced Statistics 4.0 for the IBM PC/XT/AT and PS/2. Chicago: SPSS, Inc.

Pitaktepsombati P & B Janowitz (1991). Sterilization acceptance and regret in Thailand. Contraception, 44, 623-637.

Rybo G & K Andersson (1994). IUD use and endometrial bleedings in Proceedings from the Fourth International Conference on IUDs Bardin **W** and Mishell D (eds) Boston: Butterworth-Heinemann, 210-218.

Shah, B, Bamwell, B, Hunt, P & L LaVange (1991). SUDAAN User's Manual, Release 6.20. Research Triangle Institute, NC: Research Triangle Institute.

Sivin I (1994). Extrauterine pregnancies and intrauterine devices reassessed in Proceedings from the Fourth International Conference on IUDs Bardin W and Mishell D (eds) Boston: Butterwork-Heinemann, 195 - 209.

Sokal D, Zipper J & T King. Transcervical quinacrine sterilization: clinical experience. International Journal of Gynecology and Obstetrics. In press.

Sokal D. Personal correspondence. October 15, 1994.
Sokal D, Zipper J, Guzman-Serani R & T Aldrich (1991). Cancer risk among women sterilized with quinacrine hydrochloride, 1977 - 199 1. Submitted for publication.

Sokal D, Cole L & L Laufe. Phase I, 24-hour prehysterectomy study of the transcervical administration of quinacrine pellets. Manuscript in preparation.

UNFPA (1993). A study of the factors underlying the low prevalence of oral contraceptive pill use in Vietnam. UNFPA Project VIE/92/PO5.

Wilcox L, Chu S, Eaker E, Zeger S & H Peterson (1991). Risk factors for regret after tubal sterilization: 5 years of follow-up in a prospective study. Fertility and Sterility, 55,927 - 933.

Zipper J, Rivera M, Dabancers A (1993). Sterilisation feminine non chirurgicale: utilisation de pellets endo-uterins de quinacrine et betamethasone: revision du sujet: basis experimentales-pharmacologie toxicologie efficacite. Revue Francais de Obstetrics and Gynecology, 88,1 185-1190.

Zipper J, Rivera M, Cole LP, Brown E & RG Wheeler (1987). Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization. Advances in Contraception, 3, 255-261.

Zipper J, Edelman D, Cole L & M Rivera (1983). Overview of clinical trials with quinacrine. Santiago, Chile. Research Triangle Park, NC. Philadelphia: Harper and Row, p. 172.

Zipper J, Cole L, Goldsmith A, Wheeler R & M Rivera (1980). Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. International Journal of Obstetrics and Gynecology, 18,275 - 279.

Zipper JA, Medel M, & R Prager (1968). Alterations in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. American Journal of Obstetrics and Gynecology, 101, 97 I-978.

TABLES

Table 1. Province and district of respondents

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Province/ District		
Nam Ha	51	51
Binh Luc	10	10
Ly Nhan	10	10
Hai Hau	24	24
Nghia Hung	6	6
Hai Hung	26	26
My Van	10	10
Cam Binh	7	7
Nam **Thanh**	5	5
Chau Giang	4	4
Thai Binh	23	23
Dong Hung	10	**10**
Quynh Phu	7	7
Kien Xuong	4	4
Thi xa TB	2	2

*Totals may not equal **100%** due to rounding

NOTE: For all tables, **N** = unweighted sample size

Table 2. Sociodemographic characteristics

	Quinacrine acceptors (N= 1679) %*	IUD acceptors (N-1511) %*
Age at insertion		
25-29	10	10
30-34	35	35
35-39	39	39
40-44	15	15
45-49	<1	0
Age		
-mean	34.9 years	34.3 years
-standard error	0.692	0.720
Currently married	**99.5**	**98.5**
Living children (at interview)		
o-1	<1	7
2-3	53	67
4-9	47	26
Missing	<1	
Number of living children**		
-mean	3.6	2.9
-standard deviation	0.074	0.078
Age youngest child (at interview)		
O-3	15	28
4-10	65	56
11 or older	19	16
Missing	<1	<1

*Totals may not equal 100% due to rounding
**p<.001

Table 3. Contraceptive history

	Quinacrine acceptors (N= 1679) %*	IUD acceptors (N=1511) %*
]Previous use of birth control**		
None	6	2
IUD	88	70
Pill	12	4
Condom	10	13
Injectable	8	1
Withdrawal	12	12
Abstinence	9	10
Quinacrine	--	2
Tubal ligation	<1	1
Other	--	1
Method failure+		
No	57	85
Yes, once	26	12
Yes, more than once	17	4
Missing	<1	
Specified **failures*****	(N=950)	(N=245)
IUD	85	59
Withdrawal	8	14
Abstinence	4	6
Condoms	1	12
Pills	1	4
Quinacrine	<1	5
Abortions/MRs+		
0	39	63
1	21	22
2 or more	32	15
Missing	7	
Mean number **abortions/MRs**	1.3	0.6

*Totals may not equal 100% due to rounding
**More than one response is possible
***Denominators reflect the number of failures. Up to two failures per woman are possible; 711 quinacrine users reported 950 failures and 230 IUD users reported 245 failures.
+p<.001

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Table 4. Sources of information and influence about method

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Where first heard about the method		
Health care provider	**60**	51
Friend/neighbor/relative	**25**	18
Women's Union	12	24
Mass communication	1	**<1**
Youth Union	**<1**	**<1**
Communal leader	**<1**	1
Can't remember	1	5
Other	**<1**	**<1**
Knew anyone **who used method before insertion****	**60**	88
With whom discussed method before insertion*		
Husband	76	87
No one**	17	8
Friends	15	21
Relatives	12	16
Health care provider	5	6
Women's Union	**<1**	–
Other	**<1**	**<1**
Greatest influence to woman to get method?		
Herself	91	**90**
Husband	4	7
Health care provider	3	2
Women's Union	1	**<1**
Friend	**<1**	**<1**
Relative	**<1**	**<1**
Other, unspecified	**<1**	**<1**

* Multiple responses possible for each woman.
**p<.001

Table 5. Husband's approval

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Husband approved before insertion		
No	3	1
Yes	77	91
Didn't discuss*	20	8
Not applicable	<1	<1

*p<.001

Table 6. Compensation/incentives

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
What woman received when accepting method		
Nothing	20	46
Food	53	16
Money	17	1
Both	4	<1
Medicine	5	34
Other	<1	<1
Doesn't remember	<1	1

Table 7. Pressure to accept method

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Who pressured woman to get method?		
No one	99	99
Health care provider	<1	0
Family planning worker	<1	0
Husband	0	<1
Other, unspecified	<1	0

Table 8. Informed consent*	
	Quinacrine acceptors (N= 1679) %
Were risks and benefits of method explained before insertion?	
No	16
Yes	84
Don't know	**<1**
Did you sign a consent form before insertion?	
No	**3**
Yes	**97**
Don't know	**<1**

* Informed consent is not required of IUD acceptors.

Table 9. Reasons for method choice*

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Reasons for getting method		
Convenience	**60**	**64**
Reliability	56	**32**
Long-term protection	**30**	12
Fewer side effects	**16**	11
Other methods difficult to get	**5**	15
Don't have to remember anything	**1**	6
Don't know	1	3
Not permanent	NA**	9
Reasons preferred to other methods		
More convenient	**65**	73
More reliable	**63**	42
No surgery required	**24**	**10**
More available	**6**	22
Better incentive	**0**	**<1**
Don't know	**2**	7

* More than one response may be given by each woman.
** NA=Not applicable

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Table 10. Access to services and waiting time

	Quinacrine acceptors (N= 1679) %*	IUD acceptors (N=1511) %*
Insertion performed at		
Communal health center	74	69
District maternity	18	<1
District hospital	7	10
Polyclinic	<1	20
Other	<1	<1
Number kilometers from home		
3 km or less	89	92
4-10 km	10	8
More than 10km	<1	<1
Time to get to clinic		
1 hour or less	98	99
2-3 hours	2	1
Transport to clinic		
Walk	54	49
Bicycle	46	50
Other	1	1
Total time at clinic		
2 hours or less	89	94
3+ hours	11	6
Waiting time too long	6	3

*Totals may not equal 100% due to rounding

Table 11. Counseling

	Quinacrine acceptors (N-1679) %	IUD acceptors (N=1511) %
Received counseling before procedure*	88	82
Received written **materials****	10	27
Who counseled	(N=1468)	(N=1235)
Nurse	10	6
Midwife	11	25
Physician	77	66
Don't remember	2	2
Missing	<1	
Same person as **insertor**		
Same	74	77
Different	24	22
Don't know	1	1
Missing	<1	
Told about possible problems***		
No/no answer	17	10
Pain	44	53
Bleeding	33	68
Discharge	70	34
Pelvic heaviness	11	
Menstrual irregularity	18	24
Headache	1	3
Fever	3	<1
Itching	8	—
Other	2	1
Don't remember	2	—
Told where to get help	83	90
Important information wish you had been told	6	4
What information		
Side effects	(N=107)	(N-56)
Can get pregnant again	63	76
Method is permanent	20	6
Bad influence to health	7	--
other	5	15
	5	2

*p=.014
**p<.001
***More than one answer possible.

Table 12. Insertion procedure

	Quinacrine acceptors (N= 1679) %*	IUD acceptors (N=1511) %*
Number of insertions		
One	24	100
Two	74	NA**
Three	2	
Who inserted		
Nurse	1	2
Midwife	7	17
Physician	89	79
Don't know	3	3
Missing	<1	

*Totals may not equal 100% due to rounding.
**NA=Not applicable.

Table 13. Side effects

	Quinacrine acceptors (N= 1679) %*	IUD acceptors (N=1511) %*
Experienced problems		
None	34	56
1	32	26
2 or more	35	18
What problems**		
Pain	22	14
Bleeding	12	15
Discharge	42	9
Pelvic heaviness	11	7
Menstrual irregularity	9	11
Headache	12	6
Itching	4	
Other	6	4
Return to clinic because of problems***	19	11

*Totals may not equal 100% due to rounding.
**More than one answer possible.
***p<.001

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Table 14. Illnesses and hospitalizations since insertion

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Illnesses since insertion	57	43
what **illness***	**(N=1111)**	**(N=747)**
Fever/infectious disease	64	32
Ob/gyn	11	8
Digestive system	8	9
Nervous system & sense organs	7	15
Arthritic disease	4	25
Urology	2	3
Circulatory/pulmonary	2	5
Other	2	3
Missing	**<1**	16
Hospitalized**	9	6
For specified reasons	9	6
For non-specified reasons	**<1**	**<1**
Specified reasons	(N= 147)	**(N=84)**
Ob/gyn	39	38
Fever/Infectious disease	18	14
Nervous system & sense organs	13	7
Digestive system	18	13
Circulatory/pulmonary	4	9
Other***	8	18
Uterine or cervical cancer	1	1

*Denominator reflects number of illnesses. A woman may report up to three illnesses; 954 quinacrine users reported 1113 illnesses and 645 IUD users reported 78 1 illnesses.
**p=.015
***No individual reason more than 6%.

Table 15. Changes in health noticed since insertion

	Quinacrine acceptors (N= 1679) %	IUD acceptors (N=1511) %
Changes in health since insertion*		
Lightheadedness	24	20
Weight loss	19	16
Weakness	16	8
Weight gain	14	2
Headaches	10	14
Pelvic heaviness	7	3
Mood changes	6	1
Backache, abdominal pain	5	5
Pelvic tenderness	3	2
Infection	3	2
Health improved	2	<1
Vaginal discharge	1	<1
Health worse	1	<1
Fever	1	
Amenorrhea	1	<1
Itching	<1	
Hemorrhage	<1	<1
Loss of libido	<1	<1

* More than one response possible per woman.

Table 16. Method failures for quinacrine acceptors

	Quinacrine acceptors (N= 1679) %
Percentage of quinacrine acceptors reporting pregnancy	13
Results of pregnancy	(N-222)
Live births	11
Stillbirths	1
Miscarriage	4
Abortion/MR	78
Ectopic	2
Still pregnant	3
Missing	1
Method of contraception used after quinacrine failure	(N=222)
None or still pregnant	26
IUD	21
Tubectomy	14
Quinacrine	4
Pills	4
Condoms	5
Abstinence	11
Withdrawal	9
Vasectomy	1
Injectable	1

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

FIGURES

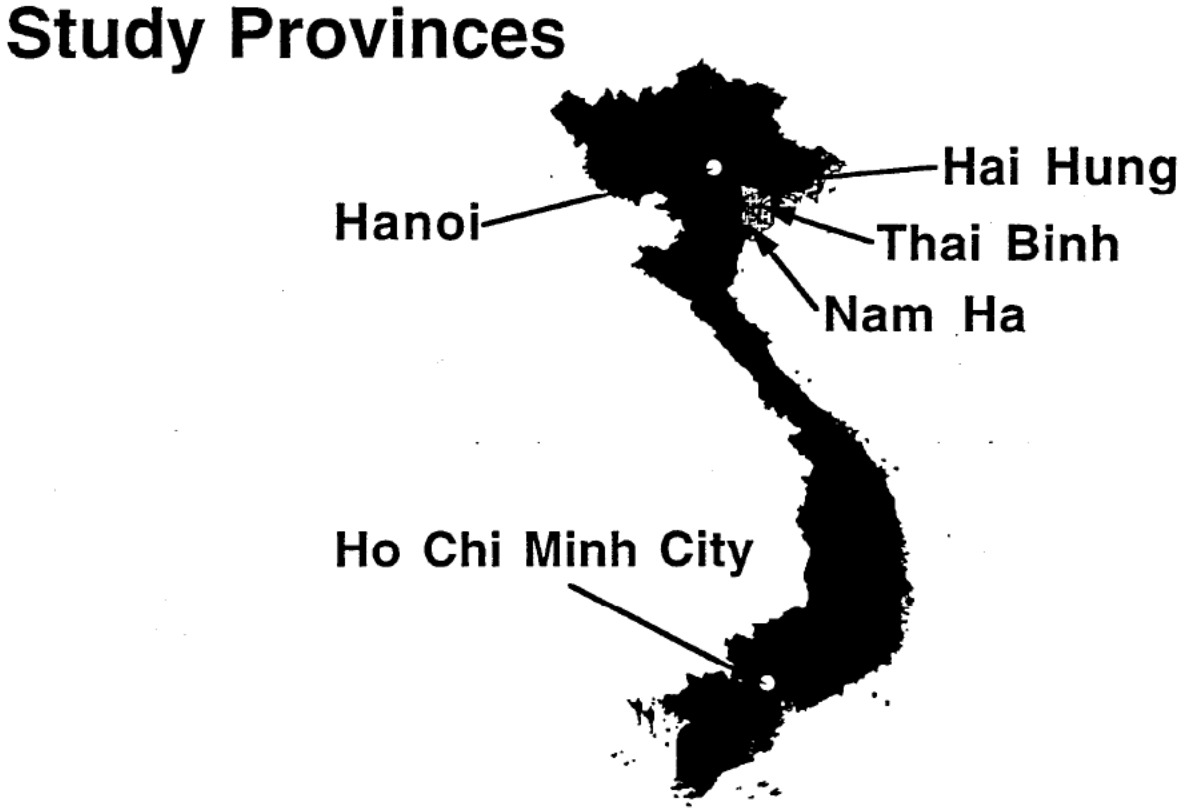


Figure 1

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

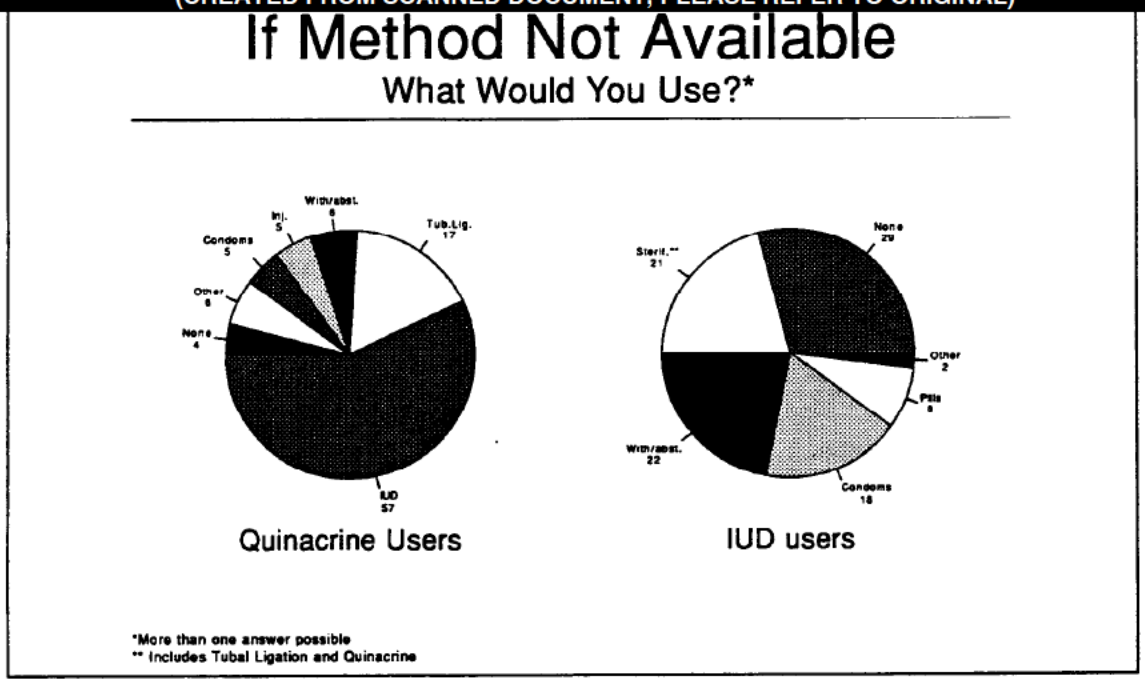


Figure 2

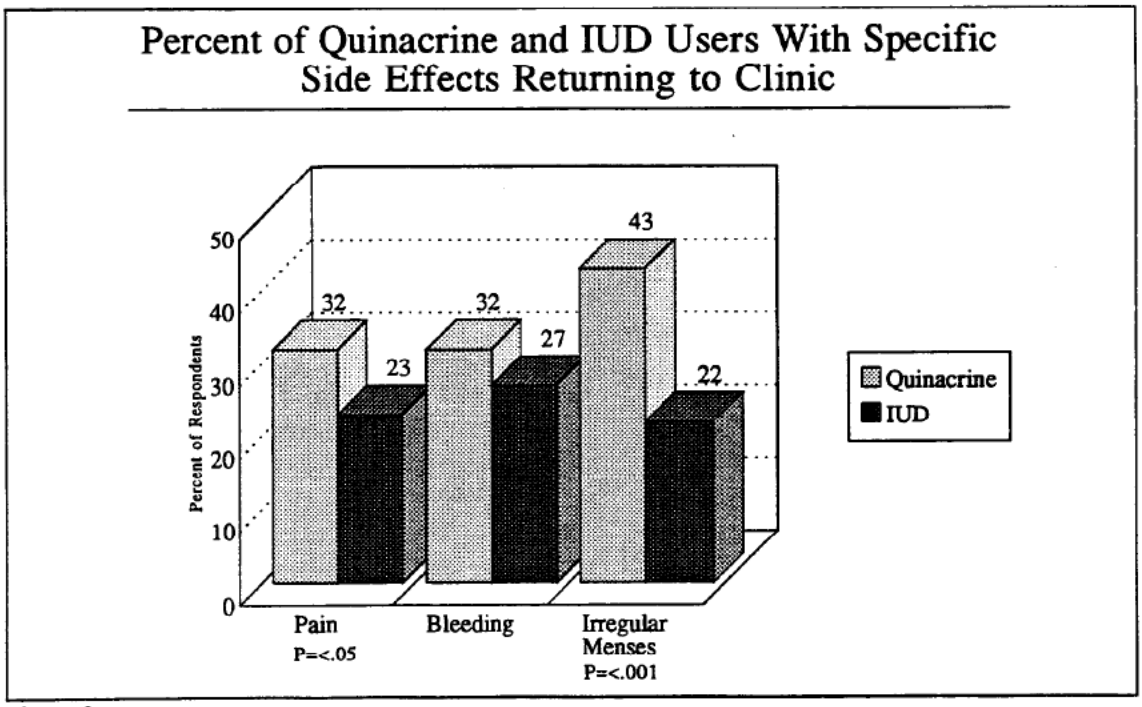


Figure 3

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

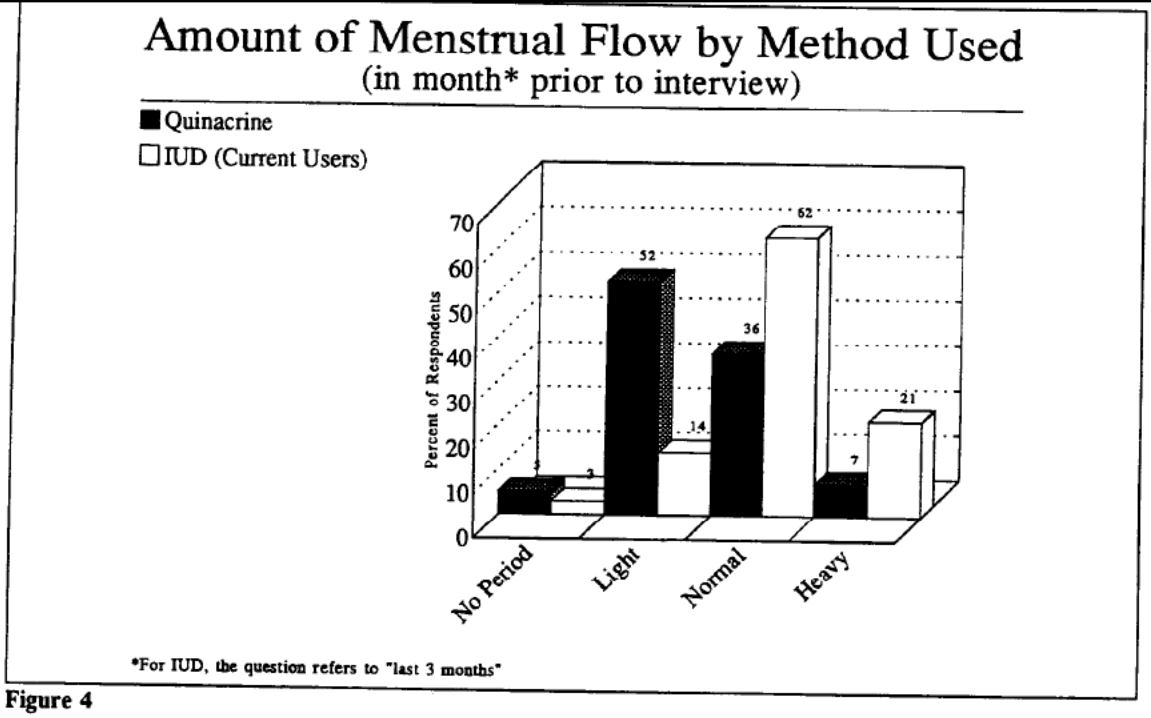


Figure 4

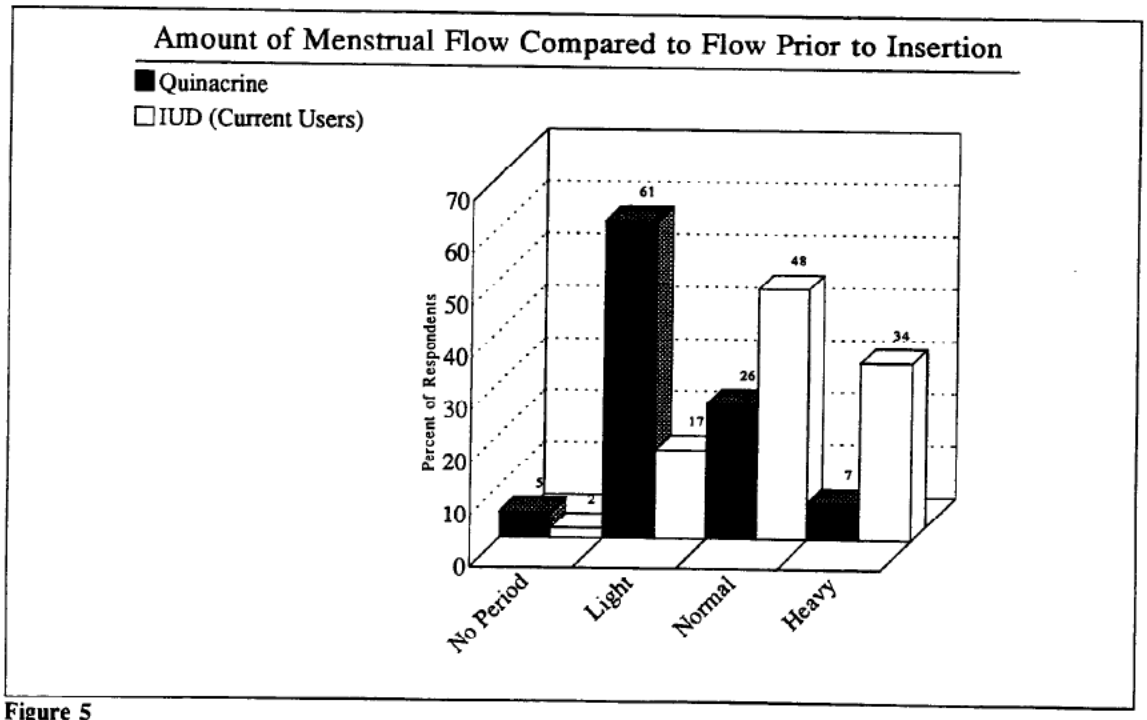


Figure 5

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

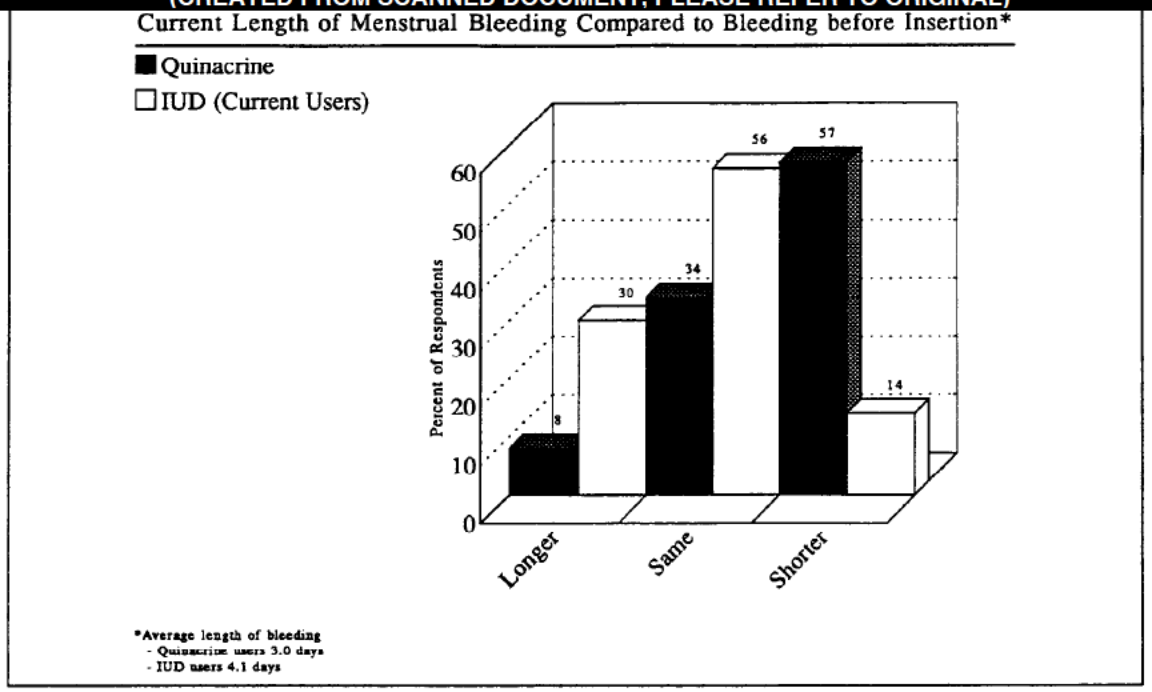


Figure 6

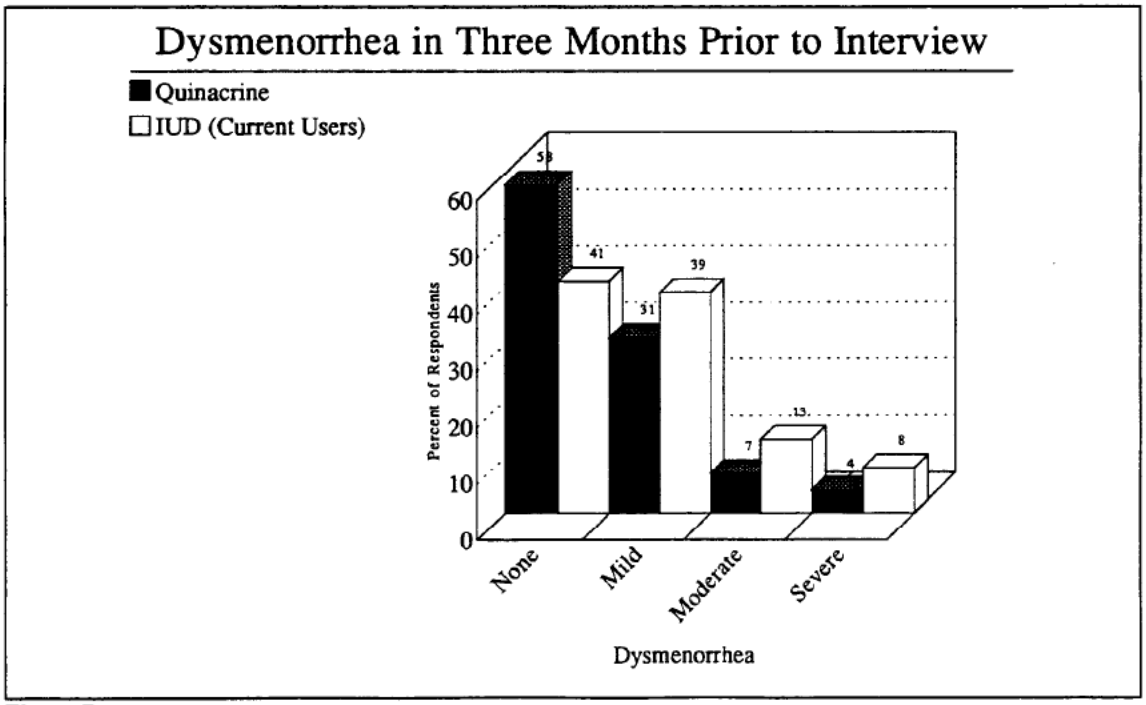


Figure 7

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Advances in Contraception, 1995; 11: 303-308

Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization

N.R. BAIRAGI (1), B.C. MULLICK (2), E. KESSEL (3) and S.D. MUMFORD (4)

(1) Indian Rural Medical Association, Andhar Manik, 24 Parganas, West Bengal, India
(2) Indian Rural Medical Association, 34A Sashi Bhusan De Street, Calcutta 700 012, India
(3) Department of Public Health and Preventive Medicine, Oregon Health Sciences University, Portland, Oregon, USA
(4) Center for Research on Population and Security, PO Box 13067, Research Triangle Park, NC 27709, USA

Abstract

To investigate relative efficacy of intrauterine diclofenac and ibuprofen as adjuvants to intrauterine quinacrine for nonsurgical sterilization, a total of 900 women were systematically allocated to 2 monthly insertions of pellets of diclofenac (75 mg) or ibuprofen (55.5 mg) as adjuvants to intrauterine quinacrine (216 mg) in a rural private practice in West Bengal, India. All women were prescribed oral contraceptives for three months from first insertion. In the middle of the study increased care was taken to insert pellets at the fundus. There was no statistically significant difference found in cumulative life-table pregnancy failure rates at 36 months for women receiving diclofenac (2.7 ± 0.82) or ibuprofen (3.4 ± 0.89). Taking care to insert pellets at the fundus resulted in a decline of failures at 24 months from 4.4 ± 0.92 to zero. Intrauterine administration of pellets of quinacrine (216 mg) plus diclofenac (75 mg) or ibuprofen (55.5 mg) with 3 months' oral contraception provides acceptable efficacy if pellets are inserted to the fundus.

Introduction

The quinacrine pellet method of nonsurgical female sterilization as developed by Zipper and his colleagues [1] involves transcervical administration of 252 mg quinacrine hydrochloride as seven pellets through a modified Copper T intrauterine device (IUD) inserter. Two doses a month apart are given to nonpregnant women

during the proliferative phase of the menstrual cycle (days 5 to 12).

The drug causes occlusion of the fallopian tubes. Prehysterectomy studies of Merchant and her co-workers [2] show that the occlusion is due to inflammation and fibrosis (its extent depending upon the quinacrine dose) after a single insertion. She also noted that more closures were found by histopathology the longer the insertion to hysterectomy interval, leading to the recommendation of three months' contraception from first insertion.

Following the large field trial of the quinacrine pellet method of female sterilization in Vietnam [3] and based also on the experience of over 10 000 cases in West Bengal, India, the Indian Rural Medical Association has recommended this method for service programs in areas of high maternal mortality, of which West Bengal is one.

Zipper and his associates [4] investigated a lower dose of quinacrine (216 mg) in six pellets with the addition of an antiprostaglandin, diclofenac (50 mg), as intrauterine pellets and found an acceptable failure rate with two insertions. However, this trial was small and results inconclusive. Much larger clinical trials are needed to confirm this finding, and we wished to undertake such a trial in India. But diclofenac is very expensive in India, especially compared to the antiprostaglandin, ibuprofen. Through personal communications with Zipper regarding his experience with antiprostaglandins, we concluded that ibuprofen similarly administered should act in the same way as diclofenac. We decided to compare the efficacy of the quinacrine pellet method when these two antiprostaglandins are used as adjuvants. If these two antiprostaglandins are found to be comparable, then we want to undertake a much larger multicenter trial to determine if intrauterine ibuprofen improves the efficacy of the quinacrine pellet method.

Materials and methods

The study was approved by the Ethics Committee of the Indian Rural Medical Association and conducted in the private chamber of one of its members (NRB). Women requesting a permanent method of contraception who were generally healthy and with at least three living children, the youngest being three or more years of age, were admitted to the study. Eligible women were asked to come to the clinic in the proliferative phase of their cycle where a physical and pelvic examination was performed. Systematically, every other subject was administered transcervically, as described by Zipper [1], six pellets of quinacrine (216 mg) and three pellets of diclofenac (75 mg) or three pellets of ibuprofen (55.5 mg). The insertions were repeated a month later.

About halfway through the study, Hieu and his co-workers [3] analyzed their data which indicated great variation in failure rates among inserting clinicians. They hypothesized that this might be due to difference in insertion technique, that some clinicians failed to consistently insert the pellets at the fundus. The recommended insertion technique of Hieu [3] involves gentle insertion to the fundus, withdrawal of the inserter for one-half centimeter and advancing the plunger to release pellets at the fundus. When the senior author was advised of this, he then took greater care to make all insertions of pellets to the fundus. To see the effects of this precaution, we divided the data set in two parts at approximately the date the senior author had been alerted.

The quinacrine pellets were custom manufactured (Sipharm, Switzerland); the release time for the quinacrine pellets was 30 min and for the diclofenac and ibuprofen 10 min. The modified Copper T inserter was cold sterilized and the pellets merely kept clean, as our experience and that of a large field trial in Vietnam [3] have shown this procedure does not increase risk of infection. Nine hundred women entered the trial between 10 September 1991 and 30 November 1993. All subjects were provided with three cycles of oral contraceptives to be started at the time of first insertion.

Systematic follow-up visits were not required, but the subjects and their families were well-known to the senior author, who practices in a rural area of West Bengal, India. To ensure that no pregnancy failures were missed, the women were offered a refund of the professional fee for the procedure (a large proportion of a family's monthly income) and a free first trimester abortion upon request for the pregnancy failures. Data were computer processed at the Indian Rural Medical Association offices in Calcutta.

Results

Table 1 shows the life-table cumulative failure rates for each combination of medications. There is no statistically significant difference in failure rates between diclofenac (2.7 f0.82) and ibuprofen (3.4 $\pm$0.89) as adjuvants to quinacrine at 36 months.

Table 1. Cumulative life-table pregnancy failure rates per 100 women after transcervical insertion of quinacrine (216 mg) with diclofenac (75 mg) ($n = 450$) or ibuprofen (55.5 mg) ($n = 450$)

	Diclofenac			*Ibuprofen*		
Period (months)	*At risk*	*Cumulative failure rates*	*SE*	*At risk*	*Cumulative failure rates*	*SE*
12	450	0.0	0.00	455	1.1	0.4
24	318	2.2	0.76	309	3.4	0.8
36	94	2.7	0.82	93	3.4	0.8

SE, standard error
Insertions: 10 September 1991 to 30 November 1993

Fertility and Sterility 2001;75:830-31.

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Table 2. Cumulative life-table pregnancy failure rates per 100 women after transcervical insertion of quinacrine (216 mg) with diclofenac (75 mg) or ibuprofen (55.5 mg) at two time periods of study: early (n = 500) and late (n = 400)

	Early insertions			*Later insertions*		
Period (months)	*At risk*	*Cumulative failure rates*	*SE*	*At risk*	*Cumulative failure rates*	*SE*
12	495	1.0	0.44	400	0.0	0.00
24	*481*	*4.4*	*0.92*	*146*	*0.0*	*0.00*
36	*187*	*4.6*	*0.94*			

SE, standard error
Early insertions: 1 September 1991 to 17 October 1992
Later insertions: 19 October 1992 to 30 November 1993

The adoption of the Hieu insertion technique to ensure consistent placement of the pellets at the fundus resulted in a statistically significant decline in failure rate for the later insertions at 24 months (4.4 ± 0.92 vs zero). The result is shown in Table 2.

We had no serious complications in this series. Side-effects were similar to those reported by Hieu and colleagues [3], except that pruritis after insertions was rare in our experience.

Discussion

We found no difference in the efficacy of the quinacrine pellet method between the diclofenac and ibuprofen groups. Thus, the effect on the efficacy of the quinacrine method of these two antiprostaglandins, if any, is the same. Zipper et al., because of the small number of subjects in their study, have not convincingly established that diclofenac improves the efficacy of the method. Larger studies than that published [4] are needed to confirm the effect of antiprostaglandins, if any, on efficacy. This study shows that ibuprofen can be used in place of diclofenac for this purpose.

Once the insertion technique was changed to ensure consistent placement of the pellets at the fundus, no further failure were observed. This finding offers further confirmation that Hieu et al. identified the major cause of failure of this method – inconsistent placement of the pellets at the fundus. Much emphasis should be placed on the importance of good training in the Hieu technique of insertion of the pellets.

The lack of systematic follow-up is the major shortcoming of this study. However, there are several good reasons to believe that few, if any, pregnancies were unrecorded. These women, all of whom tended to be very poor, had a significant economic incentive to return and report a pregnancy. Furthermore, the first author is

the only provider of abortion in the area. Since the treatment with diclofenac o ibuprofen was systematically assigned to every other case, the lack of systemati follow-up should not have affected one study group disproportionately in any case.

Acknowledgements

The pellets were provided by the Center for Research on Population and Security Research Triangle Park, North Carolina. We are grateful to Irene Rosenfeld fo editorial assistance.

References

1. Zipper J, Rivera M, Cole LP, Brown E Efficacy of two insertions of 1 OO-minute releasing quinacri hydrochloride pellets for non-surgical female sterilization Adv Contracept 1987;3:255-61
2 Merchant RN, Prabhu SQ, Kessel E Clinicopathologic study of fallopian tube closure by dose an transcervical insertion to hysterectomy interval of quinacrine pellets Int J Fertil 1995;40:47-54
3 Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Viuh DQ 3 1,781 cases of non-surgical fema sterilization with quinacrine pellets in Vietnam Lancet 1993;342:213-17
4. Trujillo V, Zipper J, Viel B, Rivera M Sterilization feminine non chirurgicale Rev Fr Gynécol Obst 1993;88:147-50

MS received 26 July 95
Acceptedforpublication 29 Aug. 95.

Resumé

Lors dune etude conduite dans le cabinet medical dune zone rurale au Bengale occidental (Inde) en vue determiner l'utilite relative du diclofenac et de l'ibuprofen en tant qu'adjuvants à la quinacrine, to administrés par voie intrauterine pour la stérilisation non chirurgicale, on a pratiqui sur un total de 9 femmes, à 1 mois d'intervalle, 2 insertions de pellets contenant soit 75 mg de diclofenac soit 55,5 d'ibuprofen en tant qu'adjuvants à 216 mg de quinacrine Des contraceptifs oraux ont été prescrits à tou les femmes pendant les trois mois qui ont suivi la premiere insertion Au milieu de la période d'étude, o veillé plus particulièrement à insérer les pellets au fond de la cavité. On n'a constati aucune differen statistiquement significative dans les taux d'échec par grossesse sur les tables de survie cumulées à 36 m que les femmes aient reçu du diclofenac (2,7 ± 0,82) ou de l'ibuprofen (3,4 ± 0,89). En prenant soin d'insé les pellets au fond de la cavité, il a été possible de ramener le taux d'échecs à 24 mois de 4,4 ± 0,92 à ze L'administration par voie intrauterine de pellets de 216 mg de quinacrine, plus 75 mg de diclofenac ou 5 mg d'ibuprofen, accompagnee dune contraception orale pendant 3 mois est dune utilité acceptable si comprimés sont insérés au fond de la cavité.

Resumen

A fin de investigar la eficacia relativa de diclofenac e ibuprofen intrauterinos como adyuvantes de quinacrina uterina para la esterilización no quirúrgica, se asignó sistematicamente un total de 900 muje a 2 inserciones mensuales de bolitas de 75 mg de diclofenac o de 55,5 mg de ibuprofen como adyuvantes 216 mg de quinacrina intrauterina en un consultorio rural privado de Bengala Occidental, India A to las mujeres se les recetaron anticonceptivos orales durante tres meses desde la primera inserción mediados del estudio se presto especial atención a la inserción de las bolitas en el fondo No se determi ninguna diferencia estadisticamente significativa en las tasas de fallo de las tablas de vida acumulativa los 36 meses en el caso de las mujeres a las que se habia recetado diclofenac (2,7 ± 0,82) o ibupro

Fertility and Sterility 2001;75:830-31.

(3,4±0,89). El cuidado en la inserción de las bolitas en el fondo originó una disminución de los fallos a los 24 meses, de 4,4±0,92 a cero. La administración intrauterina de bolitas de 216 mg de quinacrina más 75 mg de diclofenac o 55,5 mg de ibuprofen con 3 meses de anticonceptivos orales proporciona una eficacia aceptable si las bolitas se insertan en el fondo.

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

FERTILITY AND STERILITY
Copyright © 1995 American Society for Reproductive Medicine
Vol. 64, No. 2, August 1995
Printed on acid-free paper in U. S. A.

Prevalence and standardized incidence rates of preclinical cervical pathology among 1,061 women sterilized with transcervical quinacrine hydrochloride pellets*

Alfredo Dabancens, M.D.
David C. Sokal, M.D.†
Martha Pruyas, M.D.‡
Mirta Rivera, Midwife‡
Jaime Zipper, M.D.‡

Cytopathology and Cancer Control Service, Faculty of Medicine, University of Chile; Sótero del Rio Hospital, Area Sur Oriente, Santiago, Chile; and Family Health International, Research Triangle Park, North Carolina

Objective: To determine whether the incidence of in situ cervical carcinoma was increased among a cohort of women who received transcervical insertions of quinacrine hydrochloride pellets into the uterine cavity as a method of nonsurgical sterilization.

Design: Retrospective review of Papanicolaou (Pap) test results, comparing incidence of high-grade lesions among quinacrine acceptors with a comparison population.

Setting: Outpatient clinics, Santiago, Chile.

Subjects: Women attending a family planning clinic (quinacrine acceptors) and a comparison population from another area of Santiago.

Main Outcome Measure: Incidence of in situ cervical carcinoma.

Results: During 3,668 woman-years of follow-up, 8 women in the quinacrine group were found to have in situ carcinomas for an age-adjusted rate of 2.62 per 1,000 woman-years. The incidence in a comparison population was 1.62 per 1,000 woman-years, but the difference was not statistically different.

Conclusions: The age-standardized incidence of in situ carcinoma among the quinacrine sterilized women was not significantly different from the rate in a comparison population of women in Santiago. However, the study has a number of limitations.

Fertil Steril 1995; 64:444-6

Key Words: Cervical cancer, quinacrine, Pap smears, epidemiology, retrospective cohort, sterilization.

Since the mid-1970s, a number of studies of voluntary nonsurgical sterilization have been done with the intrauterine application of quinacrine hydrochloride pellets in patients at the Family Planning Clinic of the Sotero del Rio Hospital in Santiago (1). In 1977, a cytology laboratory and a pathology service were established in the hospital. Since that time, periodic (generally annual) Papanicolaou (Pap) examinations were carried out among this group of women.

The present analysis was undertaken because of concerns that have been raised about the mutagenicity of quinacrine and its potential carcinogenicity in humans (see Sokal et al. [2], this issue). The purpose of this report is to evaluate the results of the Pap smear screening program in which these women were participating and compare their results with available data for a similar population in Santiago.

MATERIALS AND METHODS

We reviewed all cytologic records of women sterilized with intrauterine quinacrine in the Sótero del

Received February 1, 1994; revised and accepted February 17, 1995.

* Supported in part by Family Health International (FHI) with funds from the Mellon Foundation. Family Health International is an international not-for-profit organization that conducts research and provides technical assistance in health, family planning, sexually transmitted diseases, and acquired immune deficiency syndrome. Views expressed in this report do not necessarily reflect those of the Mellon Foundation or FHI.

† Reprint requests: David Sokal, M.D., Family Health International, P.O. Box 13950, Research Triangle Park, North Carolina 27709 (FAX: 919-544-7261).

‡ Sótero del Rio Hospital, Area Sur Oriente.

Rio Hospital between March 1977 and October 1990, as well as the results of the histopathologic studies obtained from the archives of the hospital pathology service. Lesions were classified using the Bethesda system. Cervical intraepithelial neoplasia (CIN) grades II and III were grouped together as high-grade squamous intraepithelial lesions. In this report, we will refer to high-grade lesions as in situ carcinomas. The Bethesda classification of low-grade lesions refers to "cellular changes associated with human papilloma virus" and "mild dysplasia/CIN I." We did not compare rates of low-grade lesions for two reasons. First, there were changing criteria for diagnosis and interpretation of low-grade abnormalities among different cytologists during the study period. Second, agreement and uniformity among cytologists is better for the diagnosis of high-grade lesions.

Incidence rates of in situ carcinomas were calculated for only those women who had had a single negative Pap smear before quinacrine sterilization and were compared with rates for a similar group of Santiago women. Because the age distributions of the two groups were different, the rates were standardized on the basis of the female population of Chile in the 1970 national census (3).

Comparison data were taken from a previous report on the incidence of preclinical cervical pathology in metropolitan Santiago (4). A program for Pap screening was started in Santiago in 1966. In 1977 the program was incorporated into routine maternal and child care programs of the Ministry of Health, and in 1981 a computerized data base including all cytologic examinations was established. The previous report included data from 36,520 women who had a Pap smear in 1981 or 1982 and had at least one subsequent Pap smear in the succeeding 5 years, i.e., through 1986 or 1987, respectively. For the estimation of the incidence rate of in situ carcinoma per 1,000 woman-years, only women with a negative smear at the first exam were included. Due to changes in computer systems, we no longer had access to individual data records for the previous report, so to calculate the number of women years of exposure for each age group, we multiplied the number of women in each group by the average length of follow-up, which was 2.4 years. The two groups are from two different geographic areas, southeast Santiago (quinacrine group) and northeast Santiago (control group), but the communities have similar socioeconomic levels and cervical cancer mortality rates, and both groups receive health services from government clinics.

In the earlier study, rates were calculated separately for women with one or two negative smears, and for women with three, four, and five negative smears. Because the women in the quinacrine study were included in this analysis if they had had a single negative smear at the time of sterilization, they were compared with data for women with one or two negative smears in the earlier study. Due to various factors, perhaps including behavioral factors related to good compliance, incidence rates of in situ carcinoma are higher after only one or two negative Pap smears than after three or more negative smears (4, 5).

The methods of follow-up between the two groups were different. The quinacrine-sterilized women were participants in clinical studies and were followed-up actively. Women in the comparison group were from the general population, and no special effort was made to follow up women with negative smears. The average length of follow-up was 3.5 years in the quinacrine group and 2.4 years in the control group. To take into account the differing lengths of follow-up, rates were calculated per 1,000 woman-years. The comparison of the incidence density of in situ cancers between the quinacrine and comparison groups was performed using a maximum likelihood estimate of the rate ratio.

Table 1 Distribution By Age and Woman-Years of Observation of Women Sterilized With Quinacrine Pellets in Sótero del Rio Hospital, Santiago, Chile, 1977 to 1990

Age group	No. of women	Women-years of cytologic observation*	Intraepithelial lesions, high grade
15 to 19	1	0	0
20 to 24	8	8	0
25 to 29	84	186	0
30 to 34	243	729	3
35 to 39	301	975	3
40 to 44	266	1,047	1
45 to 49	115	536	1
50 to 54	34	I54	0
55 to 59	5	24	0
60 to 64		2	0
Unknown	3		0
Total	1,061	3,668	8

* Time in years between first and last cytologic examination.

RESULTS

The available cytologic records include a group of 1,061 women whose distribution by age at the time of the first cytologic examination and lengths of observation is shown in Table 1.

In this group of women, there were 19 patients in whom an in situ carcinoma, or cervical cancer, was found at the time of the first quinacrine pellet insertion (prevalence = 1.8%). Of these women, 18 had in situ cancers and 1 had invasive cancer. The woman with invasive cancer was diagnosed subse-

quently with adenocarcinoma of the cervix, was treated surgically, and was alive at the last follow-up in 1992. One of the women with an in situ carcinoma was lost to follow-up and was diagnosed with cervical cancer 12 years later at a different hospital. She died despite treatment.

A second group of nine women showed a change from their first cytology examination after the first insertion of intrauterine quinacrine. In this incident group, we found one patient with squamous cell carcinoma surgically treated in 1986. She was alive and free of illness at her last follow-up visit in 1990. The eight other women were found to have carcinoma in situ. Their distribution by age at the time of the first cytologic exam is shown in Table 1. The three women with unknown ages did not have any lesions and were not included in the age-adjusted analysis.

For the comparison population, the previously reported incidence rates of high-grade cervical pathology found among women ages 30-49 years in another area of Santiago and the 1970 census female population, both by 5-year age groups, are shown in Table 2. The crude incidence rates are 2.18 per 1,000 woman-years for the quinacrine group and 1.78 for the comparison group, for a crude rate ratio of 1.37, with 95% confidence limits of 0.61 to 3.07. The age-standardized rates for both groups are as follows: quinacrine group 8.62/3,285 = 2.62 per thousand woman-years; comparison group, 19.96/12,355 = 1.62 per thousand woman-years. The resulting rate ratio is 1.62, with 95% confidence limits of 0.73 and 3.61, indicating no significant difference between the two groups.

Table 2 Comparison of The Number of In Situ Carcinomas and Woman-Years of Exposure By Age Among Quinacrine-Sterilized and Comparison Women in Santiago, Chile

Age group	Quinacrine in situ cancer	Woman-years	Comparison in situ cancer	Woman-years	Chile 1970 female population*
30 to 34	3	729	13	4,951	299,200
35 to 39	3	975	5	3,374	259,400
40 to 44	1	1,046	1	2,309	248,100
45 to 49	1	535	3	1,721	200,200
Total	8	3,285	22	12,355	1,006,900

* Population used for age adjustments.

DISCUSSION

The age-adjusted incidence rate of in situ cervical carcinoma in patients treated with quinacrine (2.62 per 1,000 woman-years) is not significantly higher than the incidence rate in the comparison group (1.62 per 1,000 woman-years). While this analysis has shown no increased risk, this study has a number of limitations. The quinacrine group and comparison group were not recruited or followed in the same manner. They are from two separate geographic areas of Santiago. We do not have comparable data from the two groups on risk factors for cervical cancer such as age at first intercourse or number of sexual partners. The difference in the length and intensity of follow-up between the two groups might be a source of bias.

The relatively short average length of follow-up in the quinacrine group limits the study's generalizability. We are not aware of any data on chemically induced cervical cancer or carcinoma in situ in humans that would permit one to estimate a latent period. However, based on the latent period for known human carcinogens, it is certainly possible that insufficient time has passed since quinacrine insertion to see an effect.

The biologic plausibility of quinacrine causing cervical cancer is probably low, as most human cancers of the cervix are associated with infection by human papilloma virus. However, quinacrine is mutagenic and has the theoretic potential of being a carcinogen or cocarcinogen. The potential carcinogenicity of quinacrine is discussed in more detail by Sokal et al. (2). Additional toxicologic studies of quinacrine are being planned to better assess its potential carcinogenicity.

Acknowledgment. We thank Carrie Cummings, B.A., for her editorial assistance.

REFERENCES

1. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. Int J Gynaecol Obstet 1980; 18:275-9.
2. Sokal DC, Zipper J, Guzman-Serani R, Aldrich, TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril 1995; 00:000-000.
3. Instituto Nacional de Estadisticas. Poblacion 1960- 1975. Ministerio de Economia, Fomento y Reconstruccion, Republica de Chile (National Institute of Statistics. Population 1960-1975, Ministry of Economy, Public Works and Reconstruction, Republic of Chile, 1977:232. (Spa). 1977:232.
4. Dabancens OA. Tasas estandarizadas de patolo gia cervical preclinica obtenidas por el programa de control precoz de cancer cervico-uterino, en el area metropolitana de Santiago [Standardized tables of preclinical cervical pathology obtained by the program for early diagnosis of cervical-uterine cancer in the metropolitan area of Santiago]. Rev Chil Obstet Gineco 1989;54(4):217-24. (Spa).
5. Pettersson F, Naslund I, Malker B. Evaluation of the effect of papanicolaou screening in Sweden: record linkage between a central screening registry and the national cancer registry. In: Hakama M, Miller AB, Day NE. Screening for cancer of the uterine cervix. World Health Organization, International Agency for Research of Cancer, No. 76, 1986.

Int J Fertil, 40(1), 1995 p. 47-54

Clinicopathologic Study of Fallopian Tube Closure After. Single Transcervical Insertion of Quinacrine Pellets

Rohinee N. Merchant
S.R. Prabhu

Obstetrics and Gynecology
B.Y.L. Nair Hospital, and
Department of Pathology
T.N. Medical College
Bombay, India

Elton Kessel

Department of Public Health and Preventive Medicine
Oregon Health Sciences University
Portland, Oregon, U.S.A.

ABSTRACT **Objective-To** determine the effect on tubal closure of intrauterine quinacrine by dose and time from administration. **Design and Participants**-Subjects included 33 women of reproductive age who were awaiting hysterectomy for nonmalignant conditions at a Bombay, India medical college. Ten women received 252 mg quinacrine as pellets using a modified Copper-T IUD inserter followed by hysterectomy within 6 weeks, and 23 women received 324 mg quinacrine followed by hysterectomy 6 to 20 weeks post-insertion. Hysterosalpingograms were done before insertion, prior to surgery and on the fresh surgical specimen. The uteri and tubes were subjected to histology studies, including grading of tubal damage. For study of dose, an additional 7 women receiving 100 mg quinacrine (and previously reported) were included. **Main Outcome Measure-Tubal** closure rates by hysterosalpingogram and tubal histology. **Results and Conclusion-Tubal closures were directly related to quinacrine dose and** length of insertion-hysterectomy interval. For the 252 mg quinacrine dose, 55.0% of intramural tubal segments and 5.9% of isthmic segments showed histologic evidence of closure. For the 324 mg dose, all intramural tubal segments and 58.8% of isthmic segments showed histologic evidence of closure. Clinical conditions, such as dysfunctional uterine bleeding, were associated with lower tubal closure rates. Multivariate discriminant analysis showed quinacrine dose to be more important than quinacrine-hysterectomy interval. Int J Fertil 40(1):47-54, 1995

KEY WORDS: quinacrine (pellets), tubal closure, fibrosis, hysterectomy, sterilization (female)

INTRODUCTION

A METHOD OF NONSURGICAL female sterilization that could be delivered safely by health personnel who are not surgeons would meet an important need in developing countries [1]. Zipper's quinacrine pellet method is the leading candidate method today [2]. His group's report of the action of antiprosta-glandins as potentiating agents to improve efficacy makes it important to study this method thoroughly [3]. We have expanded our pre-

vious prehysterectomy study **[4]** to evaluate the effects of quinacrine insertion-hysterectomy intervals and quinacrine dose on rates of tubal closure.

While there are several reports [5-10] on the safety and efficacy of 252 mg of quinacrine hydrochloride pellets at monthly intervals for three insertions, there is only one report of a single insertion of 324 mg [10]. Recently, Zipper and co-workers [1 1] reported improvement in efficacy with 100-minute dissolution pellets with just two insertions a month apart as compared to lo-minute dissolution pellets with three insertions, each a month apart, the dosage being 252 mg in both instances. The pattern of failure seen in quinacrine pellet studies is that a preponderance of pregnancies occurs in the first 3 months following the first insertion. In Mullick and Kessel's study of 1,342 cases of two insertions of 252 mg of quinacrine, 45 of 55 failures (82%) occurred within 3 months (B. Mullick, E. Kessel, personal communication, 1992). This suggests that use of an additional contraceptive in this period may improve efficacy of the method. However, this may only delay pregnancy failures.

PATIENTS AND METHODS

The study was conducted at the Obstetrics and Gynecology Department of B.L.Y. Nair Hospital of T.N. Medical College in Bombay. Thirty-three women of reproductive age who were awaiting hysterectomy for prolapse or nonmalignant lesions of the cervix, who did not have menorrhagia or gross abnormality of the uterus or endometrium, and were willing to participate in the study were selected. Informed consent was obtained from each subject prior to entry into the study. Group I comprised 10 women and Group II 23 women. Thirty-minute dissolution pellets, each containing 36 mg quinacrine, were deposited transcervically in the upper uterine cavity in the proliferative phase of the menstrual cycle, using a modified Copper-T IUD inserter. In women with clinical diagnosis of dysfunctional uterine bleeding (DUB), curettage was performed, and women with gross endometrial pathology were excluded. Quinacrine was then introduced in these cases only after bleeding stopped. Seven pellets (252 mg) were inserted in each of the Group I women; nine pellets (324 mg) were inserted in Group II women. In each group, the women had a hysterosalpingogram (HSG) prior to quinacrine insertion (HSG I) and just prior to hysterectomy (HSG II), except for two Group I women whose hysterectomy was delayed as noted below.

Total hysterectomy was performed with removal of as much of the tubes as possible before the end of the sixth week post-insertion in Group I, and between the sixth and the twentieth week post-insertion in Group II. X-rays of the removed uterus and tubes were also obtained after injecting radiopaque dye through the cervical canal of the fresh specimen (HSG III). This last HSG was done to exclude functional or nonpathologic causes (e.g., tubal spasm, tubal plugs, errors in HSG technique) of tubal closure seen on HSG II. Each specimen of uterus and tubes was fixed in 10% formalin and subjected to histologic studies with sections obtained from cervix, endometrium, myometrium and serial sectioning of fallopian tubes as described earlier [**12**]. The intramural, isthmic, and ampullary portions of the fallopian tubes were sectioned into blocks of tissues taken at 3-mm intervals. Three serial sections were taken from each block. All serial sections were stained with hematoxylin and eosin. Masson's trichrome stain to study muscle tissue and hyalinization was used whenever required.

Detailed evaluation of the light microscopic histologic changes in the tubes was performed, including presence or absence of inflammation, degree and nature of inflammation, degree of necrosis, depth of

FIG. 1. Stage 0 (unaffected tube). Scanner view, x14. The lumen is patent and is lined with intact mucosa and a focal papillary fold. There is no damage to the muscle coat.

FIG. 2. Stage I (acute inflammation). Low-power view, x150. There is an acute inflammatory reaction with hemorrhage and marked mucosal damage with destruction of inner muscle coat. The lumen is not reduced.

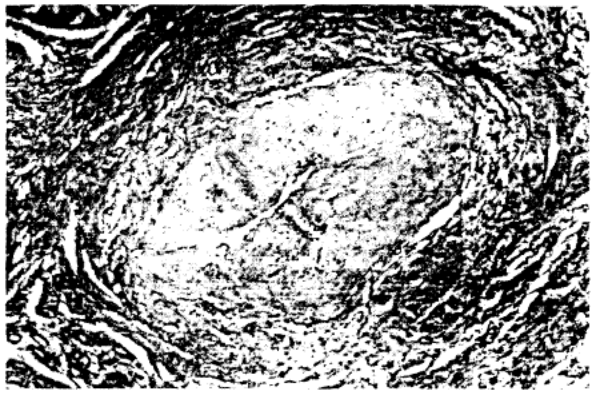


FIG. 4. Stage III (fibrosis and tubal occlusion). Low-power view, x60. There is total reduction in lumen and complete hyalinazation of inner two-thirds of muscle coat. Inflammatory cells not seen.

penetration, presence and degree of fibrosis, and status of the tubal lumen. The pathologist was kept blind to the clinical history and the study assignments of the subjects. The histologic appearance of the sections of the tubes was classified into the following four sequential histologic changes:

Stage 0 (Figure 1): Patent tube with normal lumen, intact normal epithelium, minimal or no inflammation in lamina propria, intact normal muscle. We consider this to be a tube unaffected by the chemical.

Stage I (Figure 2): Stage of acute inflammation. Damage to epithelium, with slight or no decrease in lumen. Acute inflammatory change in lamina propria, often with hemorrhage. Minimal to moderate damage to inner muscle coat. Areas of necrosis as a result of tissue damage. Heavy infiltration of submucosa and muscle by neutrophils, lymphocytes, and plasma cells with vascular congestion and vasodilatation.

Stage II (Figure 3): Stage of chronic inflammation. Loss of epithelium or flattening of mucosal lining

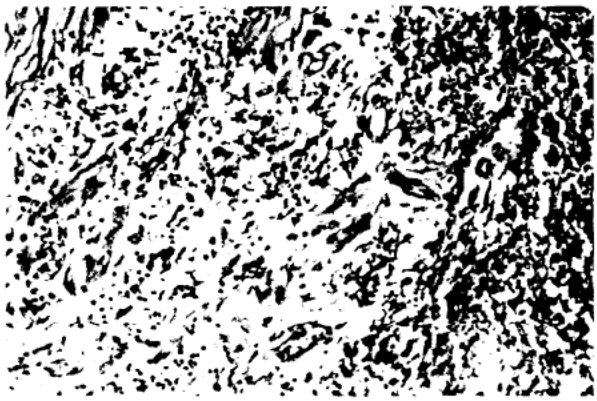


FIG. 3. Stage II (chronic inflammation) Low-power view, x150. The lumen is small with a flat lining. A few scattered inflammatory cells are seen. Distortion of inner one-third of the muscle coat is visible.

FIG. 5. Patchy recanalization. Low-power view, x200. A new lumen has formed with a lining of low, cuboidal epithelium. Destruction of inner muscle coat is seen in center of the field beneath the epithelium (arrow).

TABLE I
Clinical features in Group I women, patency status of fallopian tubes on HSC prior to insertion of 252 mg quinacrine, prior to surgery and on the hysterectomy specimen, the quinacrine-hysterectomy interval, and histologic changes in intramural tubes.

Serial no.	Age (years)	Parity	Clinical Diagnosis	Patency Status of Tubes on HSG I Rt	I Lt	II Rt	II Lt	III Rt	III Lt	Q-H Interval (weeks)	Histologic Staging of Intramural Tubes Rt	Lt
1	40		Dysmenorrhea	P	P	P	P	P	P	2	I	I
2	38	5	CIN	P	P	P	P	P	P	3	I	I
3	35	3	DUB	P	P	Bl	Bl	Bl	Bl	3.5	III	III
4	35	4	CIN	P	P	Bl	Bl	Bl	Bl	4	III	III
5	40	4	Prolapse	P	P	Bl	P	Bl	P	5	I	I
6	50	5	DUB with CIN	P	P	P	P	P	P	5	I	I
7	35	6	?DUB	P	P	P	Bl	P	Bl	5	I	III
8	35	4	Prolapse	P	P	Bl	Bl	Bl	Bl	5.5	III	III
9	36	5	CIN	●	P P	P	P	Bl	Bl	6	III	III
10	37	3	Prolapse	†P	P	P	P	Bl	Bl	7	III	III

CIN = Cervical intraepithelial neoplasia
DUB = Dysfunctional uterine bleeding

HSG I = Prior to quinacrine insertion
HSG II = Prior to surgery
HSG III = On the surgical specimen

HSG = Hysterosalpingogram
Rt = Right
Lt = Left
Q-H = Quinacrine insertion to hysterectomy
P = Patent
Bl = Blocked

'HSG II 3 weeks post-quinacrine. HSG III 6 weeks post-quinacrine.
†HSG II 2 weeks post-quinacrine. HSG III 7 weeks post-quinacrine.

with marked reduction in lumen. Hyalinization in submucosa and inner muscle coat. Chronic inflammatory cellular infiltrate in lamina propria, submucosa, and the inner muscle coat consisting of lymphocytes and plasma cells.

Stage III (Figure 4): Stage of fibrosis and tubal occlusion. Complete loss of mucosal lining with absence of lumen or severe reduction with a fish mouth slit. Organization of exudate, marked fibrosis of inner muscle coat.

Some Stage III tubes showed a process suggestive of recanalization, characterized by reepithelialization, subepithelial and inner muscle coat hyalinization with formation of a small circulating lumen. However, the lumen is neither lined with normal epithelium, nor continuous with the lumen of the rest of the tube in this series (Figure 5).

RESULTS

Group I

Table I shows patency status of fallopian tubes in women prior to quinacrine insertion (HSG I), prior to surgery (HSG II) and on hysterectomy specimens (HSG III). It also shows the salient clinical features of the women, the quinacrine-hysterectomy interval and the histologic changes in the intramural tubes. In three of the ten women in Group I, both tubes were found to be patent on HSG I, II as well as III. The histologic appearance of intramural tubes in these three cases was of Stage I, and the quinacrine-hysterectomy interval was from 2 to 5 weeks (cases 1, 2, 6). In another three women, both tubes were patent at HSG I, but a bilateral cornual

TABLE II
Clinical features in Group II women, quinacrine-hysterectomy (Q-H) interval, and histologic changes in intramural tube after insertion of 324-mg quinacrine hydrochloride pellets.

Serial NO.	Age (years)	Parity	Clinical Diagnosis	Q-H Interval (weeks)	Histologic Staging of Intramural Tubes	
					Rt	Lt
	37	3	DUB	6	II	III.
2	34	7	CIN	6	III	III
3	43	4	DUB	7	III	III
4	35	3	Prolapse	8	III	III
5	35	4	Prolapse	8	III	III
6	35	5	CIN	8	III	III
7	35	3	Prolapse	8	III	II
8	35	4	CIN	8	III	III
9	30	4	DUB	8	III	III
10	32	3	Prolapse	9	III	III
11	35	3	Prolapse	9	III	III
12	35	2	CIN	9	III	III
13	40	4	Dysmenorrhea	9	III	III
14	30	3	Prolapse	10	III	III
15	40	3	DUB	11	III	II
16	37	6	CIN	11	III	III
17	45	4	CIN	11	III	III
18	36	4	CIN	12	III.	III
19	37	6	DUB	15	III	III
20	40	4	CIN	18	III	III
21	37	3	DUB	18	III	III
22	35	2	PID	20	III	III.
23	35	4	Prolapse	25	III	III

*(III) = Tubes with patchy recanalization. DUB = dysfunctional uterine bleeding, CIN = cervical intraepithelial neoplasia.

block was detected on HSGs II and III. The histologic changes in intramural tubes in these three cases were of Stage III, and quinacrine-hysterectomy interval was between 3.5 and 5.5 weeks (cases 3, 4, 8). In subject 5, HSGs II and III showed right tube blocked and the left tube patent, but the histologic appearance of both tubes was Stage I. In subject 7, HSG II and III showed the right tube patent and the left tube blocked, and the histologic appearance was Stage I for the right tube and Stage III for the left tube. In the remaining two women, HSG II was done at 4 and 2 weeks post-quinacrine insertion and showed both tubes patent; but HSG III was performed at 6 and 7 weeks post-quinacrine insertion (cases 9 and 10), respectively, and showed both tubes blocked.

Group II

In Group II, all 23 subjects had patent tubes on HSG I and all were blocked on HSGs II and III. Table II shows the salient clinical features of women in Group II, the quinacrine-hysterectomy interval, and

TABLE III
Histologic staging by segment of fallopian tube.

Tubal Segment	Total Tubes Examined No. (%)	Histologic Stage 0 No. (%)	I No. (%)	II No. (%)	III No. (%)
Group I (252 mg quinacrine)					
intramural	20 (100.0)	0 (0.0)	9 (45.0)	0 (0.0)	11 (55.0)
isthmic	17 (85.0)	6 (35.3)	10 (58.8)	0 (0.0)	1 (5.9)
Ampullary	13 (65.0)	12 (92.3)	1 (7.7)	0 (0.0)	0 (0.0)
Fimbrial	11 (55.0)	11 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Group II (324 mg quinacrine)					
Intramural	46 (100.0)	0 (0.0)	0 (0.0)	3 (6.5)	43 (93.5)
Isthmic	34 (73.9)	6 (17.7)	8 (23.5)	0 (0.0)	20 (58.8)
Ampullary	30 (65.2)	24 (80.0)	6 (20.0)	0 (0.0)	0 (0.0)
Fimbrial	20 (43.4)	17 (85.0)	3 (15.0)	0 (0-0)	0 (0.0)

the histologic changes in intramural tubes. Hysterectomies were performed sometime after the sixth and before the twentieth week except for one patient, who underwent the surgery 6 months after quinacrine insertion. The histologic appearance of the intramural tubes showed Stage III changes in all except three tubes of separate specimens, where it was Stage II change (cases 1, 7, 15).

The sections through the regenerated endometrium, cervix, and myometrium of the uterus in all cases of Groups I and II did not reveal any abnormality, thereby indicating that the chemical has no lasting effect on these structures.

Histologic changes from intramural to the fimbrial end of the fallopian tube showed maximum changes in the intramural section. The effect was minimal on the outer parts of the tube. Table III shows a higher incidence of Stage III changes in the isthmic portion of the tube for Group II, with its higher dose of quinacrine and longer insertion-hysterectomy interval. The effect of the chemical starts from the lumen of the tube but stops short of the level of the outer muscle coat. At hysterectomy, no adhesions or other abnormal changes were detected following any quinacrine insertion.

Clinically, five women complained of some vague hypogastric pain following quinacrine insertion, one in Group I and four in Group II. The pain lasted from a few hours to three days. None required treatment.

DISCUSSION

There is a suggestion from Group I data that hysterosalpingograms taken before 5½ weeks from insertion of 252 mg of quinacrine are likely to show patency of at least one tube. This was the case in seven of the nine subjects. In all nine of these subjects, blocked tubes on HSG were associated with a Stage III histologic change, except one tube of case 5, which showed a Stage I change. This tube may have been blocked by necrotic tissue in the lumen of the tube. Cases 9 and 10, who had early prehysterectomy hysterosalpingograms showing patency, went on to show tubal occlusion on the hysterectomy specimens, when hysterectomy was delayed until the sixth and seventh week post-quinacrine insertion. This suggests the reasonable possibility that the progress of inflammation to scarring and

closure takes time, which may vary between individual women. A study by El-Kady and co-workers [13], who used similarly short quinacrine-hysterectomy intervals, also showed predominantly lower stages of inflammation.

To explore the relationship between tubal closure and quinacrine-hysterectomy interval, we pooled data of this and our previous report [4] providing a total of 40 prehysterectomy cases. If we consider Stages 0 or I histologic changes in either tube as failure of the procedure and Stage II or III of both tubes as success, the results of the pooled data can be seen for intervals before and after the seventh week quinacrine-hysterectomy interval:

	Interval (weeks)		
Changes	***0-6***	7+	Total
Success	9	22	31
Failure	7	2	9
Total	16	24	40

$P = 0.01$ (Fisher's Exact Test)

It does appear that this interval is one factor in success. The hypothesis that prolonging this interval will increase success could be tested by prescribing a contraceptive in clinical trials through the first 6 weeks after the last quinacrine insertion. An injectable progestogen would also promote a proliferative-stage-like endometrium. In fact, application in the proliferative stage appears to increase efficacy of the method [4].

In the same way, a strong dose-response effect is seen in pooling present data with our previous study:

	Dose (mg)			
Changes	***100"***	***252***	***324***	Total
Success	3	5	23	31
Failure	4	5	0	9
Total	7	10	23	40

$P = 0.01$ (Fisher's Exact Test, 252 mg vs. 324 mg)
*From previous study [4]

One would expect from Group II that a single insertion of 324 mg quinacrine would be highly effective if the women were protected with contraception until fibrosis and closure occurred. But Table III provides evidence of Stage III tubal damage (58.8 %) extending beyond the intramural portion and likely irreversibility of the method with this dosage in a high proportion of cases. Zipper's group has shown that an adjuvant, an antiprostaglandin, may be a better approach to improving efficacy than a higher dose [3]. The potentiating action of an antiprostaglandin is unknown, but it may relax the muscles at the tubal ostia, permitting more consistent entry of quinacrine into the tube.

As for clinical conditions, in the pooled data, myoma, CIN and prolapse lead to greater success as opposed to other diagnoses, which are mainly DUB:

	Clinical Condition		
Changes	***Myoma, CIN and prolapse***	***Others***	***Total***
Success	21	10	31
Failure	2	7	9
Total	23	17	40

$P = 0.02$ (Fisher's Exact Test)

Mullick and co-workers [10] and El-Kady and co-workers [14] have shown that the presence of blood lowers efficacy, and this may be the basis for less success in prehysterectomy studies among DUB cases. However, dose is still a significant factor even in "other" cases. Neither age nor parity is statistically significant in determining success as we have defined it for prehysterectomy studies.

In order to determine the relative importance of the three factors-quinacrine-hysterectomy interval, dose, and clinical condition-that are significantly related to closure of both tubes, a multivariate discriminant analysis procedure was applied to the pooled data. The standard discriminant function coefficients were as follows:

Clinical condition	0.57
Dose	0.55
Quinacrine-hysterectomy interval	0.35

The coefficients for the nonsignificant variables of age and parity were 0.34 and 0.03, respectively. The clinical condition variable is influenced mainly by DUB and we recommend that DUB cases be excluded from future prehysterectomy studies

designed to predict efficacy of intrauterine administration of quinacrine. DUB cases are probably poor candidates for sterilization by the quinacrine pellet method-a suspicion that needs confirmation in large clinical trials. The remaining significant variables of dose of quinacrine and quinacrine-hysterectomy interval appear to be the main determinants that may predict tubal closure in women choosing this method of sterilization, with dose being the more important of the two.

CONCLUSION

Our analysis suggests that some early failures of the quinacrine pellet method of nonsurgical female sterilization may be due to the extended time needed for some women undergoing quinacrine-induced inflammation to achieve tubal closure. A prospective clinical trial with and without an additional contraceptive is needed to confirm this hypothesis. While increasing the dose of quinacrine appears to increase tubal closure rates in prehysterectomy studies, a better approach to improving efficacy may be the addition of adjuvants to the present doses (or lower doses) of quinacrine now in use for sterilization.

ACKNOWLEDGMENTS

We are grateful to Professor M.Y. Raval, Head, Department of Obstetrics and Gynecology, for allowing us to carry out this project and to Dr. A.G. Naik, Head, Department of Radiology, for his help. The Nair Golden Jubilee Foundation was generous in its financial support of the undertaking. We very much appreciate the assistance of our dean, Dr. P.M. Pai, and the permission she granted to use the hospital records. We are indebted to the International Association for Maternal and Neonatal Health, Geneva, for supplying the necessary quinacrine hydrochloride pellets.

Mr. Sanat Kumar Das and Mr. A.R. Kannappan provided statistical consultation and Irene Rosenfeld, editorial assistance.

REFERENCES

1. Kessel E: Prospects for nonsurgical female sterilization. *Int J Gynecol Obstet* 29:1-4, 1989.
2. Kessel E, Zipper J, Mumford SD: Quinacrine nonsurgical female-sterilization: a reassessment of safety and efficacy. *Fertil Steril 44:293-298,* 1985.
3. Kessel E, Zipper J, Mumford SD: Surgical vs. nonsurgical female sterilization. *MCI Newsletter* 16:2-3, 1991.
4. Merchant RN, Doctor VM, Thakur SS, et al: Clinicopathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets. *Adv Contracept 2:79-90, 1986,*
5. Zipper J, Cole LP, Goldsmith A, et al: Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. *Int J Gynaecol Obstet 18:275-279, 1980.*
6. Guzman-Serani R, Bernales A, Cole LP: Quinacrine hydrochloride pellets: three year follow-up on a nonsurgical female sterilization. *Fertil Steril 44:303-306,* 1985.
7. Bhatt RV, Waszak CS: Four-year follow-up insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. *Fertil Steril 44:303-306, 1985.*
8. Raj A, Chakravarty S: Permanent female sterilization by chemical method--transcervical insertion of quinacrine, in Hingorani V, Pandit RD, Bhargava VL (eds): *Proceedings of the Third International Seminar on Maternal and Perinatal Mortality, Pregnancy Termination and Sterilization. New* Delhi, India, New Roxy Press, pp 476-480, 198 1.
9. Nisa FU: An early experience with nonsurgical female sterilization, in Kessel E, Awan AK (eds): *Maternal and Child Care in Developing Countries.* Thun, Switzerland, Ott Publishers, pp 273-277, 1989.
10. Mullick B, Mumford SD, Kessel E: Studies of quinacrine and of tetracycline for non-surgical female sterilization. *Adv Contracept 3:245-254, 1987.*
11. Zipper J, Cole LP, Rivera M, et al: Efficacy of two insertions of loo-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization. *Adv Contracept 3:255-261, 1987.*
12. Merchant RN, Prabhu SR, Chougale A: Uterotubal junction-morphology and clinical aspects. *Int J Fer-Til* 28:199-205, 1983.
13. El-Kady AA, Mansy MM, et al: Histologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. *Adv Contracept 7: l-9, 1991.*
14. El-Kady AA, Nagib HS, Kessel E: Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril 59:301-304, 1993.*

Address reprint requests to:
Dr. Rohinee N. Merchant
Dr. Merchant's Hospital
5A Sion (West)
Bombay 400 022, India

Advances in Contraception 1995; 11: 239-244

A potential single insertion protocol for quinacrine pellet non-surgical female sterilization

B.C. MULLICK (1), E. KESSEL (2) and S.D. MUMFORD (3)

(1) Indian Rural Medical Association, 34A Sashi Bhusan De Street, Calcutta 700 012, India
(2) Department of Public Health and Preventive Medicine, Oregon Health Sciences University, Portland, Oregon, USA
(3) Center for Research on Population and Security, PO Box 13067, Research Triangle Park, North Carolina, 27709, USA

Abstract

Two preliminary single-insertion clinical trials of the quinacrine pellet method of non-surgical female sterilization were compared. Both trials used transcervical application of quinacrine, 252 mg, and diclofenac, 75 mg, as pellets. In the first trial (21 April 1992 to 17 February 1993), 58 women received oral contraceptives for three months. In the second trial (19 February 1993 to 25 May 1994), 229 women received medroxyprogesterone acetate, 150 mg IM, at the time of quinacrine insertion. At 18 months, the life-table pregnancy failure rate per 100 women of the first trial was 8.6 (SE 3.7), whereas the failure rate for the medroxyprogesterone acetate group was 0.5 (SE 0.5), $p < 0.05$. There were no serious complications or side-effects in either group.

Larger confirming trials with random allocation and long-term systematic follow-up are needed to determine whether a single injection of medroxyprogesterone improves the efficacy of quinacrine.

Introduction

The quinacrine pellet method of non-surgical female sterilization as developed by Zipper et al. **[1]** involves transcervical insertion of quinacrine pellets, each containing 36 mg quinacrine, utilizing a modified intrauterine device (IUD) inserter. Seven pellets or 252 mg of quinacrine is the usual dose. Quinacrine causes inflammation and fibrosis, resulting in closure of the intramural tube [2] Efficacy is influenced by dose of quinacrine [3], number of insertions [4,5], presence of blood in the uterine

Fertility and Sterility 2001;75:830-31.

cavity [5], the addition of adjuvants [6] and, possibly, supplemental contraception for 3 months post-insertion [3] Finally, and probably an over-riding factor suggested in a large field trial [4], is insertion technique. Consistent insertion of pellets at the fundus is probably the proper technique.

The most desirable protocol for a non-surgical female sterilization method should be one that is safe, effective, inexpensive, acceptable and can be provided by paramedical personnel during a single visit [7] The Vietnam field trial [4] provides evidence for all of these desirable qualities except the single visit. We report on a protocol that may provide this last quality.

Materials and methods

The study was approved by the Ethics Committee of the Indian Rural Medical Association and was carried out at the Association's main training center in Calcutta. All procedures were performed by the senior author (BCM). Women requesting a permanent method of contraception were offered the following protocol: Single insertion of quinacrine, 252 mg (7 pellets), with diclofenac, 75 mg (3 pellets), inserted transcervically using a modified Copper T IUD inserter. Medroxyprogesterone acetate, 150 mg IM, was given in the deltoid muscle immediately after insertion in one group. This procedure was accepted by 229 women between 19 February 1993 and 25 May 1994. In a previous group, the same procedure was used except that oral contraceptives were prescribed for 3 months instead of medroxyprogesterone IM; 58 women accepted this procedure between 21 April 1992 and 17 February 1993. The cut-off date for the collection of data was 30 November 1994.

Insertions were made with a cold-sterilized inserter that was made perfectly dry by a spirit wash. Pellets were kept clean but not sterilized before loading in the inserter as quinacrine itself is strongly bacteriocidal [8] The quinacrine pellets (Sipharm, Switzerland) had a dissolution time of 30 min and the diclofenac pellets of 10 min.

Aseptic precautions, similar to those for IUD insertion were used. A vaginal speculum was introduced to expose the cervix. The uterocervical length was measured using a 4-mm plastic cannula. If the uterine length was more than 8 cm, pregnancy was first excluded. The inserter was gently introduced to the area of the fundus and the plunger advanced to release the pellets.

Several weeks into the recruitment of the medroxyprogesterone acetate group, BCM learned of the importance of the consistent placement of all pellets at the fundus from the work of Hieu and co-workers and immediately began using the insertion technique advised by them [4]: the inserter was advanced to the fundus and then withdrawn 0.5 cm before advancing the plunger.

Our resources did not permit systematic follow-up visits but subjects were encouraged to return to the clinic for any complaints. This clinic is widely known in the community as the main abortion facility in the area. Subjects were informed that, in the event of failure of the method, first-trimester abortion would be provided upon request without charge.

Results

There were no serious complications reported in this series. Side-effects were similar to those reported by others [1,4,5] except that we rarely saw pruritus. The life-table failure rates are shown in Table 1. The difference in failure rates between the two groups is not statistically significant at 6 or 12 months but is at 18 months.

Table 1. Cumulative life-table failure rates for 100 women for a single intrauterine insertion of quinacrine, 252 mg, plus diclofenac, 75 mg, comparing additional contraception of three months oral contraception (n=58)[a] or with medroxyprogesterone acetate, 150 mg IM (n=229)[b]

Contraception	*Months*	*Failures*	*At risk*	*Rate*	*SE*
Oral	6	2	56	3 45	2.40
	12	1	55	5 17	2 91
	18	2	53	8 62"	3.69
Medroxyprogesterone	6	0	225	0.00	0.00
	12	1	151	0.55	0.55
	18	0	54	0 55"	0.55

[a]Insertions 21 April 1992 to 17 February 1993; [b]Insertions 19 February 1993 to 25 May 1994; [c]$p < 0.05$

Discussion

This study has a number of serious shortcomings. Random or other systematic sampling is absent, introducing the potential for one or more biases when one group is compared with the other. For example, the change in the insertion technique during the medroxyprogesterone phase of the study may have contributed to its lower failure rate. When this study was initiated in April 1992, medroxyprogesterone was not available to us in India and it remained unavailable to us until February 1993. During the oral contraceptive phase of this study, we were troubled by the frequency of pregnancy with this single insertion method, suspecting, even before this phase was terminated, that the failure rate would be unacceptably high. When medroxyprogesterone was made available to us, the switch was made immediately.

The lack of systematic follow-up (which stems from our lack of resources) makes it impossible to completely rule out under-reporting of significant events. However, we have good reason to believe that all or most significant events are reported to us. This clinic is well known in the community and it is also well known that all treatment for complications and side-effects of all abortion and contraceptive services is free.

We have learned from previous studies in this center that women do return if they have problems. For example, in one study where tetracycline was used as the

sclerosing agent rather than quinacrine, 32 of 55 women (58%) treated returned to the clinic pregnant and in another, 35 of 102 women (34%) returned to the clinic pregnant [9]. Furthermore, in one postabortion protocol using quinacrine, 15 of 50 women returned pregnant (30%) and, in another one, 12 of 50 returned pregnant (24%) [9] (These two studies provided important evidence that blood in the uterus, for any reason, including procedure trauma, interferes with the action of the quinacrine.)

We believe that virtually all significant events are recorded. However, without a high rate of systematic follow-up, there are no assurances that all failures and serious complications are recorded. Some women, though they had declared that they wanted no more children before having the quinacrine procedure, and fully knowing that abortion is legal and safe at this clinic, may have chosen to continue their pregnancy without reporting it.

Lastly, as shown in Table 1, at 18-months follow-up, when the differences are shown to be statistically significant, the numbers of women at risk in the two study groups are 53 and 54. In life-table analyses, as a rule of thumb, 50 individuals at risk is considered to be the minimum number necessary for reliable calculations, placing the usefulness of our calculations at 18-months follow-up close to the borderline.

The important finding of this study is that the use of intrauterine application of pellets of quinacrine, 252 mg, and diclofenac, 75 mg, with a single injection of medroxyprogesterone, 150 mg IM, does apparently provide safe effective contraception at least through the first 18 months of use. Other studies [10] indicate that the risk of pregnancy failure declines over time. If this proves so with this protocol, it will provide an attractive option as a permanent contraceptive method. The short-term complications of this method [4,10] indicate that it is safer than surgical sterilization. The main long-term concern is the possibility of an increased risk of cancer of the uterus, which is probably remote [11,12]. However, as with IUDs and oral contraceptives, this increased risk, if any, can only be known after extensive and long-term use [13].

Besides providing additional contraceptive protection while fibrosis is underway, the action of medroxyprogesterone, if any, is not known. One hypothesis is that this drug may prevent spasm of the tubal ostia, resulting in a more consistent exposure of quinacrine to the intramural tube. The need for postinsertion contraception is not yet well demonstrated, although there is some evidence supporting its use [3]. The potentiating action of diclofenac [6] needs confirmation in larger studies. At this time, our protocol provides the most attractive single-insertion non-surgical female sterilization method. However, this study needs confirmation in a larger series with longer and systematic follow-up which will only come when adequate resources are made available.

Acknowledgements

The pellets for this study were provided by the Center for Research on Population and Security. We are grateful to Irene Rosenfeld for editorial assistance.

References

1. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstet 1980;18:275-9
2. Bhatt RV, Aparicio A, Laufe LE, Parmley TH, King TM Quinacrine induced pathologic changes in the Fallopian tube, Fertil Steril 1980;33:666-7
3. Merchant RN, Prabhu SR, Kessel E Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets Int J Fertil 1995;40:47-54
4. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ 31 78 1 cases of non-surgical female sterilization with quinacrine pellets in Vietnam Lancet 1993;342:213-7
5. El-Kady AA, Magib HS, Kessel E Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization Fertil Steril 1993;59:301-4
6. Trujillo V, Zipper J, Viel B, Rivera M Sterilization feminine non chirurgical Rev Fr Gynecol Obstet 1993;88:147-50
7. Klitsch M Sterilization without surgery Int Fam Plann Perspect 1982;8:101
8. Ciak J, Hahn FE Quinacrine (Atebrine): mode of action Science 1967;156:655-6
9. Mullick B, Mumford SD, Kessel E Studies of quinacrine and of tetracycline for non-surgical female sterilization Adv Contracept 1987;3:245-54
10 Sokal DC, Zipper J, King T Transcervical quinacrine sterilization: clinical experience Int J Gynecol Obstet (Suppl) 1995 [in press]
11 Blake DA, Dubin NH, DiBlasi MC, Parmley TH, Stetten G, King TM Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride In: Zatuchni GI, Shelton JD, Goldsmith A, Sciar a JJ, eds Female transcervical sterilization Philadelphia: Harper & Row; 1983:71-88
12 Tice RR, Griffith J, Recio L An evaluation of the mutagenicity and carcinogenicity of quinacrine Family Health International, Research Triangle Park, North Carolina, 1990:33
13 Kessel E Quinacrine sterilization revisited (Commentary) Lancet 1994;344:698-700

MS received 19 Apr. 95.
Acceptedforpublication 15 May 95.

Resumé

On a compare les experiences de deux essais cliniques dune insertion unique preliminaire de pellets de quinacrine dans la mithode de sttrilisation feminine non chirurgicale Dans ces deux essais, les pellets de 252 mg de quinacrine et 75 mg de diclofenac ont êté appliques par la voie transcervicale Dans le premier (du 21 avril 1992 au 17 février 1993), on a administré à 58 femmes des contraceptifs oraux pendant 3 mo s Dans le second (du 19 février 1993 au 25 mai 1994), 229 femmes ont reçu par voie intra-musculaire 150 mg d'acétate de mtdroxyprogesterone au moment de l'insertion de quinacrine A 18 mois, le taux d'échecs par grossesse du premier essai, d'après la table de survie pour 100 femmes, était de 8,6 (norme 3,7), alors qu'il Ctait de 0,5 (norme 0,5) dans le groupe de l'acétate de mtdroxyprogesterone, soit $p < 0,05$. Aucune complication ou effet secondaire grave n'est survenu ni dans un groupe ni dans l'autre

11 est nicessaire de procéder à des essais de plus grande envergure privoyant des administrations au hasard et un suivi systématique à long terme pour determiner si une seule injection de médroxy-progesterone rend la quinacrine plus efficace.

Resumen

Se comparó la experiencia de dos ensayos clínicos preliminares de una sola colocación por el método de esterilización femenina no quirúrgica de bolita de quinacrina En los dos ensayos se utilizó la aplicación transcervical de 252 mg de quinacrina y 75 mg de diclofenac en bolitas En el primer ensayo (21 de abril de 1992 a 17 de febrero de 1993), 58 mujeres recibieron anticonceptivos orales durante tres meses En el Segundo ensayo (19 de febrero de 1993 a 25 de mayo de 1994), 229 mujeres recibieron 150 mg de acetato de medroxiprogesterona IM en el momento de la colocación de quinacrina A los 18 meses, la tasa de no embarazo con tablas de vida por cada 100 mujeres en el primer ensayo fue 8,6 (S E 3,7) y la tasa de no embarazo en el grupo de acetato de medroxiprogesterona fue 0,5 (S E 0,5), $p < 0,05$. No hubo complicaciones graves ni efectos secundarios en ninguno de los grupos

Se necesitan ensayos más amplios de confirmacibn con asignación aleatoria y seguimiento sistemático a largo plazo para determinar si una sola inyección de medroxiprogesterona mejora la eficacia de la quinacrina

Fertility and Sterility 2001;75:830-31.

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.

Clinical practice

31781 cases of non-surgical female sterilisation with quinacrine pellets in Vietnam

Do Trong Hieu, Tran *Thi* Tan, Do Ngoc Tan, Pham Thi **Nguyet**, Pham Than, Dao *Quang* Vinh

Summary

The quinacrine method of non-surgical female sterilisation involves transcervical intrauterine insertion of 252 mg quinacrine as pellets during the proliferative phase of the menstrual cycle; the drug causes inflammation and fibrosis of the proximal fallopian tube. We have carried out a field trial of 31 781 cases in twenty-four provinces of Vietnam from Jan 2, 1989. until October, 1992. There were 818 pregnancies after he procedure, of which 80 were carried to term. Some women received only one dose of quinacrine; the majority received two doses with an interval of one month. Cumulative life-table pregnancy rates per 100 women at 1 year (for studies of at least 50 cases followed for 12 mon hs) were 2.63 (SE 0·17) among9461womenwhoreceivedtwodosesand5.15 (0·48) among 2225 who received only one dose. Failure rates (pregnancies) were strongly affected by the skill of the doctor or midwife. There were no deaths and only 8 serious complications were reported (0 03%); by contrast, in a similar series of women undergoing surgical sterilisation, 30 deaths and between 540 and 1812 serious complications would be expected. All reported side-effects were minor and of short duration. There were 19 ectopic pregnancies and the incidence was O-89 per 1000 woman-years of use. There was one birth defect (anencephaly), in a fetus conceived 2.5 months after quinacrine insertions; however, we believe it is not related to he procedure. An estimated 242 maternal deaths will be averted by hese 31 781 sterilisations. This method is safe and acceptably effec ive for female sterilisation.

Lancet 1993; 342: 213-17

See Commentary page 188

Introduction

Vietnam has a population of 70 million, growing by 2.2% per year, and an income per person of less than US$200.[1] Surgical female sterilisation has become the most common contraceptive method in use world wide.[2] However, in Vietnam, only 2.7% of women have been sterilised. Most developing countries, with their large rural populations, lack both the highly-trained physicians and the facilities for safe surgical sterilisation. 6.2 million women in Vietnam want no more children;[3] surgical sterilisation cannot possibly satisfy the demand for the foreseeable future. A simpler non-surgical sterilisation method is needed.

A review of current research on non-surgical methods suggests that the quinacrine-pellet method of non-surgical female sterilisation is the only one ready for large-scale use.[4,5] As developed by Zipper and colleagues,[6] it involves transcervical intrauterine administration of 252 mg quinacrine hydrochloride as seven pellets through a modified Copper T intrauterine device (IUD) inserter. Two doses a month apart are given to non-pregnant women during the proliferative phase of the menstrual cycle (days 5 to 12);[7] the drug causes occlusion of the fallopian tubes. Prehysterectomy studies[8-10] show that the occlusion is due to inflammation and fibrosis, limited primarily to the intramural segment of the tube.

At the first international symposium on this technique in Bandung, Indonesia, in 1991,[11] the results of studies on more than 25 000 women in ten countries were presented. No case of life-threatening complications was reported.

In 1989, we undertook a field trial to find out whether this method is applicable in Vietnam. The main aims were to assess safety factors (including side-effects and complications, ectopic pregnancies among women who became pregnant after the procedure, and birth defects), efficacy, method acceptance, and ease of delivery.

Patients and methods

Two preliminary clinical trials of 100 cases each were started in January and February, 1989, in Namha and Haihung Provinces, respectively. Encouraging results led to expanded trials in twenty-four provinces, involving a total of 31 781 subjects (table 1).

All subjects weremonitored for serious, life-threatening complications, pregnancy failures (ie, pregnancies after the procedure, including ectopic pregnancy), and birth defects. In the analysis of efficacy, only studies with a minimum of 50 cases at 1 year follow-up (table 2) were included. The earliest study in Namha province (Namha 1) was used for the assessment of side-effects.

The efficacy of an IUD is known to be affected by the skill (consistent application of proper insertion technique) and experience of the person who inserts it.[12] To see if this was true also of the quinacrine method, we examined the incidence of failures with increasing experience of the operator.

Maternal and Child Health/Family Plannlng Department, Ministry of Health, Hanol (Prof D T Hieu MD, D Q Vinh MD); **Gynaecology/ Obstetrics Sector, Myvan Hospltal, Halhung Province** (D N Tan MD) **and Maternal and Child Health/Family Plannlng Centres, Namha Province** (T T Tan MD) **Thalbinh Province** (P T Nguyet MD) **and Nghean Province** (P Than MD) **Vletnam**

Correspondence to Prof Do Trong Hieu MD Maternal and Child Heal h/Family Planning Department, Ministry of Health, 138A Giangvo, Hanoi, Vietnam

Province	Cases	Inserters	Pregnancies	Ectopic pregnancies	Spontaneous abortions	Induced abortions	Live-births	Still-births	Pregnancy continuing	Complications	Malformations	Pregnant at laser. tion	Hospital admissions
Namha	8325	164	245	6	2	203	31	1	2	2	1	2	2
Haihung	4122	252	108	2	0	96	8	0	2	2	0	2	3
Nihbinh	2196	131	72	3	0	64	5	0	0	0	0	0	0
Thaibinh	2615	102	62	2	3	49	1	0	7	0	0	1	3
Binhdinh	972	25	5	0	0	5	0	0	0	1	0	0	1
Hatay	1981	64	31	0	0	31	0	0	0	0	0	0	0
Hoabinh	484	20	17	0	0	15	2	0	0	0	0	0	0
Habac	1982	72	36	1	0	33	0	0	2	2	0	1	2
Hatinh	997	61	91	1	0	53	25	0	12	0	0	0	0
Sonla	216	5	1	0	0	1	0	0	0	0	0	0	0
Vinhphu	2467	60	32	0	0	32	0	0	0	1	0	0	1
Thanhhoa	1316	16	9	2	0	7	0	0	0	0	0	0	0
Nghean	2570	112	97	2	1	85	7	0	2	0	0	0	0
Quangninh	141	23	4	0	0	3	0	0	1	0	0	1	0
Bacthai	149	25	3	0	0	2	0	0	1	0	0	0	0
Baria-Vungtau	59	6	0	0	0	0	0	0	0	0	0	0	0
Bentre	28	5	0	0	0	0	0	0	0	0	0	0	0
Songbe	51	12	0	0	0	0	0	0	0	0	0	0	0
HoChiMinh City	245	59	0	0	0	0	0	0	0	0	0	0	0
Lamdong	169	42	0	0	0	0	0	0	0	0	0	0	1
Quangnam Oanang	152	15	1	0	0	1	0	0	0	0	0	0	0
Tayninh	153	6	0	0	0	0	0	0	0	0	0	0	0
Angiang	69	B	2	0	0	2	0	0	0	0	0	0	0
Binhthuan	302	22	2	0	0	2	0	0	0	0	0	0	0
Total	31761	1307	818	19	6	684	79	1	29	8	1	7	13

Table 1: Study participants and outcomes events

Trials were carried out at rural facilities, including commune health centres. After a physical examination, pellets were inserted by doctors or midwives trained in the Copper T IUD insertion technique. Women undergoing the procedure had to be at least 30 years old and had to have at least two living children, the youngest being at least 3 years old. Women with moderate or severe cervical inflammation were treated before the procedure. All patients were sexually active, not using another contraceptive after first dose of quinacrine, and at least 6 weeks beyond pregnancy termination.

In Vietnam, family planning services are offered on a strictly voluntary basis. The risks and benefits of the method and the procedure were described to interested women. Those who chose it signed a consent form attesting to their understanding of the nature of the procedure and its permanent character, as well as their preference for this method over others available.

Quinacrine pellets were inserted with a cold-sterilised Copper T IUD inserter that had been air dried after a spirit rinse. Aseptic precautions similar to those for IUD insertion were used. A vaginal speculum was introduced to expose the cervix. The uterocervical length was measured with a uterine sound. If the uterine length was more than 8 cm, pregnancy was first excluded. The inserter was gently introduced as far as the uterine fundus. It was then withdrawn about 5 mm and the plunger advanced to release the pellets before removal. Some studies required two insertions a month apart, whereas others required only a single insertion (table 2).

The pellets, which take 30 min to dissolve (Sipharm, Switzerland), were kept clean but not sterilised, since quinacrine is known to be bactericidal.[14]

Women were followed up 1, 3, 6, and 12 months after the last insertion and every 6 months thereafter. These studies have complete follow-up since they took place in communes where there is little mobility and coverage by government health services is excellent. For example, in Namha Province, 10 women moved from their communes but continued to be monitored. The cutoff dates for this analysis were in October, 1992 (table 2).

Serious complications were defined according to the Centers for Disease Control and Prevention list,[15] except for transient febrile morbidity, which is seen as a method side-effect.[16]

To assess the effect on the efficacy of the method of the operator's experience, we looked at the experience of the 88 healthworkers (61 doctors, 26 assistant doctors, and 1 midwife) who treated the 4010 women in the first two Namha studies. There were 165 procedure failures (pregnancies) among these women. Operators were ranked according to the number of insertions done and the procedure failure rate for each was calculated. It was possible for two different operators to carry out the two procedures in 1 woman. In these cases, the failure was assigned to the person who administered the first dose. In 1899 cases (47.2%), the name of person who did the second insertion was not recorded. To account for these insertions, we allocated them by weighting according to the total number of recorded insertions (by dividing the number of insertions attributed to each clinician in patient records by 0.7632). This increases total known insertions by insertor to total insertions of 8020. The number of cases for each clinician was then determined by dividing their number of weighted insertions by 2 (table 3).

The risk of ectopic pregnancy among failures was calculated. Infants of women who became pregnant were examined for malformations.

Results

In the Namha 2 study (3502 cases), 473 (13.5%) women were aged 25-30 years, 1236(35.3%) were31-35years, 1499 (42.8%) were 36-40 years, and 294(8.4%) over 40 years. 182 (5.2%) had two living children, 1159 (33.1%) had three, and 2161 (61.7%) had four or more.

The pooled data for the two-insertion studies (table 2) gave failure rates of 2.63 (SE 0.17) per 100 women at 1 year and 4.31 (0.31) at 2 years. The l-year failure rates by study varied from 0.95 (0.95) to 4.54 (0.78).

The two studies of one insertion had a much higher failure rate at 1 year (table 2). However, only one of these studies has followed up at least 50 patients for longer than 1 year. If we compare single one-insertion and two-insertion studies (for example, Nghean 1 and 2 or Haihung 1 and 2), we find substantially higher failure rates for one insertion.

To assess the effect of operator experience, we examined the rates of failure in the first two Namha studies. Among the total 4010 sterilisations, there were 165 pregnancies (crude pregnancy rate 4.1%). However, operators had widely differing crude pregnancy rates. For example, among the 32 who had failures, there were 8 who had carried out more than 100 insertions; their pregnancy rates varied from 2.5% to 9.1%. The failure rate was the highest among operators who had done 10 or fewer insertions (17.2%) and

Study	Follow-up (months) 6	12	18	24	30	First admission	Last admission
Two-insertion studies							
Nanha 1 (n = 508)							
n	499	487	467	467	66	Jan 4,	Dec 5,
Failure	158	3 76	5.34	6·54	6 54	1989	1992
(SE)	(0·55)	(0 85)	(1·00)	(1·10)	(1·10)		
Nanha 2 (n = 3502)							
n	3445	3005	1442	89		Jan 19,	April 9.
Failure	174	296	411	446		1990	1992
(SE)	(022)	(0 29)	(0·37)	(0·40)			
Nanha 3 (n = 501)							
n	494	490	240	..		Jan 19,	Jan 17,
Failure	100	140	164	..		1991	1992
(SE)	(044)	(0 53)	(0 57)				
Haihung 1 (n = 105)							
n	104	104	103	102	100	Jan2,	April 15,
Failure	0·95	0·95	1.90	2·86	286	1989	1990
(SE)	(0·95)	(0.95)	(1·33)	(1·63)	(1 63)		
Haihung 2 (n = 3083)							
n	2516	1707	816	382	84	Feb 3,	Aug 7,
Failure	0·84	180	2.56	336	4 79	1990	1992
(SE)	(0 17)	(0 27)	(0·36)	(0 55)	(0 89)		
Thaibinh (n = 760)							
n	685	625	181	53		April 26,	Oct 31,
Failure	2·94	4.54	5 08	508		1990	1992
(SE)	(0·63)	(0 78)	(0 84)	(0·84)			
Nghean 1 (n = 1002)							
n	878	629	315	51		'Jan 4.	June 18,
Failure	223	248	248	248		1990	1992
(SE)	(0 47)	(0 50)	(0 50)	(0 50)			
Total (n = 9461)							
n	8623	7048	3574	1146	260		
Failure	154	263	350	431	4·85		
(SE)	(013)	(0·17)	(0·21)	(0·31)	(0·39)		
One-insertion studies							
Nghean 2 (n = 1247)							
n	1195	1070	537	103'		Jan 15,	Dec 23,
Failure	417	506	506	506		1990	1991
(SE)	(0·57)	(0·62)	(0·62)	(0·62)			
Haihung 3 (n = 978)							
n	840	129				Oct 4,	May 12,
Failure	4.75	5 12				1991	1992
(SE)	(0·68)	(0 73)					
Total (n = 2225)							
n	2036	1085	537	103'			
Failure	442	515	515	515			
(SE)	(0·44)	(048)	(0·48)	(0·48)			

*22 months follow up.
Failure = cumulative failure rate per 100 women.

Table 2: Failure rates of quinacrine-pellet method for two insertions versus one insertion

lowest among those who had done more than 100 (5.3%). However, there was little change in failure rate for experience between 11 and 100 insertions.

56 of the 88 operators had no failures at all, including 2 who did more than 100 procedures and 4 who did 75-100. When all 88 were included in the analysis, increasing experience was not an important factor in lowering the failure rate (table 3). The crude pregnancy rate for the assistant doctors and the midwife was lower than that for senior doctors (3.0 *vs* 4.5%).

The pattern of side-effects and menstrual changes after quinacrine insertions was similar for the different studies and is reported in detail for 508 cases in Namha Province. The main side-effects after first insertion were lower-abdominal pain (15.3%), vaginal pruritis (23.2%), and headache (20.2%). These symptoms lasted a few hours to a few days. Symptoms were generally milder after the second insertion. No change in menstrual flow was reported by 77.4% of the women; 3.8% reported an increase and 18.8% a decrease. Amenorrhoea that lasted up to 3 months but required no treatment occurred in 0.3% of women.

No uterine perforations occurred, though the rate of perforation with IUD insertions is about 1 in 1000." Quinacrine insertion is less difficult than IUD insertion. The experience of our clinicians in sounding the uterus may also explain the difference; our family planning workers carried out 1.34 million abortions and 1.05 million IUD insertions in 1992.

8 (0.03%) major complications possibly related to quinacrine sterilisation were reported among the whole cohort (31 781). 2 women had severe bleeding (1 immediately after quinacrine, 1 a year later). 1 woman underwent hysterectomy 6 months after insertions because of severe pain and amenorrhoea; no abnormality was found in the surgical specimen. 1 woman had premenstrual pain and dysmenorrhoea, 1 suspected PID 18 days after quinacrine insertion, and 1 an allergic reaction (severe pruritis). 2 women had synechiae of the cervical canal; 1 was treated with dilation and 1 needed a hysterectomy. 1 other woman with synechiae had a hysterectomy after the analysis cut-off date.

5 other women were admitted to hospital with gynaecological disorders not related to quinacrine administration (1 fibroids, 1 hydatidiform mole [conceived 3 months after quinacrine], 1 infection after a subsequent abortion, 1 for abortion after 12 weeks' gestation, and 1 for surgical sterilisation after failure of quinacrine). These disorders were detected during the intensive follow-up for quinacrine side-effects.

An anencephalic fetus was conceived 2.5 months after insertions of quinacrine. Another case had occurred in the same commune 4 months earlier in a woman who had not had quinacrine insertions. All conceptions within a month of quinacrine pellet insertions were aborted by menstrual regulation.

79 other pregnancies were carried to term. All babies were examined at birth and no major malformations were noted. 1 baby was delivered preterm and died. Another baby was stillborn (conceived 11 months after quinacrine insertions). All other women gave birth to normal infants, who remain well. Of the 32 women whose sterilisations

Number of procedures done per operator	Operators who had failures (n = 32) No of operators	No of cases	Failures	Mean failure rate (%) (range)	Operators without failures No of operators	No of cases	All operators No of operators	No of cases	Mean failure rate (%)
101 466	8	1869	100	1869 5 3 (2 5 9 9)	2	214	10	2084	4 8
76 100	3	267	20	7 5 (5 1–9 1)	4	326	7	593	3 4
51 75	7	387	24	6 2 (1 8–9 1)	2	137	9	524	4 6
26 60	4	134	8	6 0 (2 2 13 0)	6	227	10	360	2 2
11 25	4	70	5	7 1(4 1 12 2)	10	175	14	246	2 0
1 10	6	47	8	17 2 (9 5 43 5)	32	157	38	203	3 9
Total	32	2774	165	5 9	56	1236	88	4010	4 1

Table 3: Sterilisation failure rates in Namha 1 and 2 studies by operator

failed and who had full-term pregnancies in Namha Province, 17 were breastfeeding at time of conception and the diagnosis of pregnancy was delayed. The other 15 declined pregnancy termination for religious reasons.

There were 2 cases of quinacrine insertion during early pregnancy. 1 was in a case of ectopic pregnancy and the other woman gave birth after the study cut-off date. The infant was normal.

There were 19 ectopic pregnancies in the whole study population and 6 in the three Namha studies (n = 45 11). 1 of these women had probably been treated in early undetected pregnancy and another had had an ectopic pregnancy 10 years previously. A survey of 18 000 IUD users in the Namha Province showed an ectopic pregnancy rate of 0.14%, similar to the 0.13% for the women who received quinacrine. Of the pregnancies after quinacrine in these three studies, 3.5% were ectopic. The ectopic pregnancy incidence per 1000 woman-years of quinacrine sterilisation use in the Namha studies was 0.89.

Acceptance of the method by operators and women is shown by the rapid increase in the number of cases and dissemination of the method to many provinces in Vietnam (table 1).

Discusslon

The quinacrine pellet method is safe. There were no deaths in this series and, to date, none have been reported for this method anywhere in the world. By contrast, studies of surgical sterilisation in developing countries report rates of 19 to 99 deaths per 100 000 cases.[15,18-22] In a series of 31 781 surgical sterilisations, 6 to 31 deaths would have been expected. Serious complications were also rare. This finding is consistent with the experience of investigators in other countries. The reported rate of serious complications with laparoscopic sterilisation is 1.7% ,[15,23] so in a series of this size, 540 serious complications would be expected. With laparotomy the rate of serious complications is 5·7%,[24] which would give 1812 serious complications in our series. All side-effects were minor and of short duration, as found by others.[16]

The lack of evidence of mutagenicity supports this finding in toxicology studies in monkeys.[25] The single infant with a birth defect diagnosed in our studies (anencephaly) was conceived 2.5 months after quinacrine insertions, when the drug will no longer be present in any tissue.[26] Agricultural chemicals in high doses are known to cause this birth defect and may explain this case of anencephaly and another in a woman from the same commune who had not received quinacrine.

All conceptions within a month of quinacrine insertions were aborted by menstrual regulation. We do not know what would happen if this practice were not continued.

We could not study risk of cancer of the uterus by exposure to quinacrine, but long-term follow-up of cases in Santiago, Chile, shows no increased risk (J Zipper, unpublished). Long-term use of this drug for malaria suppression has revealed no increased risk of any malignant disorder.[27]

The incidence of ectopic pregnancy (0.89 per 1000 woman-years) in the Namha studies is lower than the rate among US women not using contraception (2.60) but higher than the rate after surgical sterilisation (0·32).[28] We had a smaller proportion of ectopic pregnancies among all post-sterilisation pregnancies than in that US study (3.5 *vs* 15·9%[28]). Our higher incidence rate is primarily due to the higher procedure failure rate.

The quinacrine pellet method with two insertions has a failure rate of about 2% at 1 year of use. However, operator skill (consistent application of proper insertion technique) so dominated the determinants of efficacy in these studies as to mask the true efficacy of the method. The amount of experience the operator had was of little importance compared with his or her skill.

Before this field trial, quinacrine investigators thought that pellets could be placed anywhere in the uterus to achieve occlusion, since they believed that the concentration of quinacrine would be even throughout the uterine cavity. Our results suggest that this may not be the case. The effect of insertion technique on efficacy deserves further study, including a search for other determinants of skill.

There are other possibilities for lowering failure rates. For example, prehysterectomy studies show that completion of tubal occlusion takes at least 6 weeks in some women." Thus, use of contraception for this period would be advisable. It is possible that the addition of intrauterine antiprostaglandin administration (diclofenac) could reduce the failure rate and the incidence of side-effects (J Zipper, unpublished).

At the end of this trial, 1307 doctors and midwives were providing this sterilisation method in Vietnam. At a rate of 100 procedures per operator per month, 7.8 million procedures could be done during the next 5 years. The estimated unmet need in Vietnam is 6.2 million women. Thus, the ease of delivery of this method is sufficient for us to achieve our goal of fulfilling all unmet demand for sterilisation within 5 years.

The main advantages of this method for a developing country are the possibility of raising contraceptive prevalence among women who want no more children, while providing more effective contraception than temporary methods. We can calculate from the maternal mortality rate in Vietnam of 380 per 100 000 livebirths,[29] assuming that each sterilisation procedure prevents 2 pregnancies, that each 1000 sterilisations prevent 7.6 maternal deaths-ie, 242 maternal deaths will be averted by these 31 781 sterilisations. The cost of quinacrine for two insertions is less than US$1. This procedure represents our most cost-effective way of lowering maternal mortality.

Quinacrine pellets were provided by Mother and Child International Geneva We thank Dr Phan Trinh International Cooperation Department, National Committee for Population and Family Planning, Hanoi) for guidance and encouragement; Dr Elton Kessel and Dr Stephen Mumford for review of the paper, helpful suggestions, and technical assistance; and Ms Irene Rosenfeld for editorial assistance

References

1 United Nations Population Fund Vietnam: programme review and strategy development report New York: UN Population Fund, 1990
2 Ross JA Sterilization: past, present, future New York: Population Council, 1991 Working papers no 29
3 Central Census Steering Committee Vietnam Population Census-1989 Hanoi: Socialist Republic of Vietnam, 1990
4 Kessel E, Mumford SD Potential demand for voluntary sterilizations in the 1980s: the compelling need for a nonsurgical method Fertil Steril 1982; 37: 725-33
5 Kessel E, Zipper J, Mumford SD Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy *Fertil* Steril 1985; 44: 293-98
6 Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol *Obstet* 1980; 18: 275-79
7 Zipper J, Rivera M, Cole LP, Brown E Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization Adv Contracept 1987; 3: 255-61

8 Bhatt RV, Aparicio A, Laufe LE, Parmley TH, King TM Quinacrine-induced pathologic changes in the fallopian tube Fertil Steril 1980; 33: 666-67

9 Merchant RN, Doctor VM, Thaku SS, et al Clinico-pathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets Adv *Contracept 1986;* 2: 79-90

10 El-Kady AA, Mansy MM, Nagib HS, Kessel E Histopathologic changes in the cornual portion of the fallopian tube following single transcervical insertion of quinacrine hydrochloride pellets Adv *Contracept* 1991; 7: 1-9

11 Merchant RN, Prabhu SR, Kessel E Clinicopathologic study of fallopian tube closure by dose and transcervical insertion to hysterectomy interval of quinacrine pellets Int J Fertil (in press)

12 Mumford SD, Kessel E Sterilization needs in the 1990s: the case for quinacrine nonsurgical female sterilization *AmJ Obstet Gynecol 1992;* 167: 1203-07

13 Mumford SD, Kessel E Was the Dalkon shield a safe and effective IUD? The conflict between case-control and clinical trial study findings Fertil *Steril* 1992; 57: 1151-76

14 Clak J, Hahn FE Quinacrine (Atebrin): mode of action *Science* 1967; 156: 655-56

15 DeStefano F, Greenspan JR, Dicker RC, Peterson HB, Strauss LT, Rubin GL Complications of interval laparoscopic tubal sterilization *Obstet Gynecol* 1983; 61: 153-58

16 Agoestina T, Kusuma I Clinical evaluation of quinacrine pellets for chemical female sterilization Adv Contracept 1992; 8: 141-51

17 Mishell DR Jr Intrauterine devices: benefits and risks In: Mishell DR Jr, Brenner PF, eds Management of common problems in obstetrics & gynecology, 2nd ed. Oradell, New Jersey: Medical Economics Books, 1988: 638-45

18 Peterson HB, Lubell I, DeStefano F, Ory HW The safety and efficacy of tubal sterilization; an international overview Int J Gynaecol *Obstet* 1983; 21: 139-44

19 Bhatt RV Camp laparoscopic sterilization deaths in Gujarat State, India 1978-80 Asia-Oceania J Obstet Gynaecol 1991; 17: 297-301

20 Chaturachinda K The use of the laparoscope in rural Thailand Int J Gynaecol *Obstet* 1980; 18: 414-19

21 Indian Council of Medical Research (ICMR) Collaborative study on sequelae of tubal sterilization New Delhi: ICMR, 1982

22 Rosenberg MJ, Rochat RW, Akbar J, et al Sterilization in Bangladesh: mortality, morbidity, and risk factors *Int J Gynaecol Obstet 1982;* 20: 283-91

23 Bhiwandiwala PP, Mumford SD, Feldblum PJ A comparison of different laparoscopic sterilization occlusion techniques in 24,439 procedures *Am3* Obstet Gynecol 1982; 14: 319-31

24 Layde PM, Peterson HB, Dicker RC, DeStefano F, Rubin GL, Ory HW Risk factors for complications of interval tubal sterilization by laparotomy *Obstet Gynecol* 1983; 62: 180–84.

25 Blake DA, Dubin NH, Diblasi MC, Parmley TH, Stetten G, King TM Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride In: Zatuchni Gl, Shelton JD, Goldsmith A, Sciarra JJ, eds Female transcervical sterilization Philadelphia: Harper and Row, 1983: 71-88

26 Dubin NH, Parmley TH, Diblasi MC, et al Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent In: Zatuchni Gl, Shelton JD, Goldsmith A, Sciarra JJ, eds Female transcervical sterilization Philadelphia: Harper and Row, 1983: 60–70.

27 Steck EA Chemotherapy of protozoan disease, vol III Washington DC, Walter Reed Army Institute of Research US Government Printing Office, 1972

28 Franks AL, Beral V, Cates W, Hogue CJR Contraception and ectopic pregnancy risk. *Am J* Obstet *Gynecol* 1990; 163:1120–23.

29 World Health Organization Maternal mortality: rates and ratios, 3rd ed Geneva: World Health Organization, 1991: 37

Fertility and Sterility 2001;75:830-31.

Quinacrine: non surgical female sterilization

Atlaf Bashir

Mother and Child Welfare Association, 18-Gulzar Colony, Near Passport Office Faisalabad (38000) Pakistan

Abstract

Non surgical sterilization was performed on 2100 women in Faisalabad by a single insertion of 7 pellets (252 mg) of quinacrine hydrochloride through IUCD inserter. **During one year follow-up only 85 pregnancies (4%) were recorded. No serious complications or side-effects were reported,** Although the study is **of** a short **duration and of limited follow-up, it clearly shows** that **quinacrine tubal** occlusion is **a highly** acceptable **(84.1%) effective** (96%) **and an inexpensive method of contraception which has very few side effects (6.8%)** and negligible **chances of ectopic pregnancy.**

Introduction

Over the last two decades, couples undergoing sterilization has increased dramatically from 15 million to over 100 million, Voluntary sterilization if the most prevalent and effective method of fertility control in the world.

Pakistan Demographic and Health Survey 1990-91 (PDHS) demonstrates that 69.6% of married women knew about female sterilization as an effective method of contraception. Sixty-two percentage knew about the pills, IUD (51.6%), injectable (62.1%) and male sterilization (22.2%). The same *survey* shows that 4.2% of currently married non-pregnant woman had undergone sterilization, while only 0.8% were using pills, 1.5% IUD and 0.9% injectable. When asked about the preferred method of contraception for future use, the following responses were given: 18.9% of currently married non-contracepting women showed desire to undergo sterilization within the next 12 months **14.5%** opted for pills, 8.7% for IUD and 17.5% for injectables. These data indicate that female sterilization can be promoted as an acceptable and effective method of family planning in our country.

Pakistan is the ninthmost populous country in the world with officially quoted growth rate of 3.2%. There is an increase in the demand for sterilization; preference being for female sterilization, This demand far exceeds the facilities to provide services, especially in the rural areas where 70% of our population lives. The case for family planning, especially when it comes to maternal and child health, is very convincing as most maternal deaths are potentially preventable by reducing high risk pregnancy and unsafe abortions .The author and many researchers are citing TBAs as the main source of providing important information about the procedure. The fact that many women are afraid of operative procedure led to the popularity of quinacrine non-surgical tubal occlusion. Female sterilization using conventional techniques are always a major surgical procedure . Injuries to the abdominal viscera, blood vessels and morbidity is difficult to avoid during surgical manipulation. Surgical sterilization cannot be

offered on large scales because most procedures require highly trained manpower. During recent years, tubal occlusion emerged as an important option for women who want to permanently limit their ability to reproduce. The promising approach is trans-cervical insertion of pharmacologically active agents to produce tubal occlusion, as majority of women are afraid of surgery. Non-surgical procedure helps to avoid criticism from the extended family as most women do not want to tell their relatives about sterilization. Many chemical agents, strong caustics, sclerosing agents, granuloma producing agents, cytotoxic agents and tissue adhesives have been tested and tried for tubal occlusion. The most promising results have been shown by quinacrine.

Historical Background

Initially (1973) 2-4 ml of 30% aqueous suspension of Quinacrine was used transvaginally in proliferative phase of 2 consecutive cycles which induced tubal occlusion in 95% of 134 women. Zipper and his colleagues later used 3 instillation, which resulted in pregnancy rate of almost 10%. These findings were substantiated by other investigators, Zipper suggested that quinacrine Hcl pellets should be used as they prolong the contact of drug with tubal ostia and thus increase the probability of occlusion. The drug in pellet form will not exert pressure in the uterine cavity to risk rapid intravascular absorption causing toxic psychosis. Two insertion of quinacrine pellets with a gap of one month has been reported with life time failure of 5 % No operative mortality or serious morbidity has been reported.

Quinacrine pellets are cylindrical in shape with 0.35 cm diameter and 0.5 cm in length, Seven pellets containing a total dose of 252 mg are introduced into uterine cavity. Quinacrine diffuses in fallopian tube and causes damage and fibrosis limited to cornual area of the uterus and interstitial potion of fallopian tube. It has been demonstrated that, quinacrine causes subepithelial hyalinization and scarring with involvement of both the lamina propria and muscularis of the tubes, Non-surgical female sterilization using quinacrine was started in Faisalabad in 1990. This report is based on our experience with 2100 cases in one year using single insertion,

Material / **Method**

The women of reproductive age were motivated by the author, TBAs, LHVs and doctors, through street camps in rural and urban areas, The women were thoroughly examined to rule out any medical problems and pelvic pathology (e.g., PID adnexal masses, tumor of reproductive organs and uterine anomalies). They were explained the minor side effects and possible failure of the method, After screening, the women were advised to come during proliferative phase of menstrual cycle. At this time quinacrine 7 pellets were inserted into uterine cavity with the help of sterilized Copper-T IUD inserter. She was advised to come back if she had any problem like severe pain, bleedingP/V or missed period. TBA/LHVs were also instructed to have regular contact with their clients and to immediately report in case of complication.

Fertility and Sterility 2001;75:830-31.

Table 1. Comparison of women regarding surgical and non-surgical sterilization

Month (1990)	Quinacrine	Trans-abdominal tubal ligation	Trans-vaginal tubal ligation
January	47	8	6
February	40	15	18
March	177	5	18
April	173	6	16
May	291	9	2
June	260	11	9
July	306	9	13
August	292	12	7
September	276	11	37
October	80	19	38
November	33	45	23
December	117	14	48
TOTAL	2100	167	235

Table 2. Minor side effects observed in women

Complaints	No. of cases	Percentage
Pain in lower abdomen	10	2.22
Amenorrhoea for 2-3 months	5	1.11
Menorrhagia	4	0.88
Backache	3	0.66
Secondary amenorrhea	2	0.44
Feeling of heaviness	2	0.44
Irregularity of menses	2	0.44
Bleeding P/V for one month	1	0.22
Dyspareunia	1	0.22
Itching	1	0.22
TOTAL	31	6.85

Results

During 12 months (January to December 1990), 2100 women residing in rural and urban areas of Faisalabad got quinacrine insertion. The number of quinacrine acceptors and those opting for trans-abdominal and trans-vaginal tubal ligation is shown in Table 1, which indicates high acceptance of quinacrine' (84%), trans-vaginal (9.4%) and trans-abdominal (6.6%)

About 7% of women showed minor side effects in a sample study of 450 women given in Table 2. Vaginal discharge for 5-10 days was reported by all women. The next major complaint was pain in lower abdomen for l-6 days, amenorrhoea for 2-3 months, irregular menstruation, menorrhagia, backache, feeling of heaviness, dyspareunia and itching. Presently, 85 women (4%) have reported pregnancy after varying period of quinacrine insertion as shown in Table 3. Maximum number of cases are reported six months after insertion. Table 4 shows the fate of these pregnancies resulting after quinacrine insertion.

Discussion / Conclusion

The high acceptance of female sterilization (84%) particularly by younger age group is very encouraging, The fact that only a few women come for second insertion of quinacrine pellets encouraged us to start trial on single dose insertion of quinacrine. Another reason for single dose quinacrine insertion, is inflammation, fibrosis and consequent damage to fallopian tube that had occurred with single dose is probably not affected by the second dose. Clinically, the need for multiple insertions of quinacrine pellets for the achievement of acceptable efficacy has not been demonstrated. A single insertion trial is a high priority for fertility research.

In comparing the risk of ectopic pregnancy after surgical versus quinacrine sterilization, it is estimated that at the end of the first year, surgical methods have an ectopic pregnancy rate of approximately 0.75 per thousand procedures, This rises to approximately 2.15 per thousand procedures at the end of the second year. The ectopic pregnancy rate is approximately 0.24/1000 with quinacrine sterilization at the end of the first year and 0.34 per thousand at the end of the second year. These rates are one-third to one-sixth of those seen with surgical procedures. The lower ectopic pregnancy rate of the quinacrine pellet method and the virtual absence of reported serious complications of the method to-date would make quinacrine sterilization an acceptable method. The failure rate quoted by various workers is 0.5 % for surgical sterilization and 5% for quinacrine sterilization. In our studies, failure rate was 4%

Zipper, the developer of the method has found that Antiprostaglandin potentiate the effect of quinacrine possibly by relaxation of sphincter action of muscle at Ostia. A trial by giving 400mg Brufen 1/2 hour before insertion may help to enhance the effect and reduce the failure rate. Recently, brufen pellet (50mg) has been developed which is placed in uterus through the same inserter as quinacrine and reported failure rate is less than 1%. We are now using brufen tablet before inserting quinacrine. No serious complications or side effects have been reported to-date in over 1000 insertions of quinacrine pellets. Earlier studies with a liquid slurry of 1500 mg of quinacrine did produce a 2% rate of transient toxic psychosis shortly after quinacrine instillation, but this has not been reported with the use of quinacrine pellet. Although our study is of short duration and follow up, it has shown a high acceptance (84 %0, very few side effects

Table 3 Interval of between quinacrine insertion and pregnancy

Pregnancy reported	No. of cases
After 2 month quinacrine insertion	12
After 4 month quinacrine insertion	14
After 6 month quinacrine insertion	23
After 8 month quinacrine insertion	21
After 10 month quinacrine insertion	8
After 12 month quinacrine insertion	6
Unknown quinacrine insertion	1
TOTAL	85

Table 4. **Fate** of pregnancy resulting after quinacrine **insertion**

Fate of pregnancy	Cases	Percentage
Pregnancy continued	31	36.47
D & C with vaginal tubectomy	52	61.17
D & C	1	1.18
Unknown	1	1.18
TOTAL	85	100.00

Fertility and Sterility 2001;75:830-31.

(7%), high efficacy (96%) and less chances of ectopic pregnancy (0%).

Women have always risked their lives to avoid unwanted pregnancy. Birth rate, fertility rate, maternity mortality, infant mortality, family planning and contraception are all taboo topics in Pakistani society and politics. Since the country's independence, 45 years ago, only a half hearted attempt has been made to introduce family planning. No success has been made in reducing birth rate. The family size is 6-7 children and is highest in Southern Asia. Popuhtion is said to double in 22 years from 100 million to 200 million, Pakistan has very poor family record in Asia (i.e., only 1/5 of the country is covered by family planning services).

In our joint family system, most women do not like their relatives and friends to know that they are using family planning method. There is a great need for the government to approve a method of non-surgical sterilization and to offer family planning to masses at a very low cost, with minimum complications.

FERTILITY AND STERILITY
Copyright © 1993 The American Fertility Society

Vol. 69. No. 2. February 1993
Printed on acid-free paper in U.S.A.

Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization

Adel A. El Kady, F.R.C.O.G.*
Hany S. Nagib, M.Sc.*†
Elton Kessel, M.D.‡§

Boulak El-Dakrour Hospital, Giza, Egypt, and Oregon Health Sciences University, Portland, Oregon

Objective: To investigate the rates of tubal occlusion, pregnancy, and side effects of repeated, monthly transcervical insertions of 252 mg quinacrine as pellets.

Design: Clinical trial among 159 reproductive age women receiving two monthly transcervical insertions of 252 mg of quinacrine followed by hysterosalpingograms (HSGs) 1 month after last insertion and an additional monthly insertion among women without evidence of bilateral tubal occlusion. Contraception of women's choice provided until bilateral tubal occlusion achieved, and surgical sterilization provided for women failing to achieve bilateral tubal occlusion after third quinacrine insertion, Women were followed for at least 24 months for evidence of pregnancy or side effects.

Results: Among the 159 women completing the protocol, 73% had evidence of bilateral tubal occlusion by HSGs after two insertions of quinacrine pellets and 94% after a third insertion. These 149 women were followed for 24 months without a pregnancy failure or serious side effect.

Conclusion: Transcervical applications of quinacrine as pellets have potential for safe, effective, inexpensive, and easily deliverable female sterilization. Fertil Steril 1993;59:301 4

Key Words: Contraception, nonsurgical female sterilization, quinacrine

Female sterilization has become the world's most prevalent method of fertility regulation (1). In developing countries, the demand for female sterilization usually exceeds the ability of the countries to provide this service; therefore, the development of a rapid, effective, and safe nonsurgical method that can be performed by paramedical personnel remains a high priority. Such a method could save the lives of countless women (2).

For many years, Zipper and his associates (3, 4) have evaluated the transcervical application of quinacrine hydrochloride as a liquid slurry for effecting permanent sterilization. This work led to the development of quinacrine hydrochloride pellets, a delivery system designed to bring the chemical into prolonged contact with the tubal ostia and avoid accidental intravascular administration (5).

The relative safety and efficacy of surgical methods and the nonsurgical quinacrine pellet method of female sterilization have been reassessed (6). Although experience with the quinacrine pellet method is limited, it appears to have advantages for both developing and industrialized countries. The method can be delivered in any clinical service capable of performing an intrauterine device (IUD) insertion.

Its potential to raise contraceptive prevalence and avoid unwanted high risk pregnancies is its greatest advantage, especially in countries with high maternal mortality. The pregnancy failure rate after three insertions of 252 mg quinacrine in lo-minute releasing pellets has been reported as 3.1% at 1 year

Received April 16, 1992; revised and accepted October 27, 1992.
* Department of Obstetrics and Gynecology, Boulak El-Dakrour Hospital.
† Present address: Victoria Hospital, Blackpool, United Kingdom.
‡ Department of Public Health and Preventive Medicine, Oregon Health Sciences University.
§ Reprint requests: Elton Kessel, M.D., 6100 NE Mineral Springs Road, Carlton, Oregon 97111.

Fertility and Sterility 2001;75:830-31.

(5) and 3.7% at4 years (7). Zipper and his co-workers (8) found a failure rate of 2% at 1 year in a two-insertion study using 100-minute releasing pellets. Recently, he added an antiprostaglandin, diclofenac 50 mg, to each of two insertions of quinacrine pellets and found a further decline in failures as well as fewer mild side effects (9).

In a group of women scheduled for hysterectomy, we had previously studied the sequence of histopathologic changes in the cornual portion of the tube subsequent to exposure to quinacrine and confirmed the fact that quinacrine can effectively produce tubal fibrosis and occlusion (10). In this study, the safety and efficacy of the quinacrine pellet method of female sterilization were assessed when two intrauterine insertions of quinacrine pellets are followed by a third insertion if tubal patency was evident on hysterosalpingogram (HSG).

MATERIALS AND METHODS

From January 1988 to April 1989,172 women of reproductive age giving informed consent at our outpatient clinic at Boulak El-Dakrour Hospital, Giza, Egypt, were admitted to this study that was approved by the Hospital Management Committee. Women with the following conditions were excluded from the study: **[1]** suspected pregnancy; [2] preexisting systemic or medical conditions and hemoglobin < 10 g%, unless referred by an internist; [3] evidence of significant pelvic pathology: pelvic inflammatory disease, adnexal masses, tumors, suspicion of malignancy of the reproductive organs and uterine anomalies; [4] history of psychiatric disease or epilepsy; [5] if concurrent surgery was anticipated.

The study protocol included two insertions of 252 mg of 30-minute releasing quinacrine pellets a month apart in the proliferative phase (days 5 to 18) of consecutive menstrual cycles. This was followed by HSG a month later. Cases with one or both tubes patent were offered a third insertion and repeat HSG a month later. Another contraceptive of the women's choice was offered until hysterosalpingo graphic evidence of bilateral tubal closure. Follow-up visits were scheduled at 1, 3, 6, 12, and 24 months after last HSG and at any time that complications or complaints occurred. Three women failed to complete the required quinacrine insertions, and 10 women living outside the catchment area of the hospital were lost to follow-up, leaving 159 women remaining for analysis.

Of these 159 women followed for 24 months, their mean age was 36.9 years (range, 34 to 39, except one 22-year-old cardiac patient) and mean parity 7.4 livebirths (range, 2 to 13). In 11 postpartum women the procedure was performed after the uterus had completely involuted or at least 8 weeks after delivery. In 18 postabortion cases, the procedure was performed after the women had had a normal menstrual period. In women who were using an IUD, the devices were removed before the procedure, and any possibility of pregnancy was ruled out.

The quinacrine pellet is cylindrical in shape and has a diameter of 0.32 cm and contains 36 mg of quinacrine hydrochloride. The pellets were custom manufactured by Sipharm, Sissein, Switzerland. Seven quinacrine pellets (252 mg) were prepacked and sterilized in Copper-T IUD (Ortho Pharmaceutical LTD, Don Mills, Ontario, Canada) inserters. Aseptic precautions were used for inserting the quinacrine pellets into the uterus. The technique of insertion is similar to the insertion of a Copper-T device. Another seven quinacrine pellets were deposited in the uterus after the next menstrual period. Hysterosalpingogram was carried out 1 month after the second quinacrine insertion to test tubal blockage. If one or both fallopian tubes were still patent, a third quinacrine insertion was made. If there was still tubal patency after the third insertion, the patient was advised to choose another method for contraception. All HSGs were carried out under the intensifying screen using water soluble media. Additional contraceptives of the women's choice were prescribed from the first insertion to **1** month after the last insertion, to protect against unwanted" pregnancy because abortion is illegal in our country.

RESULTS

Contraceptive use in the 3 months before admission in the study and in the interval after quinacrine pellet insertions until the last HSG is shown in Table 1. Menstrual data were recorded before quinacrine insertion and at each follow-up visit. Reported menstrual changes largely disappeared by the 6-month follow-up visit, although most women with previous heavy or prolonged menses experienced a continued decrease. Intermenstrual bleeding occurred in 21 women (13.2%) after quinacrine. This was of short duration and never severe. All 42 women (26.4%) experiencing amenorrhea recovered spontaneously within 5 months.

Table 2 shows complications and complaints related to the insertion procedure reported within 10 days of any insertion. Pain and bleeding were mild.

VIII-67

Table 1 Contraceptive Use by 159 Women Before and After Quinacrine Pellet Insertions, Boulak El-Dakrour Hospital, Giza, Egypt, 1988 to 1989

	No. of women
Before quinacrine	
None	40 (25.2)*
IUDs	58 (36.5)
Orals	53 (33.31
Condoms	4 (2.5)
Foam	4 (2.51
Total	159 (100.0)
Between quinacrine and last HSG	
Orals	98 (61.6)
Abstinence	37 (23.3)
Condoms	24 (15.1)
Total	159 (100.01

* Values in parentheses are percentages.

Fever cases had a temperature above 38.2°C; none required antibiotics.

The effect of uterine length and presence of traumatic bleeding at insertion on tubal closure as compared with all cases is shown in Table 3. Five women (4.2%) with uterine length ≤ 8 cm had one or both tubes patent on HSG after two or three insertions, as did five (12.8%) with uterine length > 8 cm (Fisher's exact test, P = 0.09). No woman without bleeding at insertion remained with a patent tube after two or three insertions, whereas 10 (9.3%) with traumatic bleeding did have one or both tubes patent (Fisher's exact test, $P = 0.02$). No pregnancies occurred among the 149 women with both tubes occluded who were followed for a minimum of 2 years, without additional contraception.

DISCUSSION

Only minor complications and complaints had been reported. Variable periods of amenorrhea occurred in 26.4% of the women, a higher figure than that found by Zipper et al. (16.5%) in a three-insertion study (8). Menstruation restarted spontaneously. Women with previous heavy and prolonged periods often experienced a decrease in the amount and'duration of flow. Other complications (pelvic pain, bleeding, and discharge) were reported by a minority of cases and were transient, all disappearing within several days after the procedure.

Hysterosalpingogram performed 1 month after the second quinacrine insertion revealed tubal occlusion in 73% of cases. Giving a third quinacrine insertion to those with patent tubes improved the tubal occlusion rate (tested by HSG 1 month later) to 94%.

Table 2 Complications and Complaints Among 159 Egyptian Women After Intrauterine Insertion of Quinacrine Pellets

	No. of women
Complication/complaint •	
None	134 (84.3) †
Pelvic pain	13 (8.21
Bleeding	13 (8.2)
Fever	4 (2.6)
Transient vertigo	4 (2.6)

* Nine women had more than one complication/complaint.
† Values in parentheses are percentages.

This differs from the prehysterectomy study finding of Merchant and colleagues (11) that the number of insertions does not affect tubal occlusion; however, her study involved quinacrine pellet insertions 1 week apart.

All the women with occluded tubes had been followed for at least 2 years without additional contraceptives. No case of pregnancy had been reported, which speaks against the possibility of recanalization after 1 year suggested by Guzman et al. (12). A possible explanation for this unexpected high level of efficacy is the prescription of a contraceptive through 1 month after the last insertion. Merchant and coworkers (Merchant RN, Prabhu SR, Kessel E, unpublished observations) noted in a prehysterectomy study higher closure rates with longer insertion to hysterectomy intervals, suggesting that several weeks are required for the tubal inflammatory process to proceed to fibrosis and closure in some women.

Our data suggest that the greater the uterine length the lower the closure rate by quinacrine. The tubal occlusion rate was 95.8% in cases with 8 cm or less uterine length compared with 87.2% in cases with greater length. This finding needs confirmation in a larger number of subjects. The occurrence of minimal bleeding during the insertion procedure re-

Table 3 Closure of Both Tubes on HSG by Uterine Length, by Bleeding at Insertion, and All Cases After Two and After Two or Three Insertions of Quinacrine Pellets Among 159 Egyptian Women

	Total cases	Closures after two insertions	Closures after two or three insertions
Uterine length ≤ 8 cm	120	94 (78.3)*	115 (95.8)
Uterine length > 8 cm	39	22 (56.4)	34 (87.2)
No bleeding	52	42 (80.8)*	52 (100.0)
Bleeding at insertion	107	74 (69.2)	97 (90.7)
All cases	159	116 (73.0)	148 (93.71

• Values in parentheses are percentages.

duced the closure rate by HSG from 100% to 90.7%, a finding consistent with that of Mullick et al. (13) and Merchant et al. (11) who also found that the presence of blood in the uterine cavity lowers efficacy.

Perforation of the uterus on quinacrine pellet insertion did not occur in our study. In monkey studies, Dubin et al. (14) found monkeys survived intraperitoneal insertion of quinacrine pellets at seven times the equivalent human dose. Mullick (Mullick B, personal communication) had two perforations with deposit of 252 mg of quinacrine in the peritoneal cavity. The women experienced transient lower abdominal pain, and one woman had tinnitus for 3 days. Neither woman required hospitalization. No life-threatening complication has been reported in over 28,000 quinacrine pellet sterilization cases in international studies (15).

The quinacrine pellet system is a simple, blind method that has great potential in the area of nonsurgical sterilization. Developing countries, in particular, should have the courage to initiate trials of this promising method of nonsurgical female sterilization as a high priority in fertility research.

Acknowledgments. We thank Stephen D. Mumford, Dr. P.H. , of the Center for Research on Population and Security, Research Triangle Park, North Carolina, for his critical review of the manuscript and Ms. Irene Rosenfeld for her editorial assistance. Mother and Child International, Geneva, furnished the supply of quinacrine pellets.

REFERENCES

1. Kessel E, Mumford SD. Potential demand for voluntary female sterilization in the 1980s: the compelling need for a nonsurgical method. Fertil Steril 1982;37:725-33
2. Kessel E. Prospects for nonsurgical female sterilization. Int J Gynaecol Obstet 1989;29:1-4.
3. Zipper J, Stachetti E, Medel M. Human fertility control by transvaginal application of quinacrine on the fallopian tube. Fertil Steril 1970;21:581-9
4. Zipper J, Stachetti E, Medel M. Transvaginal chemical sterilization. Contraception 1975;12:11-21
5. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 1980;18:275-9
6. Kessel E, Zipper J, Mumford SD. Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy. Fertil Steril 1985;44:293-8
7. Bhatt R, Waszak CS. Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization. Fertil Steril 1985;44:303-6
8. Zipper J, Cole LP, Rivera M, Brown E, Wheeler RG Efficacy of two insertions of loo-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization. Adv Contracept 1987;3:255-61
9. Kessel E, Zipper J, Mumford SD. Surgical vs nonsurgical female sterilization. MCI Newsletter 1991;16:2-3
10. El Kady AA, Mansy MM, Nagib HS, Kessel E. Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets. Adv Contracept 1991;7:1-9
11. Merchant RN, Doctor VM, Thaku SS, Sinha M, Jhaveri CL, Kessel E, et al. Clinico-pathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets. Adv Contracept 1986;2:79-90
12. Guzman-Serani R, Bernales A, Cole LP. Quinacriqe hydrochloride pellets: three year follow-up on a nonsurgical method of female sterilization. Contracept Deliv Syst 1983;5:131-5
13. Mullick B, Mumford SD, Kessel E Studies of quinacrine and of tetracycline for non-surgical female sterilization. Adv Contracept 1987;3:245-54
14. Dubin NH, Parmley TH, Diblasi MC, et al. Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, editors. Female transcervical sterilization. Philadelphia: Harper and Row, 1983:60-70
15. Kessel E. Cost-effectiveness of Safe Motherhood programs: the role of the quinacrine pellet method of nonsurgical female sterilization. MCI Newsletter 1992;20:2-3

VIII-69

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

ESC

SECOND CONGRESS OF THE EUROPEAN SOCIETY OF CONTRACEPTION

UNDER THE AUSPICES OF

The Ministry of Health,
Welfare and Social Securities
The General Secreteriat of
Research and Technology
The National Drug Organization

PROGRAM
BOOK OF ABSTRACTS

6-9 MAY 1992
ATHENS - GREECE

ASTIRYALACE-VOULIAGMENI
NAFSIKAHOTEL

VIII-56

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

40 **NON SURGICAL FEMALE STERILIZATION WITH DUINACRINE PELLETS**

Randit Ljilјana. Departrent of Obstetrics and Gynecology University of Ri jeka. Ri jeka, Croatia.

Surgical sterilization is well known and very effective fertility regulation method. Since all the surgical procedures are relatively complicated, research is focused on discovery and testing of various non surgical female sterilization methods. Among these methods only cherical sterilization with Quinacrine hydrochloride pellets has entered in a preliminary clinical use.

From February 12, 1988, till March 1, 1992. we have accomplished 120 sterilizations with Puinacrine in women aged 37.2 ± 2.0 years (mean ± SD). After two consecutive renstrual periods, with inserter for "T" intrauterine contraceptive device; we have placed highly in the uterine fundal area 252 mg of Puinacrine hydrochloride in pellets of 36 mg each. One or two months after the second Quinacrine application, hysterosalpingography (HSG) was perforred and complete bilateral proximal tubal occlusion wasdemonstrated in all but two cases exarined. For each Quinacrine application, a s well as for HSG, women were hospitalized for one day, All the procedures were perforred without anesthesia and without cervical dilatation; there were no complications. The only change women have noticed was less than usual renstrual bleeding, following intrauterine Quinacrine application. On thr'total of 3227 months of use there were five intrauterine. pregnancies resulting in Pearl's index of 1.86,

According to our results as well as to those published in the literature, it seems that cherical sterilization with Quinacrine pellets could be the method of choice for great majority of women aged 35 years or sore who have decided not to have more children,

YIII - 57

Asia-Oceania J. Ohstet. Gynaecol. Vol. 17, No. 4: 297-301 1991

Camp Laparoscopic Sterilization Deaths in Gujarat State, India, 1978-1980

Rohit V. Bhatt

Department of Obstetrics and Gynaecology, Baroda Medical College and B. M. Amin General Hospital, Bnroda, India

Abstract

An early experience of camp laparoscopic sterilization in Gujarat State, India, resulted in 22 deaths among 106,500 women undergoing the operation during 1979 and 1980. Increased risk of death was seen when larger numbers of procedures were performed by year or month of year. The least experienced surgeons had the highest case-fatality rate. Improvised settings (i.e., school buildings) exacerbated the risk of death, as did advanced age, and, to a lesser extent, high parity. Errors in clinical judgment were identified in some fatal procedures. A system of health audit of large sterilization programs is needed.

Key words: sterilization deaths, laparoscopic sterilization, camp sterilization

Introduction

Female sterilization is by far the most prevalent contraceptive method used in India. Only breastfeeding has a greater demographic impact. From 1978 to 1982, female sterilizations increased in the entire country from almost 1 to over 3 million before declining, and in Gujarat State alone, they grew from 143 to 198 thousand before leveling off.[1] The slackening in recent years may be related to reports of deaths at the camps where many women appear for this procedure to be performed by a traveling surgical team. Since 1980, laparoscopic surgery has become popular both with women requesting sterilization and their doctors. Compared to minilaparotomy, the operating time is shorter for the surgeon as is the recovery period for the patients. It is widely believed, however, that sterilization deaths are attributable to the excessive numbers of these procedures performed daily, especially in laparoscopic sterilization camps.[2] Government regulations imposing limits ate frequently ignored. On the other hand, there are reports of camps doing very large numbers of sterilizations without deaths, and with only reasonable numbers of complications.[3-5]

To identify programmatic and clinical risk factors in these camps, we analyzed 22 laparoscopic deaths among 106,500 women undergoing sterilization in camps in Gujatat State, India, from 1978 to 1980, giving a mortality of 20.65 per 100,000 procedures. There were three additional deaths after 42 days of this surgery that could not be attributed to these

Received: July 18, 1991
Reprint request to: Dr. Rohit V. Bhatt, 1, Shivani Society, Vasana Road, Baroda 390015, India

procedures. In contrast, recent experience in the United States reports a death rate of 1.5 per 100,000 hospital sterilization procedures, mostly performed by laparoscopy.[6]

This paper analyzes data from an earlier program of laparoscopic camp sterilizations in Gujarat State. The skill of their surgeons has since improved, but insight into the problems that arose and how they were addressed can be of considerable benefit to those who are initiating similar camps in other states and countries.

Methods

Laparoscopic sterilization camps are organized by government health personnel to take place in district hospitals, primary health centers, and school buildings. Counseling, screening examinations and follow-up care are the responsibility of health personnel in the camp area. The operations we evaluated were performed by ten gynecologists who formed 10 teams with their surgical nurses and other assistants. These teams traveled to the camp locations, with laparoscopic and other surgical equipment and supplies, performed the procedures in one or a few days and returned to their home base.

The surgical equipment included single-puncture operating laparoscopes with silicone rubber band applicators, Veress needles, trocar and cannulae, light source and air pumps for pneumoperitoneum. In school buildings, any available table was used for operating, with bricks placed at the foot to produce a Trendelenburg position. Primary health centers and district hospitals were equipped with standard operating tables.

All procedures were performed under local aaesthesia, after premedication. An anesthetist was seldom part of the surgical team. The local anesthetic used was 3-5 ml of 1% lignocaine infiltrated at the site of the periumbilical incision. Pneumoperitoneum was produced with 500–3,000 ml of atmospheric air.

Gloves were changed by team members after each procedure, but gowns only at the time of rest breaks. Instruments were supposed to be sterilized with formalin vapor or Cydex solution (Johnson and Johnson, Bombay) for at least 10 minutes. All deaths were investigated by a review committee of which the author was a member. Their scrutiny revealed that these precautions were frequently inadequate because of the short intervals between them. It was also evident that patients were often not monitored for pulse and blood pressure during surgery.

Results-Clinical

The cause and timing of deaths is shown in Table 1. Of the 5 occurring on the operating table, 2 were reported as due to lignocaine sensitivity, 2 to cardiac arrest and 1 to air embolism. Time of other deaths ranged from 1 to 20 days. The 2 tetanus cases were postpartum sterilizations of mothers following home delivery and may not have been due to the operation. On the other hand, errors in clinical judgment were evident. Bowel injury caused infection in 4 cases and uterine perforation in 1; these women were not hospitalized. The death due to hemorrhage involved laceration of the mesentery, apparently not

Table 1. Cause, time and number of camp laparoscopic sterilization deaths in Gujarat State, India, 1978-1980

Cause of death	Time of death	No. deaths	No. autopsied
Air embolism	On operating table	1	1
Lignocaine sensitivity	On operating table	2	1
Cardiac arrst	On operating table	2	0
Hemmorrhagic shock	10 hours	1	1
Pulmonary embolism	16 hours	1	0
Peritonitis (4 bowel injury)	2-8 days	9	7
Septicemia	5–20 days	4	3
Tetanus	> 15 days	2	0

visualized through the laparoscope.

Results-Programmatic

Table 2 shows the pattern of laparoscopic camp sterilizations and deaths by age and number of living children of the women and by year, month of year and sterilizations per camp. There is a trend of increased risk of death by age and number of living children as an estimate of parity. The trend is strongest for age and, indeed, there were no deaths among women less than 30 years old with 4 or more living children, while there were 6 deaths among women older than 30 with fewer than 4 children. As expected, at greatest risk are women 30 or more years of age with 4 or more living children who accounted for 10 of the 22 sterilization deaths.

Table 2. Number of laparoscopic camp sterilizations, deaths and case fatality rate by age, number of living children, year, month of year, and sterilizations per camp in Gujarat State, India, 1978-1980

Variable	Sterilization	Death	Rate per 10^5
Age (years)			
<25	6,603	0	
26-30	52,822	9	17.0
31-35	35,674	9	25.2
36-40	9,904	4	40.4
41+	1,594	0	
Living children			
1	640	0	
2	25,240	3	11.9
3	36,636	9	24.6
4	37,275	8	21.7
5+	6,709	2	29.8
Year*			
1978-9	19,167	3	15.7
1979980	62,219	17	27.3
1980**	25,450	2	7.8
Month			
January	22,154	5	22.6
February	17,040	5	29.3
March	27,690	6	21.7
April-November	17,251	1	5.8
December	22,365	5	22.4
Sterilization per camp			
<50	23,430	3	12.8
50-100	20,650	6	29.0
101-200	35,795	8	22.3
200+	26,625	5	18.8

* Fiscal years April 1 through March 31
** April 1 through December 31

There was a tripling of the number of sterilizations in fiscal year 1980 compared to 1979, with a near doubling of risk of death. Camp sterilizations in India tend to occur mainly from December through March. This period avoids both the hot and rainy seasons and corresponds to a government sponsored campaign to meet targets set for each state by end of the fiscal year. There is a uniformly high risk of deaths in camps in this campaign season and a markedly reduced risk in the balance of the year.

Camps with SO-100 sterilizations each had a higher risk of 29 per 100,000 procedures compared to other sized camps. The reason is that in 1979-80, laparoscopy in a camp setting had just been introduced. The patient demand was greater than the availability of trained surgeons. Therefore, surgeons with lesser experience in laparoscopy were sent to small camps carrying out up to 100 procedures per day and more experienced surgeons were sent to places where the case load was high. Four of the 6 deaths occurring in camps with 50-100 operations each were attributed to sterilizations performed by surgeons with less than 6 months' experience in laparoscopic sterilization, and 4 of the 6 deaths occurred in operations in school buildings. A striking effect of experience on risk of camp laparoscopic sterilization death is reflected in Table 3.

Nevertheless, a marked increased risk of 71

Table 3. Number of camp laparoscopic sterilizations, deaths and case fatality rate by months of experience and number of sugeons in Gujarat State, India, 1978-1980

Experience (months)	Surgeons No.	Sterilizations No.	Deaths No.	Rate per 10^5
<6	3	9,220	5	54.2
6-12	3	24,560	8	32.6
13-24	2	35,520	6	16.9
25+	2	37,200	3	8.1

Table 4. Number of camp laparoscopic sterilizations and camps, average number of sterilizations per camp, deaths and case fatality rate by site of camps in Gujarat State, India, 1978-1980

Camp site	Sterilizations No.	Camps No.	Sterilizations per camp	Deaths No.	Rate per 10^5
District hospital	19,490	120	162	3	15.4
Primary Health Centre	74, 340	412	180	10	13.5
School building	12,670	62	204	9	71.0

deaths per 100,000 operations performed in school buildings is shown in Table 4. Four of the 9 deaths were in smaller camps of 50-100 sterilizations per camp, where less experienced surgeons were in attendance. But large camps in school buildings still appear to have an independent increased risk.

Discussion

The salient findings of the study are the association of risk of death with large numbers of sterilizations, evident in fiscal year 1980 and in the larger camps situated in school buildings. Advanced age appears as a risk factor. These are frequently high parity women who tend to be more anemic, and require careful preoperative screening and meticulous monitoring during surgery. They should be operated on only by the most experienced surgeons, such as those who performed fully one-third of the procedures with a risk of death to their patients of one quarter of surgeons with 6 to 12 months' experience. Camps are clearly not the place to train surgeons in laparoscopic sterilization, as observed in the extraordinary risk of women dying when their surgeons have less than six months' experience.

However, our analysis shows that even if school buildings were excluded as camp sites, and training in laparoscopic sterilization in camps ended, an unacceptable risk of death would remain in these facilities. There is evidence in this study and from investigations of these deaths that more of them could be prevented through improved surgical technique, including sterilization of equipment, and improved surgical judgment in the case of complications.

The need for speedy completion of the sterilizations is felt by the surgical teams who are anxious to return to their home base. The payment of fees to the surgeon per operation performed and the pressure by the local camp organizers to assure that women requesting the operation be served and government quotas be filled are additional factors contributing to unsatisfactory outcomes. Government regulations concerning number of sterilizations to be performed per surgical team per day in different types of camp facilities are largely ignored.

While reductions in risks in laparoscopic sterilization camps can be achieved through better training, sufficient experience and more suitable facilities, it is our opinion that the greatest need is for a system of medical audit of these services, to be performed by a panel of distinguished gynecologists. All deaths and cases of serious complications would be audited. Information to be reviewed by peers of the operating surgeons at a regular meeting arranged for this purpose would be gleaned from three records: first, a screening examination form (indicating that the women is not pregnant, severely anemic, hypertensive, or with pelvic infection), signed by the screening physician; second, a surgical complication form signed by the surgeon; and third, a 48-hour follow-up visit by a nurse, recording temperature, blood pressure and signs of wound infection. The confidential examination of such records would, we predict, markedly improve the quality of surgical services in camp sterilizations. At present, medical personnel responsible for these services work in the confidence that any complication related to poor medical practice will never be traced back to them as individuals nor will it ever affect their reputation among their peers. A system of medical audit would change this and

very likely encourage all health personnel involved in these camps to perform their duties in a more responsible manner. There is actually no substitute for such an audit if these surgical services are to be improved.

Acknowledgments

Irene Rosenfeld provided editorial assistance.

References

1. Ross JA, Rich M, Molzan JP, Pensak M. Family Planning and Child Survival: 100 Developing Countries. Center for Populations and Family Health, New York. 1988
2. Rai U. High sterilisation death toll. New Delhi: The Times of India, August 31, 1989
3. Bhatt RV, Engineer AD, Gupta S, et *al*. Evaluation of laparoscopic sterilisations in rural camps. Demography India 1988; 17: 148-160
4. Mehta PV. A total of 250, 136 laparoscopic sterilisations by a single operator. *Br J Obstet Gynaecol* 1989; 96: 1024-1034
5. Sheth SS, Desai VJ, Pawar A, Pawar V. India laparoscopic female sterilisation camps. *Lancet 1988;* ii: 1415-1416
6. Escobedo LG, Peterson MB, Grubb GS, Franks AL. Case fatality rates for tubal sterilisation in U.S. hospitals, 1979 to 1980. Am *J Obstet Gynecol* 1989; *160: 147-150*

Fertility and Sterility 2001;75:830-31.

Histopathologic changes in the cornual portion of the fallopian tube following a single transcervical insertion of quinacrine hydrochloride pellets

A.A. ELKADY (1), M.M. MANSY (2), H.S. NAGIB (1) and E. KESSEL (3)

(I) Department of Obstetrics and Gynecology, Boulak El-Dakrour Hospital, Giza, Egypt
(2) Lecturer in Pathology, Kasr EI-Aini Faculty of Medicine, Cairo University, Egypt
(3) Department of Public Health and Preventive Medicine, Oregon Health Sciences University, Portland, Oregon

Abstract

To study the sequence of histopathologic changes taking place in the comual portion of the fallopian tube subsequent to exposure to quinacrinc, 252 mg were inserted transcervically in 12 women awaiting hysterectomy for non-malignant conditions of the uterus. All patients who underwent surgery within ten days of insertion were found to have necrosis of the cpithclial lining and an acute inflammatory reaction. Later on, the changes observed included progressive absorption of the inflammatory cellular exudate, progressive fibrosis, with partial or almost complete occlusion of the lumen, and failure of regeneration of the cpithelial lining. Our results support other studies indicating that quinacrine can cffcctivcly product tubal fibrosis and occlusion.

Introduction

Considcrablc research has focused on tubal occlusion techniques involving the injection of pharmacologic agents and adhesive materials into the oviduct, either through the hystcroscopc or through a blind transcervical delivery system. tipper and associates have observed that quinacrinc has an occlusive effect on the intramural portion of the human fallopian tubes [1]. In spite of the cxtcnsivc clinical studies (2-6 and others], histopathological research on the changes that occur when quinacrine is placed into the uterus is scarce [7–9].

Davidson and Wilkins found that three out of the four patients who underwent surgery within one week of a single intrauterine instillation of a suspension of quinacrinc had lesions suggesting tubal inflammation [7].

Bhatt and hi colleagues studied the specific histologic effects upon the tubal ostia in 23 women undergoing hysterectomy 30 days after intrauterine insertion of a single

dose of 250 mg of quinacrine pellets. They divided the changes identified in the 23 hysterectomy cases into three groups: group 1 (16 cases), no identifiable damage to the fallopian tube; group 2 (6 cases), subepithclial hyalination and scarring involving both the lamina propria and the muscularis of the tube; group 3 (23 cases), destruction of the epithelium of the tube, as well as the changes seen in group 2 [8].

After a comprehensive study of the histologic changes in the fallopian tube following transcervical insertion of quinacrine hydrochloride pellets in 33 women undergoing hysterectomy, Merchant and colleagues found that 75.8% of the cases had occlusive changes which became progressively less marked on moving away from the uterine cavity. They also indicated that neither the number of insertions nor the place of deposition of the pellets (whether at the fundus or at the comual areas) affected the degree of tubal inflammation and fibrosis (9).

In this study the sequence of histopathologic changes taking place in the cornual portion of the fallopian tube between 3 and 25 days subsequent to a single transcervical insertion of 252 mg quinacrine hydrochloride as pellets is presented.

Materials and methods

Twelve healthy women of reproductive age awaiting a hysterectomy for prolapse or non-malignant lesions of the uterus agreed to participate in the study. The presence of pelvic inflammatory disease, adnexal masses, tumors, suspicion of malignancy of the reproductive organs, and uterine anomalies was excluded before selecting these cases. Quinacrine hydrochloride (7 pellets, 36 mg each) was inserted at the fundus by means of Copper-T IUD inserters. Total abdominal or vaginal hysterectomy was performed at various intervals, between 3 and 25 days, after quinacrine insertions. Blocks of tissue containing the 'intramural portion of the fallopian tubes were removed from both cornua, and routine htmatoxylin and eosin sections were then prepared and examined.

Results

There were no untoward effects or complications noted in any of the subjects. Table 1 lists the cases by age, parity, clinical diagnosis and insertion to hysterectomy intervals. Table 2 summarizes the histologic findings in each intramural tube. The associated figures illustrate the progression of the inflammatory response. The histologic changes could be classified into two main groups:

L Immediate or 'acute' changes: observed during the first 10 days after insertion. These changes were in the form of necrosis of the cpithtlial lining and an acute inflammatory reaction. There was dilatation and congestion of blood vessels and inflammatory cellular infiltrate of the wall and lumen. The inflammatory 'infiltrate was composed mainly of neutrophils, lymphocytes and plasma cells.

2. Delayed or 'subacute' changes: observed after 10 days of insertion. There was progressive absorption of the inflammatory cellular exudate, progressive fibrosis with partial or almost complete occlusion of the lumen and failure of regeneration of the epithelial lining.

Table 1 Age, parity, clinical diagnosis and insertion to hysterectomy interval for women receiving 252 mg intrauterine quinacrine prehysterectomy

Case	*Age*	*Parity*	*Clinical diagnosis*	*Insertion – hysterectomy interval (days)*
1	40	7	Myoma	3
2	46	5	DUB	5
3	41	1	Myoma	7
4	U	6	Prolapse	7
5	43	5	DUB	8
6	45	10	Prolapse	10
7	35	5	Prolapse	11
8	4a	5	Myoma	12
9	so	4	DUB	13
10	46	7	DUB	21
11	47	8	Prolapse	22
12	47	6	DUB	25

DUB = Dysfunctional uterine bleeding

In cases No. 8 and 9 (12 and 13 days post insertion) focal regeneration of the epithelium was observed in one side, while, paradoxically, specific histopathologic identification was not possible in the other side in spite of thorough serial sectioning of the comual area. This could be the result of complete obliteration of the tubal lumen by the quinacrine. Focal regeneration of the epithelium was also seen in case No. 7 (11 days post insertion). Moreover, complete regeneration of epithelium occurred in case No. 12 (25 days post insertion). All six cases at 10 or fewer days post insertion showed complete absence of epithelium.

Discussion

This study shows that early changes observed in the comual portion of the fallopian tube after a single transcervical quinacrine insertion varied according to the duration between insertion and the subsequent hysterectomy. The results of this study differ from that of Davidson and Wii [7] in that all four cases who underwent surgery within one week of quinacrine insertion showed evidence of tubal inflammation. This may reflect the difference between instillation of a quinacrine slurry and insertion of quinacrine pellets. There were also fewer method failures between insertions of pellets compared to the earlier use of a quinacrine slurry in clinical trials [5]. Failures between monthly administration of quinacrine virtually disappeared with pellets.

Fertility and Sterility 2001;75:830-31.

Table 2 Histopathologic changes in intramural tubes after intrauterine insertion of 252 mg quinacrine

Case	Right tube	Left tube
1	– Complete absence of epithelium. – Lumen occluded by necrotic debris, fibrin, acute inflammatory cells and some RBCs. – Lamina propria, submucosa and musculosa heavily infiltrated by neutrophils, lymphocytes and plasma cells with dilated and congested blood vessels (Figure 1).	– Same changes.
2	– The same as Case 1.	– Same changes.
3	– Complete absence of epithelial lining. – Lumen filled with immature granulation tissue made up of fibroblasts, numerous newly formed capillaries and collagen. – Lamina propria and submucosa infiltrated by lymphocytes, macrophages, plasm8 ceils and some neutrophils (Figure 2).	– Complete absence of epithelium. – Lumen contains necrotic debris, fibrin and inflammatory cells mostly neutrophils. – Dilated congested vessels in the submucosa. – Submucosa and musculosa heavily infiltrated by lymphocytes and plasma cells.
4	– Complete absence of epithelium. – Lumen partially filled with necrotic debris. – Submucosa and musculosa heavily infiltrated by acute and chronic inflammatory cells with dilated and congested blood vessels.	– Same changes.
5	– Complete absence of epithelium. Lumen partially filled with necrotic debris. Moderate infiltration by inflammatory cells in submucosa and musculosa.	– Same changes.
6	– Complete absence of epithelium. Lumen almost completely obliterated by mature fibrous tissue made up of fibrocytes, collagen bundles rnd few capillaries. – Chronic inflammatory cellular infiltrate consisting of lymphocytes and plasma cells in lamina propria and submucosa and to a lesser extent in the muscle layer with thickening of blood vessels.	– Same changes.
7	– Focal absence of epithelium. – Patent lumen. – Minimal chronic inflammatory cellular infiltrate in submucosa.	– Same changer.
8	– Tube could not be identified.	– Focal absence of epithelium with patent lumen. – Submucosa show fibrosis and few chronic inflammatory cells (Figure 3).

Case	Right tube	Left tube
9	– Focal absence of epithelium with partial oblitention of lumen with mature fibrous tissue. – Submucosa shows fibrosis, minim81 inflammatory cells and thickening of blood vessels.	– Tube could not be identified.
10	– Complete absence of epithelial lining. – Lumen completely occluded by partially hyalinosed fibrous tissue. – Very few chronic inflammatory cells in lamina propria 8nd submucosa.	– Same changes.
11	– Complete absence of epithelium. – Complete oblitention of lumen. – Marked fibrosis in submucosa with minimal inflammatory cellular infiitntc (Figure 4).	– Same changes.
12	– Epithelium intact. – Lumen partially occluded by mature fibrous tissue infiltrated by inflammatory cells. – Submucosa shows fibrosis, minimal inflammatory cells ● d thickened blood vessels (Figure 5).	– Same changes.

Our study suggests focal or even complete regeneration of damaged epithelium beginning 10 days post ● insertion of quinacrine as pellets. However, the studies of Bhatt and co-workers [8] and Merchant and co-workers [9] show that the epithelium is lost after 30 days in a majority of cases after a single insertion of quinacrinc pellets. This was also the finding in two of our seven subacute cases, case No. 10 and 11 (21 and 22 days post insertion).

There appears to be a process of acute injury to intramural tubal epithelium after exposure to quinacrinc followed by attempts to regenerate that, however, frequently fail. The pathophysiology of this process remains to be described. Further early and late prchysterectomy studies comparing different release times of quinacrine pellets and the effect of potentiating drugs arc needed to better understand this process.

At this time there is considerable unmet demand for sterilization in developing countries which could be met by the quinacrinc pellet method [10,11]. tipper and co-workers have shown that two insertions of quinacrint pellets a month apart in the proliferative phase of the menstrual cycle arc as efficacious as three insertions [12]. Mullick has confirmed this in a large field trial showing a life-table failure rate of 33 per hundred women at one year [13]. Further reducing the failure rate and number of needed insertions is a desirable research objective. It is also true, as Kessel has shown, that the present method, by extending sterilization services in developing countries,

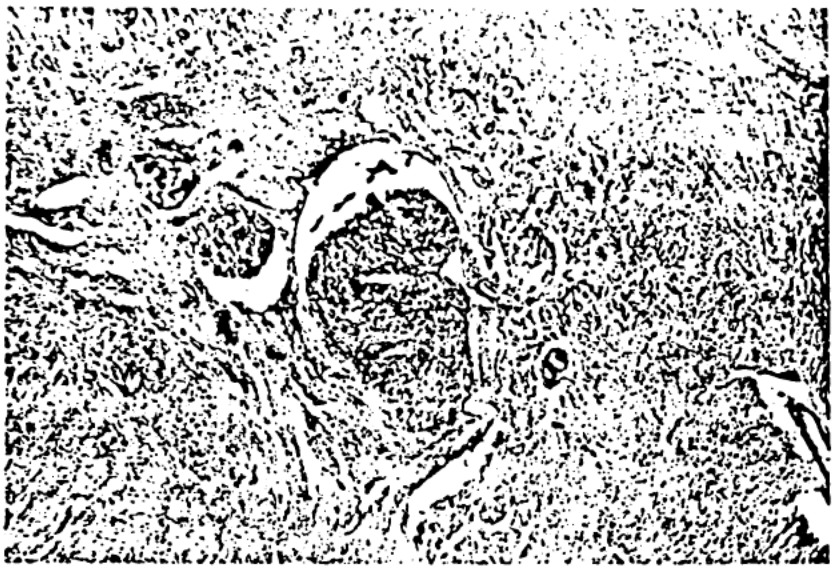


Figure 1 Necrosis of the epithelial lining with acute inflammatory reaction in the wall and lumen (x 100)

Figure 2 Lumen invaded by immature granulation tissue with inflammatory reaction in the submucosa (x 100)

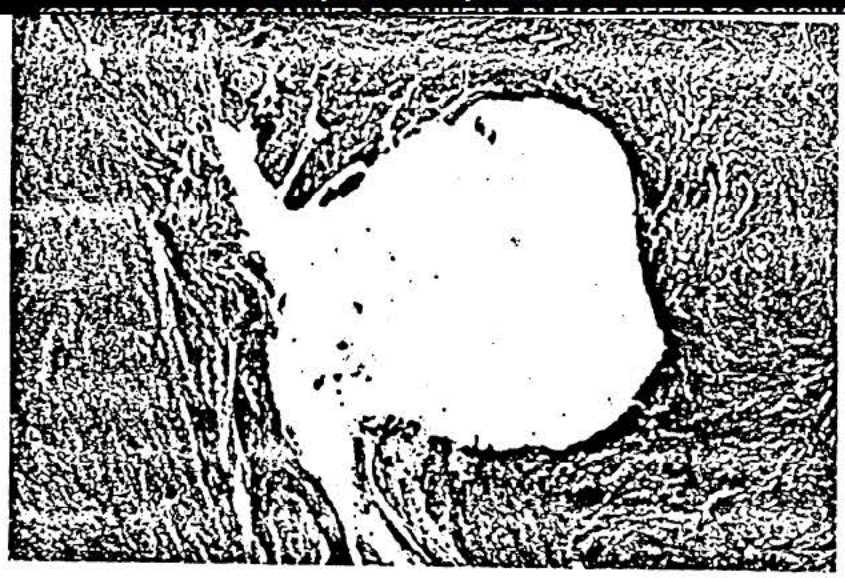


Figure 3 Focal regeneration of epithelium surrounding a patent lumen. Fibrosis and sparse chronic inflammation in the submucosa (× 100)

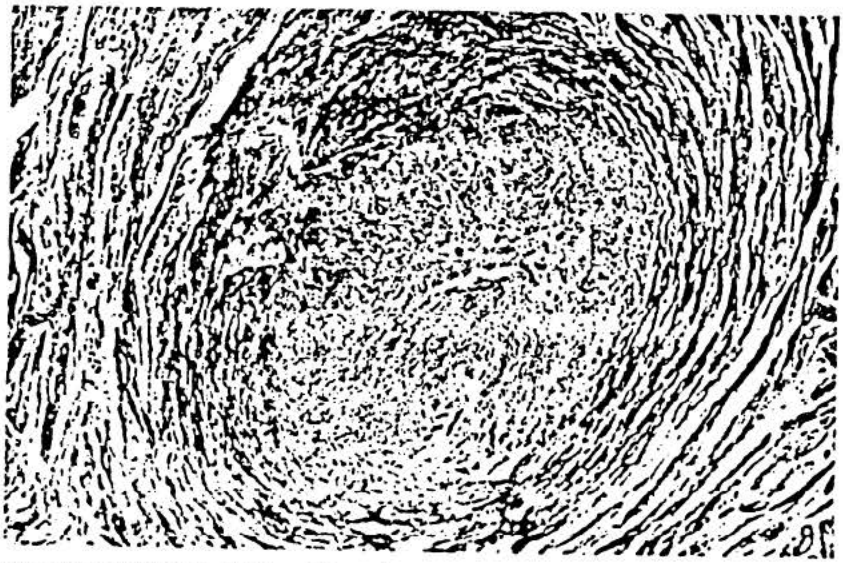


Figure 4 Complete loss of epithelium with complete obliteration of the lumen. Marked fibrosis and sparse chronic inflammation in the submucosa (× 100)

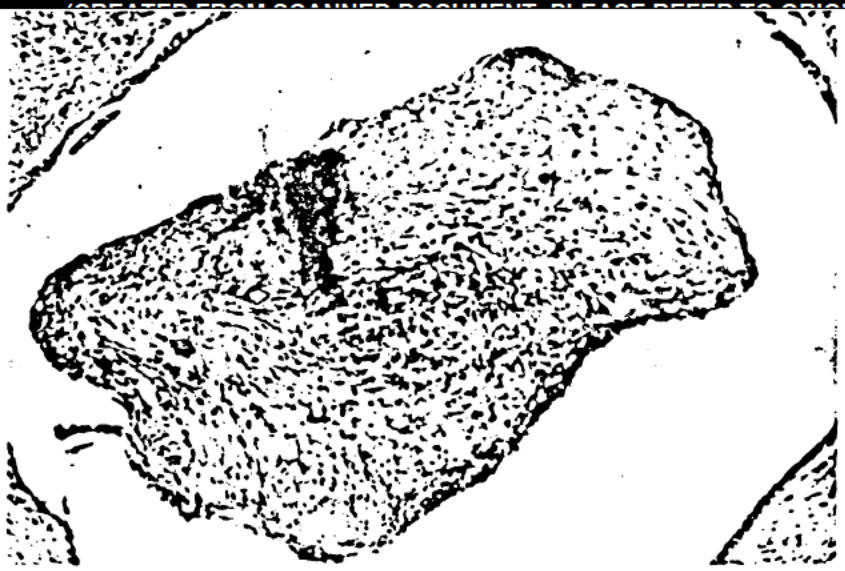


Figure 5 Complete regeneration of epithclium surrounding a partially occluded lumen by the mature fibrous tissue. Fibrosis and sparse chronic inflammation in the submucosa (x 100)

can improve the health and actually save the lives of many women of reproductive age [10]. It is for this reason we have introduced this method at Boulak El-Dakrour Hospital in Cairo. Over the past 3 years we have been trying two-monthly insertions of quinacrine pellets, followed by hysterosalpingography one month later, for women requesting permanent contraception. The findings are promisiig, with a low HSG post insertion failure rate, and without a single pregnancy. These findings will be reported in detail at a later date.

References

1. Zipper. J., Stachetti, E. and Medel, M. (1970) Human fertility control by transvaginal application of quinacrine on the fallopian tube *Fertil. Steril.*, 21, 581–589
2. Benoit, A, Melancon, J and Gagnon, M (1975). Chemially induced tubal occlusion in the human female using intrauterine instillation of quinacfinc *Contraception*, 12, 95–101
3. Zipper, J., Medel, M., Goldsmith, A, Edclman, D., Pastene, L. and Riven, M. (1976). The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization *Int. J. Gynecol. Obstet.*, 14, 499–502
4. Israngkun, C., Phaosavadi, S., Neuwirth, RS. and Richart, RM. (1976). Clinical evaluation of quinacrine hydrochloride for sterilization of the human female *Contraception*, 14, 75–80
5. Zipper, J., Cole, L.P., Goldsmith, A, Wheeler, R and Riven, M. (1980). Quinacrinc hydrochloride pellets preliminary data on a non-surgical method of female sterilization. *Int. J. Gynecol. Obstet.*, 18, 275–279
6. Guzman-Serani, R., Bernales, A and Cole, L.P. (1983). Quinacrinc hydrochloride pellets: three-year follow-up on a non-surgical method of female sterilization *Contracept. Deliv. Syst.*, 5, 131–135

7. Davidson, 0. and Wilkins, C (1973). Chemically induced tubal occlusion in the human female following a single instillation of quinrcrine. *Contraception*, 7, 333–339
8. Bhatt, RV., Aparicio, A., Laufe, L.E., Parmley, T. and King, T.M. (1980). Quinacrine-induced pathologic changes in the fallopian tube. *Fertil. Steril.*, 33, 666–667
9. Merchant, RN., Doctor, V.M., Thaku, S.S., Sinha, M., Jharveri, CL, Kessel, E and Mumford, S.D. (1986). Clinico-pathological study of fallopian tubes after transcervical insertion of quinrcrine hydrochloride pellets. *Adv. Contracept.*, 2, 79–90
10 Kessel, E. (1989). Prospects for nonsurgical female sterilization. *Int. J. Gynecol. Obstet.*, 29, 1–4
11. Kessel, E, Zipper, J. and Mumford, S.D. (1985). Quinacrine non-surgical female sterilization: a reassessment of safety and efficacy. *Fertil. Steril.*, 44, 293–298
12. Zipper, J., Cole, L.P., Rivera, M., Brown, E and Wheeler, RG. (1987). Efficacy of two insertions of 100-minute releasing quinrcrine hydrochloride pellets for non-surgical female sterilization. *Adv. Contracept.*, 3, 255–261
13. Mullick, B. (1990). Personal communication.

MS *received 15 July 90.*
Accepted for publication 14 Nw. *90.*

Resumé

Pour étudier la succession des changements histopathologiques qui se produisent dans la portion cornée de la trompe de Fallope après une exposition A la quinrcrine, on a inséré par k col utérin 252 mg de cette substance chu 12 femmes qui devaient subir une hystérectomie pour des raisons autres quc des tumeurs malignes. On a constaté chu toutes les patientes opérées dans les dix jours suivant l'insertion une nécrose de la bordure épithéliale et unc réaction inflammatoire aigüe. Ultérieurement, les changements observés comprenaient la résorption progressive de l'exudat cellulaire inflammatoire, une fibrose progressive avec occlusion partielle ou presque totale de la cavité et une absence de régénération de la couche épithéliale. Nos résultats vicnnent à l'appui d'autres études indiqwnt que la quinacrine peut effectivement produire la fibrose et l'occlusion des trompes.

Resumen

Pan estudiar la sucesión de cambios histopatológicos que se producen en la porción córnea de la tromp8 de Falopio después de la exposición a la quinrcrina, seinsertaron por cl cuello del útero 252 mg de esta sustancia en 12 mujeres a las que se ks practicaría una histerectomía por motivos quc no eran los de tumores malignos. Se verificó en todas las pacientes operadas dentro de los dier días posteriores a la inserción una necrosis del revestimiento epitelial y una reacción inflamatoria aguda. Posteriormente, los ambios observados comprendieron la reabsorción progresiva dcl exudado celular inflamatorio, una fibrosis progresiva con oclusión parcial o casi total de la cavidad y la falta de regeneración de la capa epitelial. Nuestros resultados apoyan otros estudios que indican que la quinacrina puede efectivamente producir fibrosis y oclusión de las trompas.

Maternal and Child Care in Developing Countries
Edited by E. Kessel, A. K. Awan

7.3 An Early Experience with Nonsurgical Female Sterilization

by **Fakhar-un-Nisa**
Pakistan

Our experience performing nonsurgical sterilization in women at Lady Wellingdon Hospital was very limited, but the results were so encouraging that I thought it appropriate to report our preliminary study at this gathering of professionals.

Voluntary sterilization is the most prevalent method of fertility regulation, the estimated number of couples using it having increased dramatically from 15 million in 1970 to 100 million in 1980, and about 135 million couples today. Pakistan is the ninth most populous country in the world and, as in other developing nations, the demand for sterilization is steadily increasing there; the preference is for female sterilization. This demand far exceeds the ability to provide such services, especially in the rural areas where most of our countrywomen live. We have been sending extension teams to perform minilaparatomies in far-flung regions from time to time, but it is not possible to cover the entire rural population. Moreover the risks associated with surgery grow in a camp setting.

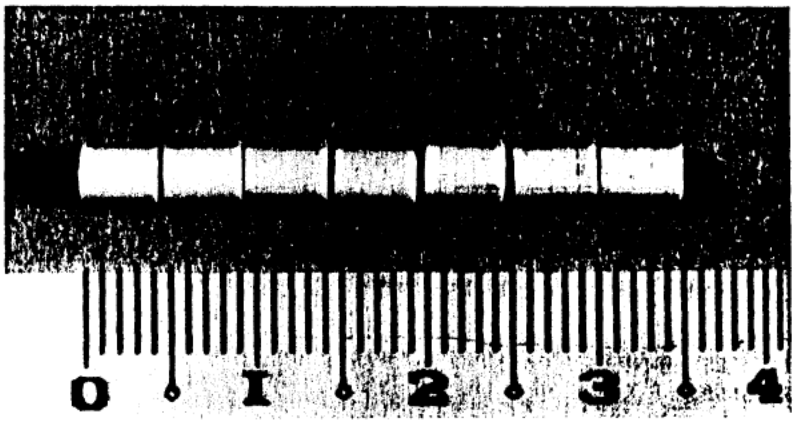
A chemical, or nonsurgical, method of female sterilization was demonstrated to me by Professor Robert Neuwirth at St. Luke's Hospital, New York, in 1977. Although it was in an experimental stage, I found the procedure fascinating. So I was very pleased when Dr. Elton Kessel sent me a supply of quinacrine pellets and invited me to participate in the multinational study of female nonsurgical sterilization in December 1986. The method was developed by Dr. Jaime Zipper of Santiago, Chile (1), It has been shown that the tissue damage and fibrosis caused by intrauterine administration of quinacrine is limited to the cornual area of the uterus and interstitial portion of the Fallopian tubes (2,3).

Methodology

The quinacrine pellet is cylindric in shape, 0.5 cm long, with a diameter of 0.35 cm. Seven pellets, containing a total dqse of 250 mg of quinacrine hydrochloride, are introduced into the uterine cavity, using a sterilized IUD inserter,

VIII-33

Figure 1: One insertion of quinacrine pellets (250 mg); length in centimetres



during the proliferative phase of the menstrual cycle (Figures 1 and 2). Some analgesic tablets are given in case the patient should feel any pain or discomfort.

She is asked to return for a second insertion after the menstrual period. Seven pellets containing 250 mg are inserted a second time to ensure blockage of the tubes. The woman is asked to observe temporary methods of contraception until her next period. Follow-up is scheduled at one week and at 1, 3, 6, 18 and 24 months. A test to check tubal patency by either insufflation or hysterosalpingography was carried out after the second menstrual period in selected cases.

Results

We did ten hysterosalpingograms and a few insufflations in our short series of 105 cases. Only in one instance were tubes found patent; in the rest, there was cornual blockage.

Average parity was 5.0 and average age was 35.5 years. Age of the last born child varied from six months to six years. It is interesting to note that 70% of these clients requested the procedure soon after the last abortion. No pregnancy has been reported so far after 3 to 18 months of follow-up.

Table 1 shows a comparison of average age, parity, failure rate, mortality and morbidity of the quinacrine pellet method with surgical sterilization at Lady Wellingdon Hospital, Lahore.

Table 1: Surgical and nonsurgical female sterilization.
Lady Wellingdon Hospital, Lahore, from January 1 to September 30, 1987.

Cases (No.)	Method of Sterilization	Age (Av.)	Parity (Av.)	Failure (Rate)	Procedure Mortality	Procedure Morbidity
2170	Surgical	35 1	5 1	Nil	Nil	2.38%
105	Nonsurgical	35.5	5.0	Nil	Nil	Nil

VIII-34

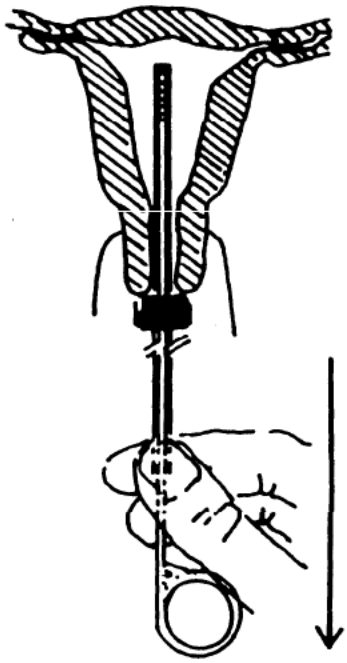


Figure 2: Quinacrine pellet insertion technique using an IUD inserter

Discussion

Ectopic pregnancy is reported as 0.24/1000 procedures at two years for quinacrine nonsurgical sterilization as compared to 2.15/1000 procedures after two years of surgical sterilization (4). Toxicity of the drug is virtually nil with the present dosage schedule. Fortunately, this drug was used as an antimalarial agent in the oral dosage of 100 mg daily by millions of soldiers during World War II. In this extensive experience, there were a few cases of dermatitis and transient toxic psychosis; the only common side effect was discoloration of skin after chronic use. In the recent study completed by Johns Hopkins University using rats and Cynomolgus monkeys, no chromosomal abnormality or teratogenic effect was observed (5).

Conclusion

Nonsurgical sterilization of women by quinacrine pellets is an effective, much less expensive and simpler procedure than surgical sterilization. The cost is Rs 350 for surgical and Rs 75 for nonsurgical sterilization, for instance. The procedure can be carried out as safely in rural areas as an office IUD insertion. In spite of the estimated lifetime failure rate of 5 per 100 women (6), we regard it as a safe and deliverable method that has the potential to meet the expected de-

mand for sterilization in the coming decade. It follows, therefore, that more expanded trials of the quinacrine pellet method should be given high priority for fertility research. Introduction of this method in our national program may help us to reduce the population growth rate to a desired level of 2.5% in the next five year-plan.

References

1. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M: Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. Int J Gynaecol Obstet 1980; 18:275-9
2. Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM: Quinacrine-induced pathologic changes in the Fallopian tube. Fertil Steril 1980; 33:666-7
3. Merchant RN, Doctor VM, Thaku SS, Sinha M, Jhaveri CL, Kessel E, Mumford SD: Clinico-pathological study of Fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets. Adv Contracept 1986; 2:49-90
4. Kessel E, Zipper J, Mumford SD: Quinacrine nonsurgical sterilization: a reassessment of safety and efficacy. Fertil Steril 1985; 44:293-8
5. Blake DA, Dubin NH, DiBlasi MC, et al: Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra JJ, eds. Female transcervical sterilization: proceedings of an international workshop on Nonsurgical Methods of Female Tubal Occlusion. Chicago, Illinois, June 24, 1982. Hagerstown: Harper and Row, 1983: 71-88.
6. Guzman-Serani R, Bernales A, Cole LP: Quinacrine hydrochloride pellets: three-year follow-up on a non-surgical method of female sterilization. Contracept Deliv Syst 1983; 5:131-5

Resume'

L'auteur décrit son experience d'une méthode simple de stérilisation féminine non chirurgicale. Le procédé consiste à appliquer par voie transcervicale des tablettes de 250 mg. de *qtrinacrine,* en utilisant un introducteur de DIU (dispositif intra-utérin, stérilet) modifié. L'introduction est réalisée dans la phase proliferative du cycle menstruel et répétée une fois, un mois plus tard.

Cette manière de faire entraine une inflammation et un processus cicatriciel limités à la region des cornes utérines et de la partie intramurale des trompes. Le taux d'échec sur la durée de la vie (lifetime failure rate) est dit être de 5%. Dans son suivi limité de 105 patientes, l'auteur n'a pas note d'échecs. Elle n'a pas non plus observe de complications alors que, dans sa pratique au Lady Wellingdon Hospital à Lahore, elle enregistre des complications dans 2,38% des cas de sterilisation chirurgicale. Vu le potentiel qu'aurait cette méthode d'être utilisée largement, y compris dans les regions rurales, il est souhaité que des études complementaires soient entreprises rapidement.

VOL 24

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT. PLEASE REFER TO ORIGINAL)

Resumen

Describimos nuestra experiencia cop un método simple de esterilizacidn sin cirugia en la mujer. El proceder consiste en la inserción a través de la cerviz de 250 miligramos de *quinacrina* en la forma de pelletas, usando un instrumento modificado de inserción de IUD. La inserción se lleva a cabo en la fase proliferativa delperíodo menstrual y es repetida una vez más, después de un mes. El método produce inflamación y cicatriz unicamente en la Area cornual y intramural de la trompa de Falopio. Se reporta que este método tiene un promedio de 5% de insuficiencia o fallo. En nuestro estudio de continuación en 105 pacientes, no se han encontrado ningún fracaso. No se notaron complicaciones cuando estos pacientes se compararon con otros pacientes que tuvieron el método quirúrgico de esterilizacidn femenina al hospital Lady Wellingdon. Debido a que este método podria llevarse a cabo en la comunidad rural de Pakistan, se recomienda que más investigaciones que tienen prioridad alta se empiecen rápidamente.

ملخص

تقدم الورقة خبرتنا فى طريقة مبسطة غيرجراحية لتعقيم المرأة، وتتمثل الطريقة فى إدخال «حبيبات» مادة الكوناكرين خلال عنق الرحم بواسطة آلة تركيب اللولب. ويتم ذلك فى الفترة التالية لانتهاء الحيض، وتكرر بعد شهر من ذلك الحين. وهذه الطريقة تؤدى إلى التهاب وتليف نهاية قناة فالوب وما حول مدخلها إلى الرحم.

وقد نشر من قبل أن هذه الطريقة تفشل فى ٥٪. ولكن تجربتنا فى تعقيم ومتابعة ١٠٥ حالة بهذه الطريقة لم تحدث أية حالة فشل. كذلك لم نلاحظ مضاعفات ويقارن ذلك بمعدل مضاعفات قدره ٢٫٣٪ فى تجربتنا بالطرق الجراحية للتعقيم بمستشفى السيدة ليدجتون.

ونظراً لاحتمال انتشار هذه الطريقة الجديدة فى الباكستان، حتى فى المناطق الريفية، فإننا ننصح ان تستمر التجارب الإكلينيكية على هذه الطريقة، ولإعطاؤها أولوية خاصة.

VIII-38

Studies of quinacrine and of tetracycline for non-surgical female sterilization

B. MULLICK[1], S. D. MUMFORD[2] and E. KESSEL[3]

[1]Indian Rural Medical Association, 8 Sarojini Naidu Sarani, Calcutta 700 017, India
[2]Center for Research on Population and Security, P .O. Box 13067, Research Triangle Park, North Carolina 27709, USA
[3]Department of Public Health and Preventative Medicine, Oregon Health Sciences University, Portland, Oregon 97201, USA

Abstract

The transcervical quinacrine pellet method developed by Zipper and co-workers is potentially a much needed safe, inexpensive, and effective non-surgical method of female sterilization. This method utilizes an intrauterine device inserter to deposit 250 mg of quinacrine hydrochloride as pellets in the uterine cavity. No complications or side effects, other than temporary pain and oligomenorrhea, have been reported.

Tetracycline has an established track record for safety. It also has been reported to have properties similar to quinacrine as a sclerosing agent, with potential as a non-surgical method using the quinacrine insertion technique.

To expand the experience with quinacrine and to study tetracyline as an alternative, studies were undertaken under the auspices of the Indian Rural Medical Association in Calcutta, India. During the period 14 August, 1979 to 28 June, 1984, 414 women received three insertions of 200 mg of quinacrine. There were 29 failures and a three-year life table failure rate of 8.5. During the period 25 April, 1984 to 28 December 1984, 55 women received three insertions of 200 mg of tetracycline. By 1 June, 1986 there were 32 failures among the 55 cases for a failure rate of 58%. A more recent study using a single dose of 1000 mg of tetracycline also produced unacceptably high failure rates.

Advances in Contraception. ISSN 0267-4874.

Voluntary sterilization is the most prevalent method of fertility regulation, and its use is widespread in both developed and developing countries. The country reporting the highest prevalence of use is the United States, where 31.3% of married women of reproductive age are protected by surgical sterilization or by vasectomy of their husbands [1].

The potential benefits of sterilization are considerable. In the developing world, the risk of maternal and infant mortality is high [2], and such risks are greater for high-parity women, even in developed countries [3]. Maternity is the single greatest cause of death in women of reproductive age in developing countries and is mainly due to high-order pregnancies and births (>4). High-order births (>4) in the least developed countries account for a full one-half of all infant deaths [4]. In most developing countries there is no other feasible health service that could match the positive impact of sterilization on health [5].

Sterilization also offers important socioeconomic benefits. High-parity women tend to belong to the least privileged segments of society. Because higher fertility frequently leads to greater poverty and because sterilization is ultimately the most cost-effective of the available methods, it has the most to offer from a socioeconomic standpoint.

Not to be ignored is the most important role that sterilization must play in maintaining peaee and security given the disastrous implications of world overpopulation [6].

Non-surgical versus surgical sterilization

In the developing world, especially in the most populous countries, the demand for sterilization is steadily rising, the preference being for female sterilization. At the beginning of this decade it was estimated that there would be a demand for 180,000,000 sterilizations worldwide during the decade of the 1980s (excluding China), about 80% of the demand appearing in the developing world [5]. This would be a 5-fold increase in demand there and a 20-fold increase in rural areas.

However, at mid-decade the demand continues to far exceed the supply of surgical sterilization services, which are virtually non-existent in the rural areas where approximately 80% of the women live. Because of the fragile condition of health care delivery systems in the developing world and the rural residence of the population, it is unrealistic to expect surgical sterilization to meet the projected need. A non-surgical method must be relied upon.

An acceptable non-surgical female sterilzation method has been described as one that is safe, 95% effective, that can be performed by non-physicians on an outpatient basis after a brief training period, and that requires only a single visit by the woman [7]. The transcervical quinacrine pellet method developed by Zipper and colleagues [8] over the last 15 years, which utilizes an intrauterine device inserter to deposit 250 mg of quinacrine hydrochloride as pellets in the uterine cavity, has potential for meeting this description.

The quinacrine pellet method

Studies have shown that quinacrine produces inflammation and fibrosis that is confined primarily to the intramural portion of the Fallopian tube [9]. Quinacrine pellets (250 mg) [8] (Figure 1) are inserted through an IUD inserter (Figure 2) at monthly intervals in the proliferative phase of the menstrual cycle for three insertions.

This method can be performed by non-physicians on an outpatient basis after a brief training period or by any personnel capable of performing an intrauterine device insertion. Most important, the cost of materials for this procedure is very low; approximately US $1 .OO. All but the very poorest women in the world can afford this procedure.

In the studies of the quinacrine pellet method reported to date [10-12], which included over 1000 insertions, the method appears to be quite safe. No complications or side-effects, other than temporary pain and oligomenorrhea, have been reported.

Toxicology studies were previously performed and approved by the United States Food and Drug Administration for premarketing requirements of quinacrine used orally as a malaria suppressant drug during World War II by millions of soldiers in the dose of 100 mg daily. In this extensive experience, there were a few cases of dermatitis and rare cases of convulsions or transient toxic psychosis reported; the only common side-effect was discoloration of the skin after chronic use [13]. More recently, toxicology studies of the quinacrine sterilization method in cynomolgus monkeys were encouraging with twice the comparative human dose in the form of a solution for both intravascular and intrauterine administration [14,15].

The major concern with this method has been the potential of toxic psychosis, and with good reason. Earlier studies with a liquid slurry of 1500 mg of quinacrine, 6 times the current dose, did produce a 2% rate of transient toxic psychosis shortly after quinacrine instillation, but this has not appeared with the 250 mg quinacrine pellet method [8].

Neither the optimal dose nor the optimal number of insertions of quinacrine has been firmly established [16]. Recently, Zaneveld and Goldsmith concluded that the animal models used for the study of quinacrine are not adequate for these purposes and that there are no animal models which are known to be appropriate [17]. As with other methods of fertility control, these answers are only going to come from clinical field trials.

Merchant and colleagues [18] recently found in a prehysterectomy study that greater height of the endometrium may play a protective role against the action of quinacrine. This finding suggests that vacuum aspiration of the uterus just prior to quinacrine insertion would enhance the effectiveness of the procedure. Merchant also found that a recent history of menorrhagia markedly reduced the effects of the quinacrine on the tube with respect to histological changes.

Tetracycline as an alternative sclerosing agent

The potential toxic effects of quinacrine have prompted a search for other drugs that are equally effective in producing inflammation and fibrosis of

Fertility and Sterility 2001;75:830-31.

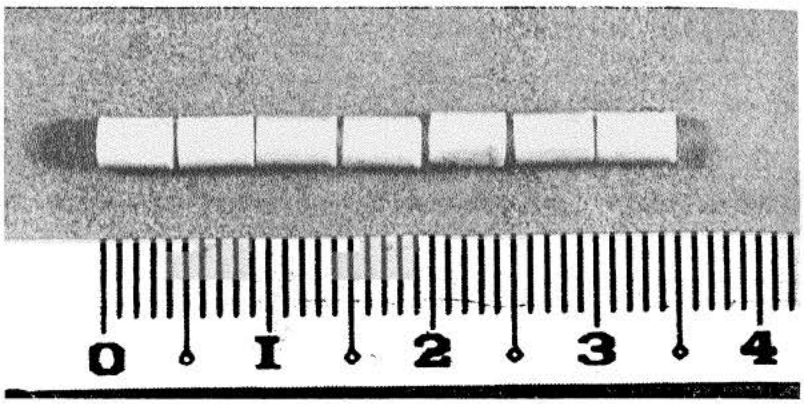


Figure 1 One insertion of quinacrine pellets (250 mg); length in centimetres

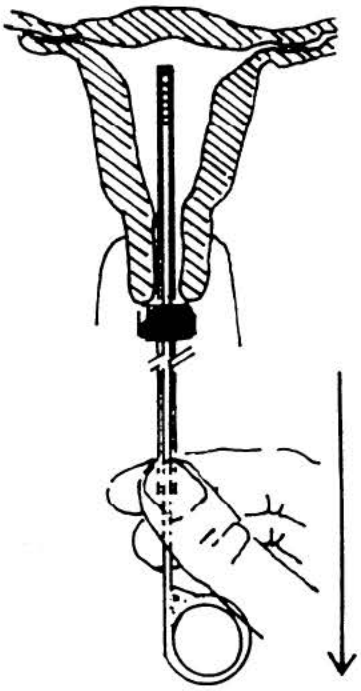


Figure 2 Quinacrine pellet insertion technique using an IUD inserter

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

the tube but having no known risks of side-effects. Recent studies [17,19,20] indicate that tetracycline hydrochloride may be as effective as quinacrine in producing tubal closures when administered directly to the uterotubal junction. One study [19] has demonstrated that tetracycline when directly applied to the uterine lumen in rats resulted in morphologic changes similar quantitatively and qualitatively to that of quinacrine.

A study of cynomolgus monkeys indicates that the intrauterine administration of tetracycline is capable of inducing lesions in the reproductive tract. These lesions are morphologically comparable to those caused by administering intrauterine quinacrine pellets in this species [20]. Blood chemistry, hematology tests, and liver and kidney biopsies indicate that the dosage used for tetracycline is non-toxic. Blood levels achieved in monkeys following intrauterine pellets or solutions of 100 mg tetracycline are comparable to those levels achieved when 2 g of tetracycline were administered via the intraperitoneal route in women [21,23]. Thus, it is expected that intrauterine instillation of tetracycline in a dose of 1 g in humans would result in blood levels well within the safe range, even in the event of accidental intraperitoneal spillage [20].

Furthermore, studies have demonstrated the sclerotic action of tetracycline in treating neoplastic pleural effusions [23,24]. One randomized study demonstrated greater efficacy in the treatment of pleural effusions with tetracycline compared to quinacrine [24] and the patients treated with tetracycline had less fever and pain. Tetracycline apparently has not been studied as a potentiating agent for the Zipper quinacrine method.

Tetracycline is indeed an attractive alternative to quinacrine because its safety is very well established. Some investigators were being told that tetracycline looked sufficiently promising to cause them to hold up on undertaking quinacrine studies. One large research agency in India delayed the decision to undertake a field trial with the Zipper method when informed that tetracycline would almost surely replace quinacrine. This agency awaited the determination of whether tetracycline produced comparable results before proceeding with planned studies using quinacrine.

Materials and methods

All cases reported here were performed by the first author at an Indian Rural Medical Association clinic in Calcutta, India. All follow-up was done by the first author and the follow-up reported is until 16 October 1986. At the time of recruitment of these women, they were informed of the risks of failure and that they would be given an MR (menstrual regulation procedure) in the event of failure at no charge. The women were not charged for the non-surgical sterilization procedure, nor were they paid to Participate in the research. The costs of these studies were entirely borne by the first author.

The first of the nine studies reported here was undertaken on 14 August 1979 in order to expand on the work of Zipper and others, though a slightly more conservative dose of 200 mg was used. As tetracycline emerged as a possible alternative to quinacrine a 200 mg x 3 insertion series was initiated to examine effectiveness since the safety of

tetracycline was well established. It soon became apparent that at this dose level tetracycline would not be adequate. Since it appeared that tetracycline was having some effect, it was thought that it might enhance the effectiveness of quinacrine and a series using 200 mg of quinacrine and 200 mg of tetracycline was initiated to see if it would serve as a potentiating agent for the quinacrine method.

With the finding of Merchant that increasing height of the endometrium reduced the effects of the quinacrine, a series was initiated in which the uterus was vacuum-aspirated before insertion of the pellets. This procedure was done in order to minimize the height of the endometrium in the hope of increasing the effectiveness of the procedure. This modified procedure was first attempted with the combined 200 mg quinacrine + 200 mg tetracycline procedure. Failures continued. It was decided that the tetracycline may be interfering with the action of the quinacrine and its use as an adjunct was terminated.

It was reported that there were no clinical trials which showed that three insertions of quinacrine were more effective than one. A series using a single insertion of quinacrine after vacuum aspiration of the uterus was initiated. After failures continued, the dose was increased to 300 mg. As follow-up of all uterine vacuum aspiration cases continued, it became apparent that aspiration of the endometrium was reducing the effectiveness of the procedure.

Terminating the use of vacuum aspiration of the uterus, a series using only a single insertion of 300 mg of quinacrine was initiated. The effectiveness was much improved. However, at this point it was decided that the ineffectiveness of the tetracycline method may be due to the low dose used. A series was undertaken using the maximum dose previously determined to be safe in women, 1000 mg. Subsequently, a second series using only a single insertion of quinacrine at a dose of 324 mg was initiated.

The periods of the insertions for all nine studies are given in Tables 1, 2 and 3. The nine studies were done consecutively, the recruitment for one study being completed before the next study was initiated.

Results

The results of the four studies of quinacrine without aspiration of the uterus are shown in Table 1. Most important, the 414 women who received three insertions of 200 mg each had a 3-year life table failure rate of 8.5. The 41 women who had received a single insertion of 300 mg had a failure rate of 15% after 9-11 months of follow-up. Admission to the study of a single insertion of 364 mg of quinacrine continues with 62 women admitted as of 16 October 1986. There have been no failures with this very limited follow-up (4 months or less). When 200 mg tetracycline was inserted at the time of a single insertion of 200 mg quinacrine, the failure rate was an unacceptable 24% after 20-22 months of follow-up.

The two tetracycline studies, the results of which are shown in Table 2, were both most disappointing. The 200 mg x 3 insertion technique had a failure rate of 58% after 21-29 months of follow-up. The study of a single insertion of 1000 mg of tetracycline showed a failure rate of 34% after only 4-9 months of follow-up.

Table1 Quinacrine non-surgical female sterilization: failure rates by dose and number of insertions. Follow-up to 16 October 1986

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	3	414	14 Aug. 79-28 June 84	29	7*
300	1	41	27 Oct. 85-1 Jan. 86	6	15
200+200 tetracycline	1	50	30 Nov. 84-28 Feb. 85	12	24
324	1	62	9 June 86-24 Sept. 86	0	0

* 3-year life table failure rate = 8.5

Table 2 Tetracycline uon-surgical female sterilzation: failure rates by dose and number of insertions. Follow-up to 16 October 1986

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	3	55	25 Apr. 84-28 Dec. 84	32	58
1000	1	102	4 Jan. 86-10 June 86	35	34

Table 3 Quinacrine non-surgical female sterilization following vacuum aspiration of the uterus: failure rates by dose and number of insertions. Pollou-up to 16 October 1986

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	1	17 50	12 June 85-8 July 85	4	24
300	1		14 July 85-26 Oct. 85	15	30
200+200 tetracycline	1	50	28 Feb. 85-11 June 85	12	24

The results of the studies, which included the vacuum aspiration of the endometrium , are shown in Table 3. Failure rate for these studies ranged from 24% to 30% with 12-19 months of follow-up.

In none of these nine studies was there a single serious complication or side-effect.

Discussion

While the 414 women accepting the three insertion-200 mg method had a 3-year life table failure rate of 8.5, this method has much to offer the tens **of millions** of women who have no hope of ever having a surgical sterilization operation. The study of a single insertion of 300 mg of quinacrine suggests that this method has promise, but the failure rate of this method cannot be established with these small numbers and with this short follow-up period. The study of a single insertion of 324 mg of quinacrine also shows promise but suffers from the same shortcomings.

The two studies of tetracycline all but rule out the use of this chemical for this purpose. Though sclerosing may occur in some cases, the

failure rate is unacceptably high. When used with quinacrine, it might even interfere with the action of the quinacrine on the tubes in ways that are not clear.

Vacuum aspiration of the uterus for the purpose of diminishing the heights of the endometrium for the purposes of enhancing the effectiveness of quinacrine is counterproductive. The reason for this may be related to Merchant's finding that there was a markedly reduced effect of the quinacrine on the tubes in women who had a recent history of menorrhagia. It may be that the presence of blood at the time of insertion of the quinacrine in some way reduces the effect of the quinacrine.

These studies suggest that a three-insertion technique of quinacrine for chemical female sterilization does show promise, though the best dose level has not yet been established. They also show that a single insertion technique may possibly be as effective or nearly as effective as a three-insertion technique.

An important lesson learned from these studies is that research of the quinacrine pellet three-insertion method should continue with all deliberate speed. We should not be distracted by possible alternatives, such as tetracycline, until the alternatives have been well proven.

Acknowledgements

The authors wish to thank Robert Wheeler and Family Health International, Research Triangle Park, North Carolina, for assistance in the analysis of the data.

References

1. Westoff, C.F. and Jones, E.F. (1977). Contraception and sterilization in the United States, 1965-1975. Fam. Plann. Perspect., 9, 154-157
2. Omran, A.R. (1976). Health risks related to family formation. In: Family Formation Patterns and Health, A.R. Omran, C.C. Standley, eds., World Health Organization, Geneva, p.18
3. Yerushalmy, J., Bierman, J.M., Kemp, D.H., Connor, A. and French, F.E. (1956). Longitudinal studies of pregnancy on the island of Kauai, Territory of Hawaii. I. Analysis of previous reproductive history. Am. J. Obstet. Gynecol., 71, 80-96
4. Wyon, J.B. and Gordon, J.E. (1962). A long-term prospective-type field study of population dynamics in the Punjab, India. In: Research in Family Planning, C.V. Kiser, ed., Princeton University Press, Princeton, pp. 17-32
5. Kessel, E. and Mumford, S.D. (1982). Potential demand for voluntary female sterilization in the 1980s: the compelling need for a nonsurgical method. Fertil. Steril., 37, 725-733
6. Global 2000 Report to the President: Vol. 4 (1980). U.S. Government Printing Office, Washington, DC
7. Klitsch, M. (1982). Sterilization without surgery. Int. Fam. Plan. Perspect., 8, 101-104
8. Zipper, J., Cole, L.P., Goldsmith, A., Wheeler, R. and Rivera, M. (1980). Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int. J. Gynaecol. Obstet., 18, 275-279
9. Bhatt, R.V., Aparicio, A., Laufe, L.E., Parmley, T. and King, T.M. (1980). Quinacrine-induced pathologic changes in the fallopian tube. Fertil. Steril., 33, 666-667
10. Zipper, J., Edelman, D., Cole, L.P. and Rivera, M. (1983). Overview of clinical trials with quinacrine. In: Female Transcervical Sterilization: Proceedings of an International Workshop on Nonsurgical Methods of Female Tubal Occlusion, Chicago, Illinois, 24 June, 1982. G.I. Zatuchni, J.D. Shelton, A. Goldsmith and J.J. Sciarra, eds., Harper & Row, Hagerstown, pp. 94-99
11. Guzman-Serani, R., Bernales, A. and Cole, L.P. (1983). Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. Contracept. Deliv. Syst., 5, 131-135
12. Raj, A. and Chakravarty, S. (1980). Permanent female sterilization by chemical method of transcervical insertion of quinacrine. In: Proceedings of the Third International Seminar on Maternal and Perinatal Mortality, Pregnancy Termination and Sterilization, V. Hingorani, R.D. Pandit and V.L. Bhargava, eds., New Roxy Press, New Delhi, pp. 476-480
13. Steck, E.A. (1972). Chemotherapy of Protozoan Disease, Vol.III. Walter Reed Army Institute of Research, U.S. Government Printing Office, Washington, DC, pp. 23.163-23.176

14. Dubin, N.H., Strandberg, J.D., Craft, C.F., Parmley, T.H., Blake, D.A. and King, T.M. (1982). Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry, and hematology in cynomolgus monkeys. Fertil. Steril., 38, 741-747
15. Dubin, N.H., Blake, D.A., DiBlasi, M.C., Parmley, T.H. and King, T.M. (1982). Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. Fertil. Steril., 38, 735-740
16. Kessel, E., Zipper, J. and Mumford, S.D. (1985). Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy. Fertil. Steril., 44, 293-298
17. Zaneveld, L.J.D. and Goldsmith, A. (1984). Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception, 30, 161-167
18. Merchant, R.N., Doctor, V.M., Thaku, S.S., Sinha, M., Jhaveri, C.J., Kessel, E. and Mumford, S.D. (1986). Clinico-pathological study of fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets. Adv. Contracept., 2, 79-90
19. Dubin, N.H., Pannley, T.H., Ghodgoankar, R.B. and King, T.M. (1984). Comparative effects of intrauterine instillation of analogs of quinacrine and tetracycline on uterine morphology in the rat. Contraception, 29, 553-559
20. Dubin, N.H., Parmley, T.H., Ghodgoankar, R.B., Rosenhein, N.B. and King, T.M. (1984). Effect of intrauterine administration of tetracycline on cynomolgus monkeys. Contraception, 29, 561-571
21. Greenberg, P.A. and Sanfore, J.P. (1967). Removal and absorption of antibiotics in patients with renal failure undergoing peritoneal dialysis. Ann. Intern. Med., 66, 465-479
22. Bulger, R.J. and Bennett, J.V. (1965). Intraperitoneal administration of broad-spectrum antibiotics in patients with renal failure. J. Am. Med. Assoc., 194, 140-144
23. Austin, E.H. and Flye, M.W. (1979). The treatment of recurrent malignant pleural effusion. Ann. Thorac. Surg., 28, 190-203
24. Bayly, T.C., Kisner, D.L., Sybert, A., MacDonald, J.S., Tsou, E. and Schein, P.S. (1978). Tetracycline and quinacrine in the control of malignant pleural effusions. Cancer, 41, 1188-1192

MS received 4 Dec. 86.
Accepted for publication 1 April 87.

Resumé

La methode d'implantation transcervicale de pellets de quinacrine mise au point par Zipper et ses collaborateurs est potentiellement une méthode non chirurgicale beaucoup plus sûre, meilleur marché et efficace de stérilisation feminine. Cette méthode utilise un dispositif d'insertion intra-utérine pour deposer, dans la cavité uterine, 250 mg de chlorhydrate de quinacrine sous forme de pellets. Aucune complication ou reaction secondaire n'a été signal&e, si ce n'est des douleurs et une oligoménorrhée passagères.

Par ailleurs, la tetracycline présente une sécurite largement établie. On a également signalé qu'elle avait des propiétés similaires à celles de la guinacrine en tant qu'agent sclérosant et qu'elle pourrait être utilisée comme methode non chirurgicale en appliguant la technique d'insertion de la quinacrine.

Des études ont été entreprises sous l'égide de l'Association indienne de médecine rurale à Calcutta (Inde), dans le but d'elargir l'expérience acquise avec la quinacrine et d'étudier la tetracycline en tant que méthode de remplacement. Au cours de la période du 14 août au 28 juin 1984, 3 insertions de 200 mg de quinacrine ont été pratiquées sur 414 femmes. On a constaté 29 échecs et, d'après une table de survie portant sur 3 ans, un taux d'échec de 8.5%. Au cours de la période du 25 avril 1984 au 28 décembre 1984, 55 femmes ont reçu 3 insertions de 200 mg de tetracycline. Au 1 juillet 1986, il y avait eu 32 Qchecs parmi les 55 cas, soit un taux de 58%. Une étude plus récente basée sur une seule insertion de 1000 mg de tétracycline a également produit une proportion d'échecs d'une importance inacceptable.

Resumen

El método transcervical de comprimidos de quinacrina desarrollado por Zipper y colaboradores, es Potencialmente un métodc no quirúrgico que hacia mucha falta, seguro, economic0 y efectivo para la esterilización femenina. Este métodc utiliza un insertador de dispositivos intrauterinos para depositar 250 mg de comprimidos de hidroclorato de quinacrina en la cavidad uterina. No se han denunciado otros efectos colaterales mas que dolor Pasajero Y oligomenorrea.

La tetraciclina tiene una trayectoria establecida con antecedentes de seguridad. También se sabe que posee propiedades similares a la guinacrina comc agente esclerosante, con potencial para método no quirúrgico usando la técnica de inserción para la quinacrina.

Adv. Contracept. 2 (1986) 79-90

Clinico- pathological study of Fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets

R. N. MERCHANT[1], V. M. DOCTOR[2], S. S. THAKU[1], M. SINHA[2], C. L. JHAVERI[3], E. KESSEL[4] and S. D. MUMFORD[5]

[1]*B. Y. L. Nair Hospital and T. N. Medical College, Bombay 400008, India*
[2]*Breach Candy Hospital, Bombay 400026, India*
[3]*Chairman, Indian Fertility Research Programme, Bombay 400012, India*
[4]*Consultant, International Federation for Family Health, Chapel Hill, North Carolina, USA*
[5]*President, Center for Research on Population and Security, Research Triangle Park, North Carolina, USA*

Abstract

This study lends support to others indicating the apparent safety and effectiveness of multiple transcervical insertions of quinacrine hydrochloride as pellets in 240mg dosage to achieve permanent sterilization. In order to study the effects of the number of quinacrine pellet insertions and the site of placement of the pellets in the uterus of prehysterectomy volunteers, a scoring system of histological changes in the Fallopian tube was designed. Quinacrine pellets were deposited at the fundus using a straight inserter in 16 women, and at the cornua using a curved inserter in 17 women. Each group had at least five women receiving one, two or three insertions at one-week intervals. Results indicate that neither the number of insertions nor the place of deposition of the pellets affects the degree of tubal inflammation and fibrosis.

Introduction

There is an urgent need for a safe, effective and inexpensive non-surgical method of Fallopian tube occlusion to meet the rising demand for female sterilization, especially in rural areas of developing countries [1]. The method developed by Zipper and colleagues involving three transcervical insertions of 250mg of quinacrine hydrochloride a month apart using a modified copper-T IUD inserter has potential for meeting this need because of its simplicity, low cost and apparent

V-4

Fertility and Sterility 2001;75:830-31.

safety in limited clinical trials. The life-table failure rate is reported as 3.1% at one year after the third insertion in 128 women [2] A confirming study showed failure rates of 3.8% and 4.3% at the end of the second and third year respectively after the third insertion in 149 women [3].

Previous histopathologic studies of transcervical insertion of quinacrine pellets in prehysterectomy volunteers indicate that tubal occlusion is by inflammation and fibrosis is limited to the cornual area and intramural portion of the tube [4]. The endometrium appears to recover from any inflammatory response. Zipper provides evidence that the limited area of fibrosis is due to the protective action of zinc which is found to be at high levels in the endometrium but low in the Fallopian tube [5]. Wheeler has hypothesized that repeated insertions of quinacrine pellets are needed as it was thought that approximately half the open tubes were closed by each insertion [6].

Early studies of transcervical instillation of a slurry of quinacrine did indicate that repeated instillations improved efficacy [7]. Limited animal studies suggest that close placement of pellets near the ostia results in more intense inflammation and presumably fibrosis [8]. There is a need, however, for further clinical studies to determine the optimal number of transcervical insertions and placement of quinacrine pellets for tubal occlusion.

The purpose of this study was to observe hystopathologic effects on the uteri and Fallopian tubes of women receiving one, two or three transcervical insertions at one-week intervals of 240mg of quinacrine as pellets, when the pellets were deposited at the fundus or at the comual areas.

Materials and methods

Thirty-three women of reproductive age who were awaiting a hysterectomy for prolapse, non-malignant lesions of the cervix or dysfunctional uterine bleeding and who gave consent to participate in the study were selected. Four pellets of quinacrine hydrochloride, each of 60 mg, were inserted into the upper segment of the uterine cavity by means of a plastic cannula and a rod in a manner similar to

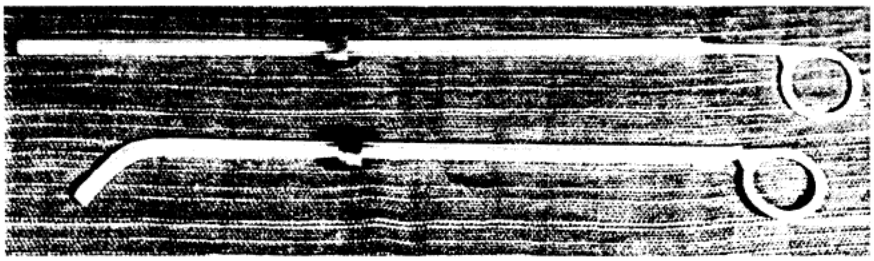


Figure 1 Straight and curved inserters for transcervical administration of quinacrine pellets at the fundus and at the cornua

the insertion of an IUD. As shown in Figure 1, two types of inserter were used: with the curved inserter, two quinacrine pellets were deposited in each cornu of

√- 5

Fertility and Sterility 2001;75:830-31.

the uterus and with the straight inserter, four quinacrine pellets were deposited

Table 1 Histopathological changes in intramural segment of Fallopian tubes by insertion technique and number of transcervical insertiqns of quinacrine pellets

Type and no. of insertions	*No. of cases*	*Total no. of intramurai tubes*	*Type of histopathological change* A	B	C
Straight Group I					
1	5	10	0	1	*9*
2	6	12	3	*2*	*7*
3	ɔ	10	4	*1*	ɔ
Total	16	32	7	4	21
			21.8%	*12.5 %*	*65.69'0*
Curved Group II					
1	7	14	4	4	*6*
2	5	10	2	1	*7*
3	5	10	3	0	*7*
Total	17	34	9	*5*	*20*
			26.5%	*14.7%*	*58.8%*

at the fundus. The study therefore included two groups of women (Table 1) who were alternately assigned to Group I (16 women) in whom straight inserters were used, and Group II (17 women) in whom curved inserters were used.

The number of insertions in each group was based on operating room schedules and the patient's need for surgery. In Group I, five women had one insertion of quinacrine, six had two insertions and five had three insertions. In Group II, seven women had one insertion, five had two insertions and five had three insertions. The second and third insertions were carried out at weekly intervals after the first. The first insertion was intended to be in the proliferative phase of the cycle (soon after cessation of the menstrual flow). This was so in the majority of women.

A total hysterectomy with bilateral salpingectomy (partial in most cases) was carried out at various intervals, usually between two and 12 weeks after the last quinacrine insertion. However, three women in Group I failed to keep their scheduled surgery dates and hysterectomy was carried out at eight months in two women and at nine months in one woman following the last quinacrine insertion. Similarly in Group II, hysterectomy was performed six months after the last quinacrine insertion in one woman and 11 months after in a second woman.

Each of the 33 uteri with varying segments of their Fallopian tubes were used for histopathological studies, with sections obtained from the cervix, endometrium, myometrium and different areas of each tube. Blocks of tissue 3mm thick were obtained serially from both cornua so as to obtain full lengths of intramural and isthmic tubes as described earlier by Merchant and colleagues [9]. The number of tubal sections averaged 16 per case. Routine haematoxylin and eosin sections were then prepared.

Fertility and Sterility 2001;75:830-31.

The pathologist was kept blind to clinical history and study assignment of subjects, and the histological changes identified in the Fallopian tubes were divided into the following three types:

Type A: A patent lumen, an intact epithelial lining and absence of significant inflammatory response or hyaiinization marked this group. Cases showing minimal submucosal inflammation were, however, included in this group. Figure 2 is an example of this type.

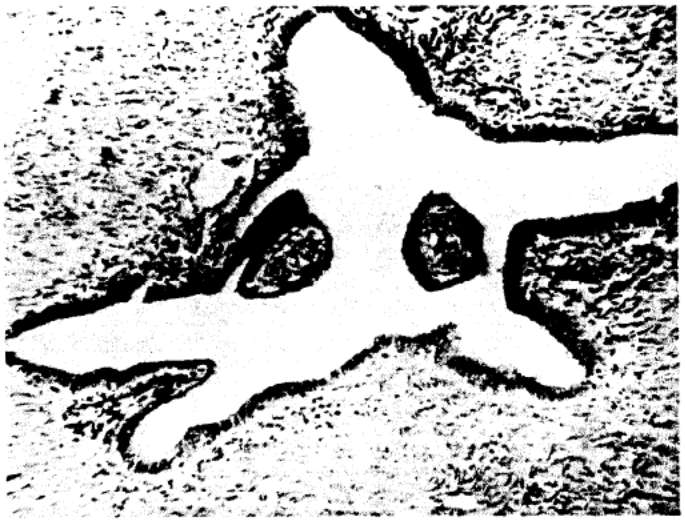


Figure 2 Type A change. The star-shaped patent lumen is lined by an intact mucosa. A sparse chronic inflammation is noted in the submucosa (x 100)

Type B: A spectrum of reactions ranging in intensity as in an inflammatory process was evident. The lumen was patent or slit-like, with an intact epithelial lining. The lamina propria or the muscularis revealed collections of inflammatory cells consisting of lymphocytes, histiocytes, eosinophils and frequently foreign body giant cells forming a granuloma, which at times was encroaching upon the tubal musculature or was associated with marked subepithelial hyalinization and fibrosis. Figure 3 is an example of this type.

Type C: The striking feature of this type was complete occlusion or only a slit-like lumen. The epithelial lining was completely lost. The surrounding lamina propria and muscularis showed a quiescent hyalinization to a variable depth. Figures 4 and 5 are examples of this type.

Histologically we would consider the 'B' and 'C' changes as having affected the tube with potentially occlusive changes, and 'A' changes as not having significantly affected the tubes, with likelihood of complete recovery.

V-7

Fertility and Sterility 2001;75:830-31.

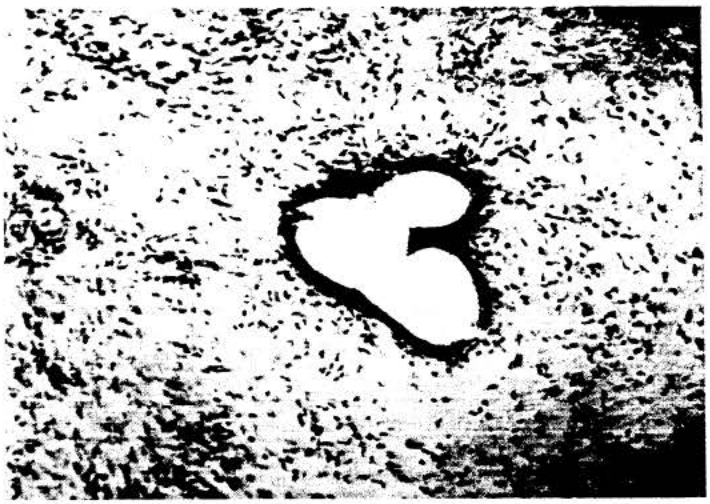


Figure 3 Type B change. Around the intact mucosa surrounding a patent lumen is seen variable fibrosis of the muscular layer. A sparse inflammation is present (x 100)

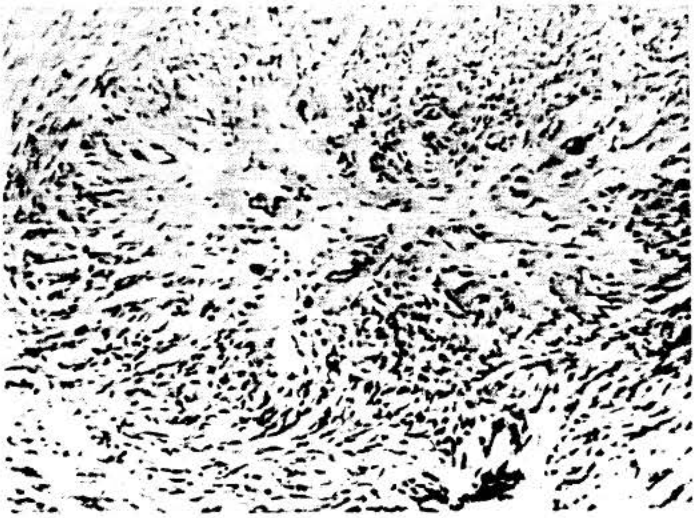


Figure 4 Type C change. There is complete loss of mucosa around a slit-like lumen. The muscular layer is fairly well preserved (x100)

V-8

Fertility and Sterility 2001;75:830-31.

Figure 5 Type C change. A slit-like lumen is seen with complete denudation of the epithelium. There is extensive fibrosis of the muscular layer (x 100)

Results

Table 1 shows the type of histological changes produced in both groups of cases and the number of weekly quinacrine insertions. Neither fundal or cornual placement of the pellets, i.e. curved or straight insertion technique, nor the number of quinacrine pellet insertions had any significant effect on the outcome of histopathological changes in the intramural tube.

Table 2 shows bilateral type B or type C changes by insertion technique, number of insertions, age, parity, clinical diagnosis, recent history of menorrhagia, time of quinacrine insertion in the menstrual cycle, insertion/hysterectomy interval and height of the endometrium in the hysterectomy specimen. Table 3 shows the same information for women with a type A change in either Fallopian tube. Bilateral occlusive-type changes (i.e. B or C type changes) were more likely to occur when quinacrine pellet insertions were in the proliferative phase of the menstrual cycle. Only one of the 21 women (4.7%) with the occlusive-type changes (Table 2) did not have at least one insertion by day 14 of the menstrual cycle and this woman had a recent history of menorrhagia. All of the 15 women with bilateral type C changes had at least one insertion as early as day 14 of the menstrual cycle. Of the 12 women with a type A change, two (16.7%) did not have an insertion of quinacrine pellets by day 14 of the menstrual cycle (Table 3). Of the four women with bilateral type A changes, all tended to have insertions late in the menstrual cycle and three out of four had a recent history of menorrhagia. One-third of the women with occlusive-type changes had a recent history of menorrhagia whereas half of the women with a type A change had such a history.

V-9

Table 2 Type B and Type C histological changes

Type and no. of insertions	Age (years)	Parity	Clinical diagnosis	Menorrhagia (recent)	Insertion day(s) of menstrual cycle (next cycle)	Insertion/ hysterectomy interval (weeks)	Type of histological changes in tubes		Height (mm) and menstrual phase or condition of endometrium in hysterectomy specimen	
							Right	Left		
Straight inserter										
Group I										
1	46	2	Myoma	–	10	3	C	C	3	Early secretory
3	34	5	Myoma	–	12 (4 12)	4	C	C	1	Proliferative
2	45	3	Myoma	+	8 14	8	C	C	2	Secretory
1	41	3	DUB	–	10	32	C	C	3	Proliferative
1	35	4	CIN	–	8	12	C	C	1	Proliferative
1	48	5	Prolapse	–	14	36	C	C	2	Proliferative
2	41	3	CIN	–	10 17	6	C	C	2	—
2	35	4	CIN	–	13 18	32	C	C	3	Proliferative
3	40	6	DUB	+	8 13 22	2	B	C	2	Necrotic endomctrium
1	32	7	DUB	+	16	6	B	C	1	Proliferative
2	35	3	CIN	–	12 19	6	B	B	1	Proliferative
Curved inserter										
Group II										
3	55	5	Myoma and DUB	–	7 13 18	11	C	C	7	Mild cystic hyperplasia
1	30	8	DUB	–	10	2	C	C	1	Proliferative
2	43	3	CIN	–	8 15	3	C	C	2	Proliferative
3	40	7	CIN	–	10 (6 13)	4	C	C	1.5	Secretory
2	45	6	DUB	–	10 15	4	C	C	3	Proliferative
1	43	4	Myoma	+	11	6	C	C	4	Cystic glandular hyperplasia
3	42	5	CIN	+	25 (6 13)	24	C	C	1	Proliferative
2	40	4	DUB	+	6 13	8	C	B	1	Secretory
1	47	2	Prolapse	–	9	12	C	B	2	Proliferative
1	40	4	DUB	+	11	6	B	B	2	Proliferative

DUB = dysfunctional uterine bleeding
CIN = cervical intraepithelial neoplasia

V-10

V-11

Table 3 Type A histological changes

Type and no. of insertions	Age (years)	Parity	Clinical diagnosis	Menorrhagia (recent)	Insertion day(s) of menstrual cycle (next cycle)	Insertion/hysterectomy interval (weeks)	Type of histological changes in tubes: Right	Type of histological changes in tubes: Left	Height (mm) and menstrual phase or condition of endometrium in hysterectomy specimen
Straight inserter									
Group I									
2	31	4	DUB and prolapse	+	14 20	6	A	A	4 Early secretory
3	35	1	DUB	+	13 17 24	8	A	A	4 Secretory
2	40	3	Prolapse	+	11 18	7	C	A	8 Proliferative
3	38	4	DUB and prolapse	+	11 20 27	11	A	C	1 Proliferative
3	35	0	DUB	+	5 11 20	12	C	A	1 Secretory
Curved inserter									
Group II									
1	45	3	Chronic PID	–	6	44	A	C	3 Proliferative
1	35	2	DUB	+	17	8	A	A	5 Secretory
3	35	3	CIN	–	25 (18) (21)	10	A	A	3 Secretory
2	35	3	Prolapse	–	10 17	6	C	A	3 Proliferative
2	45	5	CIN	+	12 20	7	C	A	1 Proliferative
3	45	6	Prolapse	–	12 19 23	12	C	A	8 Secretory
1	40	3	DUB	–	8	8	A	B	1 Proliferative

DUB = dysfunctional uterine bleeding
CIN = cervical intraepithelial neoplasia
PID = pelvic inflammatory disease

M

Fertility and Sterility 2001;75:830-31.

Neither the clinical diagnosis nor the insertion/hysterectomy interval appears to be related to histological changes in the Fallopian tubes.

The average age and parity of women with occlusive-type changes was 40.8 and 4.4 compared to 38.3 and 3.1 for women with a type A change. However, it is likely that this difference is due to the age distribution of women with and without a recent history of menorrhagia. The average age and parity of women without a recent history of menorrhagia was 40.8 and 4.1 compared to 33.6 and 3.5 for women with a recent history of menorrhagia.

The average height of both proliferative and secretory endometrium in specimens with occlusive-type intramural tube changes was 1.9 mm. For specimens with a type A change the average height of the proliferative endometrium was 2.8 mm and of the secretory endometrium 4.2 mm.

Table 4 Type of histological change by segment* of Fallopian tube and type of inserter among 33 women receiving one, two or three transcervical insertions of quinacrine pellets

Type of inserter and segment of Fallopian tube	Total tubes examined No.(%)	Type of histological changes		
		A No. (%)	B No. (%)	C No. (%)
Straight inserter				
Group I				
intramural	32 (100.0)	7 (21.9)	4 (12.5)	21 (65.6)
Isthmic	28 (87.5)	12 (37.5)	8 (25.0)	8 (25.0)
Ampullary	16 (50.0)	14 (43.8)	2 (6.2)	0 (0.0)
Fimbrial	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Curved inserter				
Group II				
Intramural	34 (100.0)	9 (26.5)	5 (14.7)	20 (58.8)
Isthmic	30 (88.2)	10 (29.4)	4 (11.8)	16 (47.0)
Ampullary	15 (44.1)	11 (32.4)	3 (8.8)	1 (2.9)
Fimbrial	4 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)

*** Available segments in surgical specimen**

Table 4 shows that the type of insertion technique (straight or curved inserter) did not influence the extent of the tube affected. However, with either delivery system the tube is progressively less affected on moving away from the uterine cavity. The fimbrial end was never affected, and no peritoneal involvement was noted at surgery.

There were no changes in the endometrium on examination of the uteri, and no changes were noted in the cervix. The presence of quinacrine was noted in the uterine cavity of four uteri where hysterectomy was performed within four weeks of the last quinacrine insertion, but no quinacrine was found in uteri examined four or more weeks after insertion.

In two cases which revealed a myoma (5-6 mm in size) at hysterectomy, only one tube out of four showed type C changes, while the other three showed type B changes.

V-12

Fertility and Sterility 2001;75:830-31.

No untoward side-effects of quinacrine pellet insertion were reported by any of the women. Six women complained of mild pain in the lower abdomen for a few hours to four days, but did not require any specific treatment. Ten women complained of a yellow vaginal discharge (quinacrine) for a few days following insertion.

Discussion

The present study supports other studies indicating that transcervical insertion of quinacrine pellets in a dosage of 240mg is free from serious side-effects. In this form and dosage the chemical remains in the uterine cavity for about three weeks, during which time it is absorbed or discharged into the vagina. Over this period it is believed to bring about inflammatory and fibrotic changes in the Fallopian tubes by physical contact.

An important drawback to the quinacrine pellet method of female non-surgical sterilization is the presumed need for three insertions, recommended generally at monthly intervals. The results of this study suggest that the **second** and third insertions may not contribute significantly to the efficacy of the method. Although our insertions were done at weekly rather than monthly intervals, the inflammatory process is likely to be well advanced in this time period.

Placement of these lo-minute dissolution pellets at the cornua did not affect the inflammatory process when compared to placement at the fundus. It is likely that as the pellets disintegrate a slurry is formed which is equally distributed throughout the uterine cavity.

The early work of Zipper and colleagues [7] with a quinacrine slurry indicated that the secretory endometrium would interfere with the action of quinacrine and Zipper has therefore recommended application in the proliferative phase of the menstrual cycle. Our data support this recommendation for the quinacrine pellet method and also suggest that greater height of the endometrium plays a protective role against the action of quinacrine.

The results of this study suggest that even a single insertion of quinacrine will be highly effective in bringing about occlusion of the tube provided the insertion is carried out during the proliferative phase of the cycle in a woman with no endometrial abnormality. Zipper's recommendation of repeated applications of quinacrine was based on his observations of the liquid quinacrine slurry [2,7]. Clinical trials of the quinacrine pellet method of non-surgical female sterilization do not provide evidence that repeated insertions improve efficiency. In Zipper's quinacrine pellet study [2] there was only one pregnancy between the first and third insertion of quinacrine pellets, which would only marginally raise the pregnancy rate of the method; there were no pregnancies between insertions in a confirming study [3]. Only a prospective trial of one insertion of quinacrine pellets can determine whether or not the second and third insertions increase efficacy of the method, and if so by how much.

A marked decline in side-effects of the quinacrine method of female sterilization was noted with the change from slurry to pellet [2]. Additional experience with

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

the quinacrine pellet method is needed to be confident that there are no rare or serious complications. If the safety can be documented and the single application of pellets does not appreciably increase the failure rate compared with the present recommended three insertions, as is suggested in our-data, a most useful new method of fertility control will be available to meet the growing demand for female sterilization in the world today. The benefits of the method could accrue to women in both deveioped and developing countries [l0].

Acknowledgements

We are grateful to Dr C. M. Alwani, Head of Department of Obstetrics and Gynaecology, Nair Hospital and the Dean, Dr B. Kalke, T. N. Medical College and Nair Hospital for permitting us to use the hospital data. The help of the Surgical Pathology Department of Breach Candy Hospital is much appreciated. This study was designed, monitored and supported by the Indian Fertility Research Programme.

References

1. Kessel, E. and Mumford, S. D. (1982). Potential demand for voluntary female sterilization in the 1980s: the compelling need for a non-surgical method. Fertil. Steril., 37, 725-733
2. Zipper, J., Cole, L. P., Goldsmith, A., Wheeler, R. and Rivera, M. (1980). Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. Int. J. Gynaecol. Obstet., 18, 275-279
3. Guzman-Serani, R., Bernales, A. and Cole, L. P. (1983). Quinacrine hydrochloride pellets: three-year follow-up on a non-surgical method of female sterilization. Contracept. Deliv. *Syst., 5,* 131-135
4. Bhatt, R. V. Aparicio, A., Laufe, L. E., Parmley, T. and King, T. M. (1980). Quinacrine-induced pathologic changes in the Fallopian tube. Fertil. *Steril.,* 33, 666-667
5. Zipper, J. and Insunza, S. (1972). Pharmacological agents that potentiate or inhibit the occlusive action of quinacrine in the rabbit tube and rat uterus. In: Female *Sterilization,* G. Duncan, R. D. Falb and J. J. Speidel, eds., Academic Press, New York and London, pp. 131-137
6. Wheeler, R. G. (1983). Delivery systems for applied quinacrine as a tubal closing agent. In: *Female transcervical sterilization. Proceedings* of *an international workshop on non-surgical methods of female occlusion, Chicago, Illinois, 24 June, 2982,* G. I. Zatuchni, J. D. Shelton, A. Goldsmith and J. J. Sciarra, eds., Harper & Row, Hagerstown, Maryland, pp. 105-113
7. Zipper, J., Stacchetti, E. and Medel, M. (1975). Transvaginal chemical sterilization: clinical use of quinacrine plus potentiating adjuvants. *Contraception, 12, 11-21*
8. Parmley, T. H., Dubin, N. H., Strandberg, J. and Laufe, L. E. (1983). Histologic changes following intrauterine administration of quinacrine hydrochloride. In: *Female transcervical sterilization. Proceedings of an international workshop on non-surgical methods of female occlusion, Chicago, Illinois, 24 June, 2982,* G. I. Zatuchni, J. D. Shelton, A. Goldsmith and J. J. Sciarra, eds., Harper & Row, Hagerstown, Maryland, pp. 89-93
9. Merchant, R. N., Prabhu, S. R. and Chougaie, A. (1983). Uterotubal junction-morphology and clinical aspects. *Int. J. Fertil.,* 28, 199-205
10. Kessel, E., Zipper, J. and Mumford, S. D. (1985). Quinacrine non-surgical female sterilization: a reassessment of safety and efficacy. *Fertil. Steril., 44, 293-298*

MS received Sept. 85.

Fertility and Sterility 2001;75:830-31.

Accepted for publication Jan. 86.

Resume

Cette etude vient appuyer d'autres recherches qui ont indique la securite et l'efficacite apparentes d'insertions transcervicales multiples de doses de 240 mg d'hydrochlorure de quinacrine en pillules pour obtenir une sterilisation. Pour Ptudier les effets d'un certain nombre d'insertions de piilules de quinacrine et d'insertions de pillules dans l'uterus de volontaires en pre-hysterectomie, un systeme de comptage des points a été conçu pour noter les changements hystologiques dans la trompe de Fallope. Des pillules de quinacrine ont été placées au fond de l'uterus de 16 femmes à l'aide d'un tube d'insertion droit et dans le col de 17 femmes à l'aide d'un tube d'insertion recourbé. Dans chaque groupe, au moins 5 femmes ont reçu une, deux ou trois insertions à une semaine d'intervalle. Les résultats indiquent que le nombre d'insertions et le point d'insertion de ces pillules n'ont aucun effet sur le taux d'incidence des inflammations des trompes et de fibroses.

Resumen

Este est-udio corrobora las conclusiones de ot-ros autores indicando la aparente inocuidad y efectividad de multiples inserciones transcervicales de 'pellets' de hidroclorato de quinacrina de 240 mg, a efecto de establecer una esterilización permanente. A fin de estudiar los efectos del número de inserciones de 'pellets' de quinacrina y el lugar de su emplazamiento en el útero, se estableció un sistema de puntaje para evaluar los cambios histológicos en la trompa de Fallopio en mujeres que iban a ser histerectomizadas. Los 'pellets' de quinacrina fueron depositados en el fondo del útero utilizando un insertor recto en *16* mujeres; y a nivel de los cuemos uterinos utilizando un insertador curvo en 17 mujeres. Cada grupo tuvo no menos de 5 mujeres con una, dos o tres inserciones semanales. Los resultados indican que ni el número de inserciones ni el lugar de emplazamiento de los 'pellets' afecta el grado de inflamación y fibrosis tubaria.

V. 15

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Scientific Articles

FERTILITY AND STERILITY

Vol. 44, No. 3, September 1985
Printed in U.S.A.

Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization*

Rohit Bhatt, M.D.
Cynthia S. Waszak, M.A.†

Baroda Medical College and Hospital, Baroda. India, and Family Health International, Research Triangle Park, North Carolina

Eighty-four women were admitted to a study in Baroda, India, designed for evaluation of the efficacy of three transcervical insertions of quinacrine hydrochloride pellets, each 1 month apart, in producing occlusion of the oviducts. A 4-year follow-up has been completed for 100% of the women. Three women became pregnant during the time between the first and thirdadministrations. Of the 81 women remaining in the study after administrations were complete, 3 became pregnant during the 4-year follow-up period, which resulted in a cumulative life-table pregnancy rate of 3.7 at 48 months. The results of this study indicate that intrauterine insertion of quinacrine pellets can be a safe, effective nonsurgical sterilization procedure.
Fertil Steril 44:303, 1985

The problems involved with the development of nonsurgical sterilization methods are (1) identification of the safest, most effective occluding agents (in the correct doses) and (2) provision of the appropriate form and typical delivery system. Richart[1] has reviewed the literature concerning methods and materials tested for this purpose. Chemicals that have been and are still being tested include silver nitrate, ethanol formalin, phenolmucilage, methylcyanoacrylate, quinacrine, and tetracycline. Delivery systems have included lavage, hysteroscopically guided tubal cannulation, intrauterine devices, and an intrauterine balloon instrument delivery system.

Received February 12, 1985; revised and accepted June 3, 1985.

*Supported in part by Family Health International with funds from the U.S. Agency for International Development and the Andrew W. Mellon Foundation.

†Reprint requests: Cynthia S. Waszak, M.A., Senior Research Analyst, Clinical Trials, Family Health International, Research Triangle Park, North Carolina 27709.

This article describes a clinical trial in which quinacrine hydrochloride pellets were inserted in the uterus via a plastic tube with a push rod, similar to an intrauterine device inserter. For over a decade Zipper and colleagues,' in Santiago, Chile, have been evaluating the use of quinacrine hydrochloride as an agent for occluding the oviducts. Their work has demonstrated the feasibility of the use of quinacrine in nonsurgical sterilization procedures. The quinacrine pellet dissolves and destroys the endometrium and the surface layers of the intramural portion of the tissue, which usually leads to occlusive fibrosis. This investigation was designed to evaluate this same method of Zipper et al.,[2] with the use of quinacrine in pellet form as a means of nonsurgical sterilization.

MATERIALS AND METHODS

This study was conducted at Baroda Medical College in Baroda, India. Eighty-four women who gave informed, consent were admitted to this study from June 1979 through January 1980. A

250-mg dose of quinacrine hydrochloride, in the form of seven cylindrical pellets, 3.3 mm in diameter, each 3 to 4 mm in length, was inserted into the uterus of each patient at each administration. Each woman was to receive one quinacrine administration upon admission. The second and third administrations were completed 1 and 2 months, respectively, after the first. Insertions were to be done during the proliferative phase of the menstrual cycle in interval women (women not pregnant within the last 42 days). No adjunctive methods of contraception were used after the first administration. Follow-up was scheduled at 6, 12, and 48 months after the last administration. Women were also asked to return at any time there were complications or complaints.

Women were admitted to the study if they requested sterilization for family planning reasons and if they did not have a history of medical or psychiatric problems. Excluded were women who had pathologic pelvic conditions (except cervicitis) or those who appeared unusually nervous. Those women who had to be excluded were offered a choice of surgical sterilization or another method of contraception.

PATIENT CHARACTERISTICS AND MOTIVATION

The majority of the women in this study were from urban areas (77.4%); the religion of almost all of the women was Hindu. The mean age was 31.3 years, ranging from 25 to 39 years. The median number of years of education was 4.4 years.

The mean number of live births for this population was 3.9, with a range of 2 to 6 live births. Most women had been using no contraceptives in the 3 months before this procedure. Most women reported that either they or their husbands were the most important people in their decisions to request sterilization, and over half the women (51.2%) cited the undesirable side effects of other contraceptive methods as the reason for choosing sterilization. The last pregnancy outcome before sterilization for over 80% of the women was a live birth, and the mean time interval between last pregnancy termination and first administration was 18.5 months.

RESULTS

All 84 women completed the first administration. One required analgesia during the procedure. Three procedures were associated with difficulties at the first administration; in each case the last quinacrine pellet fragmented during the insertion. Ten women (11.9%) experienced mild pain during the procedure. Two women (2.4%) had psychoemotional reactions to the procedure, described for both as "restlessness" and in one case "talking irrelevantly." Both reactions were short-lived and treated with diazepam.

Two women were discovered to be pregnant before the second quinacrine administration visit. Diagnosis was made by pelvic examination or a combination of pregnancy test and pelvic examination. In each case it was determined that the pregnancy occurred after the first quinacrine administration. Eighty-two women completed the second procedure. Mild or moderate pain was experienced by five women (6.1%) at the second administration.

An additional pregnancy was diagnosed by a pregnancy test and pelvic examination before the third quinacrine administration. Eighty-one women completed all three quinacrine administrations. Cervical dilation (7 mm) was required for one woman. One woman's last pellet fragmented during insertion. Four women reported mild pelvic pain (4.9%). One psychoemotional reaction for which no further description was given was reported at the third administration.

Follow-up was excellent in this study. All women who continued in the study were seen for a 4-year follow-up visit. Three pregnancies were diagnosed at 23, 25, and 26 months after completion of the last administration. One of these pregnancies occurred in a woman whose last pellet fragmented during the first administration. The cumulative life-table pregnancy rate at 48 months (Table 1) was 3.7/100 women.

Complications and complaints reported at follow-up visits are listed in Table 2. The most serious complication reported during this study was a

Table 1. *Pregnancy Rate Among 81 Women* Who Completed *Three Administrations*

Months after administration	Pregnancy rate	Follow-up rate[a]
		%
6	0.0 ± 0.0	100.0
12	0.0 ± 0.0	100.0
24	1.2 ± 1.2	100.0
36	3.7 ± 2.1	100.0
48	3.7 ± 2.1	100.0

[a]Follow-up rate is defined as the percentage of women not pregnant who returned for a follow-up visit.

Table 2. Complications and Complaints" Reported Within 4 Years After Three Administrations of Quinacrine Pellets (n = 81)

Complications/ complaints	No.	%
Amenorrhea	1	1.2
Menorrhagia	1	1.2
Hypertension	1	1.2
Pain in lower abdomen	2	2.4
Backache	3	3.6
Leukorrhea	4	5.0

[a]More than one complication/complaint may occur for each woman.

case of menorrhagia in a 37-year-old woman. An abdominal hysterectomy was performed 3 years after the sterilization procedure. Two women who reported abdominal pain were examined at their 48-month follow-up visit; for one woman there was a thickening in the right fornix, and for the second patient tenderness was elicited in the left fornix but no mass was felt. Other follow-up complaints included leukorrhea, backache, hypertension, and amenorrhea. None of these complications on complaints appeared to be related to the sterilization procedure itself.

A comparison of the menstrual cycle length and the duration of menstrual flow between presterilization and poststerilization data indicated no significant differences (Table 3).

DISCUSSION

The pregnancy rate for this study was acceptable for a nonsurgical method of sterilization and was comparable with another similar study in Valdivia, Chile.[3] The Chilean study, in which 151 women received the same quinacrine treatment, showed a 3-year pregnancy rate of 4.3. Studies have also been conducted in which quinacrine was delivered in three instillations in a solution (1500 mg of quinacrine hydrochloride dissolved in 5 ml of 2% lidocaine) rather than in pellet form. The results indicate that the solution method is less effective; the reported 24-month pregnancy rate was 13.1.[2]

The psychoemotional reactions (restlessness, talking irrelevantly) reported for three women in this study during the administration of the pellets were mild, were all treated effectively, and were transient. These reactions are similar to reactions seen by the investigator in women undergoing surgical sterilization and are considered to be related to the woman's feelings about the sterilization. Similar psychoemotional reactions have been reported previously in studies evaluating intrauterine administration of quinacrine hydrochloride in both pellet and liquid form. The incidence has been low in all reports.[2, 4, 5]

Chandra and Malaviya[6] have demonstrated the toxicity of intraperitoneal and intravenous administrations of quinacrine in rhesus monkeys, although intrauterine administrations in the same study were well tolerated. Researchers developing quinacrine as a tubal occluding agent are concerned about the possibility of quinacrine spilling into the abdominal cavity as a result of uterine perforation at insertion. There were no uterine perforations during the insertions in this study, however; nor have any perforations been reported for other similar studies.

The results of this trial suggest that quinacrine hydrochloride may effectively occlude the oviducts. However, both oviducts are not always occluded at the first insertion, so the repeat procedures are necessary. The need for repeat procedures was demonstrated by a study conducted to determine the histologic effects of quinacrine pellets.[7] One dose of 250 mg of quinacrine pellets was administered to volunteers scheduled for hysterectomies in 30 days. Tubal specimens indicated that quinacrine can induce tubal fibrosis with subsequent permanent tubal occlusion. However: "The most striking finding of this limited study was the erratic distribution of pathologic lesions. The presence of a lesion in the tubes studied was not predictable. In a single specimen, the right tube might have revealed luminal obliteration while the left tube appeared to be intact. This finding may relate to the delivery system and may explain the need for three instillations to achieve an acceptable pregnancy rate for a chemical sterilization program."[7]

Table 3. *Menstrual Pattern Data Before and After Sterilization*

	Before procedure (N=84)	6 months (n = 81)	48 months (n = 78)
Average cycle length (days)			
Mean	28.2	28.6	28.4
Range	26-34	25-36	24–35
% Irregular	2.4	1.2	0.0
Average duration of flow (days)			
Mean	3.6	3.4	3.7
Range	2-6	2–6	2-8

One cannot judge from the data gathered for this study whether two administrations might have been as effective as three. One woman who received only two administrations did get pregnant before her third administration. There is no way to estimate how the 2- and 3-year pregnancy rates for two administrations would compare with those of women receiving three administrations without an appropriate comparison group. The rate of release of quinacrine and the possible use of adjunctive therapies to improve passage of quinacrine from the uterus to the oviducts are areas in which future nonsurgical sterilization research needs more work. Additionally, new occluding agents need to be identified. Trials are currently being conducted by Family Health International with tetracycline, which, like quinacrine, has been used to adhese the pleura in human beings and which might have a higher therapeutic index.

Even though mortality related to surgical sterilization is low, there are still some risks associated with the surgical procedure. Anesthesia overdose, tetanus, intraperitoneal hemorrhage, and infection have been identified as reasons for sterilization-related deaths in the Indian subcontinent country of Bangladesh.' These risks, as well as the unmet demand for sterilization, are reasons for the urgent need for the development of nonsurgical sterilization procedures.

REFERENCES

1. Richart R: The use of chemical agents in female sterilization. In Female Transcervical Sterilization. Philadelphia, Harper & Row, 1983, p 24
2. Zipper J, Edelman D, Cole L, Rivera M: Overview of clinical trials with quinacrine. In Female Transcervical Sterilization. Philadelphia, Harper & Row, 1983, p 94
3. Guzman-Serani R, Bernales A, Cole L: Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. Contracept Deliv Syst 5:131, 1984
4. Dubin N, Parmley T, Diblasi M, Ghodgaonkar R, Jiffry M, Blake D, King T: Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In Female Transcervical Sterilization. Philadelphia, Harper & Row, 1983, p 60
5. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M: Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 18:275, 1980
6. Chandra H, Malaviya B: Toxic effects of quinacrine hydrochloride in rhesus monkeys. Contraception 24:269, 1981
7. Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM: Quinacrine-induced pathologic changes in the fallopian tube. Fertil Steril 33:666, 1980
8. Grimes D, Peterson H, Rosenberg M, Fishburne J, Rochat R, Khan A, Islam R: Sterilization-attributable deaths in Bangladesh. Int J Gynaecol Obstet 20:149, 1982

Non-Surgical Tubal Occlusion

R. Guzman-Serani, M. Potts and R. G. Wheeler

Department of Obstetrics and Gynecology, Austral University of Chile, Valdivia Chile *and Family Health International, Research* Triangle Park, *North Carolina, 27709, USA*

ABSTRACT

Out of 151 women provided with chemical female sterilization with three insertions of 250 mg. of quinacrine spaced one month apart, there were *seven* pregnancies in *3 years.* If these pregnancies were a result of failure to occlude the entrance to one *or* both fallopian tubes, birth events should decrease exponentially with time. Unexpectedly, the low failure rate has not decreased significantly *over* the S-year observation period.

INTRODUCTION

A non-surgical transcervical method of tubal occlusion, if perfected, would be particularly useful in countries where medical services are overstretched but the demand for voluntary sterilization high *(3).* Of the numerous transcervical methods of female sterilization under development (5) ,quinacrine hydrochloride in a tableted dosage is a leading contender. If chemical sterilization is to become generally available, it is important to determine the long-term effects.

METHODS

We reported on the results of 3 years of follow-up on 151 women who volunteered for intrauterine administration of quinacrine hydrochloride (2). Quinacrine tablets 3.2 mm in diameter containing 250 mg had been delivered to the uterus through an IUD-inserter tube. Each subject received three separate insertions of 250 mg tablets separated by an interval of I month. Three-year follow-up has now been completed. By the end of the 38th month of observation, seven pregnancies had occurred and were distributed evenly over the whole interval. The 36-month life-table pregnancy rates are reproduced in Table 1. This short report compares the expected exponentially distributed frequency of pregnancies with the observed frequency to illustrate the need for a better understanding of the mechanism of failure.

RESULTS

Figure 1 represents three different models to explain the observed spacing of the pregnancies. These data correspond to the life-table results presented in Table 1, by Guzman-Serani et al. (2). The solid curve assumes a constant pregnancy rate and assumes that the pregnancy rate for the women lost to follow-up was the same as the rate for the women who were fc lowed for 38 months. The broken curve assumes a'constant pregnancy rat e but also assumes all women who started the program and experienced an accidental pregnancy returned to the clinic. Both models fit the observ ed pregnancy distribution reasonably well. Quinacrine "sterilization" results in a constant low pregnancy rate of 1. 5-2 per 100 women per year. One hypothesis concerning the action of tubal sclerosing agents is that method failure is more commonly unilateral than bilateral. One patent tube sho uld give a fecundity one-half the normal, or conservatively 0.1 pregnancies per month for each subject with one tube patent, Given that seven pregnancies occurred and the pregnancy rate was 0.1 per month, then the most likely times for the pregnancies number I, 2, ... 7 are 1.27, 2.73, 4.46, 6.58, 9.31, 13. 16 and 19.74 months, respectively. The broken curve in the figure is based on these times; it does not fit the observed pregnancies .

DISCUSSION

The uniform distribution of pregnancies is similar to that of a model for an effective contraceptive and does not support a hypothesis that sterilization method failure leave one or both tubes patent. Thus, the term "non-reversible chemical contraception" may be more accurate than chemical or non-surgical sterilization. These data, based on three insertions of quinacrine spaced I month apart, raise an interesting question about wha: the pregnancy distribution would be if only one insertion were used. Would the treatment act like a contraceptive with a low efficacy, a mixture of tubal occlusion-and no occlusion, or some other combination? Is there a constant probability of tubal repair?

The quinacrine tablets used in this study had a nominal dissolution time of IO min. Preliminary studies with 100 min dissolution time tablets indicate they may be associated with a greater probability of tubal occlusion than the IO mln tablets (4). If this suggestion is confirmed, we hope to compare results with one, two and three insertions. These results may provide a basis for estimating the relative importance of failure to occlude and repair of occlusion as causes of method failure. It is intended to continue intensive follow-up of this group of women, together with parallel studies by Zipper (4) and Bhatt and Waszak (1) to maintain a cohort of women who have been treated with quinacrine pellets. We expect them to be increasingly valuable for studying the long-term event rates of tubal occlusion with quinacrine hydrochloride.

VIII-15

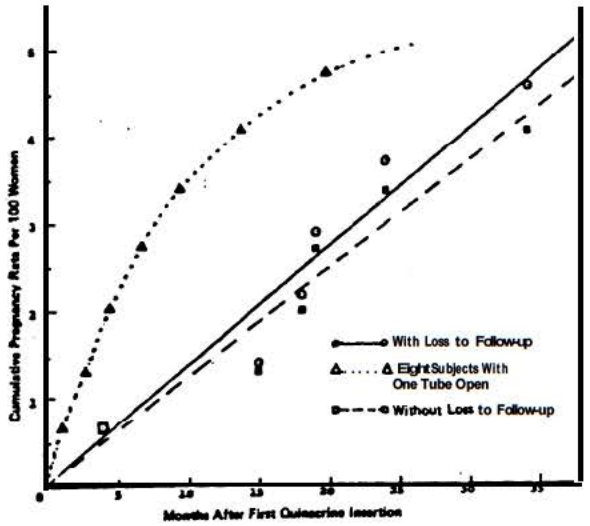


Figure 1. Time distribution of seven pregnancies occurring after 150 women were treated with three intrauterine doses of 250 mg quinacrine tablets at the beginning of months I, 2 and 3. The-ordinate is the cumulative risk of pregnancy conditional upon surv v ng to the beg nn ng of the month w thout a pregnancy The solid and broker lines represent a model in which the risk of pregnancy remains constant over time. The broken line assumes all pregnancy women come back to the clinic and the solid line is based on an observed follow-up rate of .09921 per month. In the dotted curve, the most likely distribution of pregnancies and cumulative hazard rate is illustrated assuming that eight of the 150 procedures failed to close one tube. This model does not fit the observations.

Table 1. Cumulative gross life-table pregnancy rates per 100 women who completed three insertions of quinacrine hydrochloride pellets.

Period of IUD use (month)	Pregnancy rate	Follow-up rate
6	0.7±0.7	loo. 0
12	0.7±0.7	99 3
24	3.4±1.5	97 2
36	4.3±1.7	81.1

N = 149

REFERENCES

1. Bhatt, R. and Waszak, C. (1984). Quinacrine hydrochloride pellets: four-year follow-up on nonsurgical method of female sterilizatic n. *(In* preparation).
2. Guzman-Serani, R, Berna es Al, and Cole, L.P. (1984). Quinacrine hydrochloride pellets : Three-year follow-up on a nonsurgical method of female sterilization. Contracept, Deliv. Syst. 5 131-135
3. Kessel, E., a n d Mumford, M (1982). Potential demand for voluntary female sterilization in the 1980s: the compelling need for a nonsurgical method. Fertil.' Steril 37.
4. Letter from Dr. Jaime Zipper dated December 1983 (Santiago Chile)
5. Zatuchni, C.I., Shelton, J.D Goldsmith, A. and Sciarra, J.D. (19'83) Transcervicai Sterilization, PARFR Series *on* Fertility Regulation, Harper & Row, Philadelphia.

VIII-16

Fertility and Sterility 2001;75:830-31.

FERTILITY AND STERILITY

Vol. 44, No. 3. September 1985
Printed in USA.

Quinacrine nonsurgical female sterilization: a reassessment of safety and efficacy

Elton Kessel, M.D., M.P.H.
Jaime Zipper, M.D.
Stephen D. Mumford, Dr.P.H., M.P.H.

International Federation for Family Health, Chapel Hill, North Carolina, Hospital Sotero del Rio, Puente Alto, Chile, and Center for Research on Population and Security, Research Triangle Park, North Carolina

Sterilization is currently the most prevalent contraceptive method in the world; the demand for female sterilization, especially in developing countries, is likely to sharply rise in the remainder of this decade.[1] The need for a safe, inexpensive, and effective method of female sterilization to meet this need is a high priority for fertility research. The acceptable nonsurgical female sterilization method has been described as one that is safe, 95% effective, that can be performed by nonphysicians on an outpatient basis after a brief training period, and that requires only a single visit by the woman.[2]

The transcervical quinacrine pellet method developed by Zipper and co-workers,[3] which utilizes an intrauterine device inserter to deposit 250 mg of quinacrine hydrochloride as pellets in the uterine cavity, has potential for meeting this description. Prehysterectomy studies of the quinacrine pellet method in women showed that quinacrine produces inflammation and fibrosis that is confined primarily to the intramural portion of the fallopian tube.[4]

This method can be performed by nonphysicians on an outpatient basis after a brief training period or by any personnel capable of performing an intrauterine device insertion. In the studies of the quinacrine pellet method for female sterilization reported to date,[5-7] the method appears to be quite safe. No complications or side effects, other than temporary pain and oligomenorrhea, have been reported. However, greater experience is needed to ensure that there will not be a rare, serious complication.

The method does appear to be 95% effective after 3 years[6]; this is with three insertions of quinacrine pellets, each 1 month apart. However, a survey of the literature reveals that three insertions of the pellets has never been clinically shown to be superior to a single insertion.

Both the safety and effectiveness of the quinacrine pellet method must be judged in comparison to surgical methods. In this article, we reexamine reported complications and pregnancy failures of surgical methods and the quinacrine method of female sterilization in order to evaluate each method's relative safety; we also examine the presently assumed need for multiple insertions of quinacrine pellets for the achievement of acceptable efficacy.

RELATIVE SAFETY OF THE QUINACRINE PELLET METHOD

We studied three parameters in order to examine the relative safety of the quinacrine pellet female sterilization method. These were toxicology, complications, and mortality.

TOXICOLOGY

Toxicology studies were previously performed and approved by the United States Food and Drug Administration for premarketing requirements of quinacrine used orally as a malaria suppressant drug during World War II by millions of soldiers in the dose of 100 mg daily. In this extensive experience, there were a few cases of dermatitis

and rare cases of convulsions or transient toxic psychosis reported; the only common side effect was discoloration of skin after chronic use.'

Toxicology studies of the quinacrine sterilization method in cynomolgus monkeys were encouraging with twice the comparative human dose in the form of a solution for both intravascular and intrauterine administration.[9,10] Quinacrine was localized in nuclei of epithelial and stromal cells of the endometrium and in epithelial cells of the intramural section of the tube after intrauterine administration, which is consistent with reports that quinacrine intercalates with deoxyribonucleic acid." This however does not appear to be the basis of tissue damage, because quinacrine was detected by histofluorescence in nuclei of these tissues after intravascular quinacrine administration with no histologic damage to any reproductive tissue observed at 24 hours. Within 1 month all tissue levels of quinacrine were at or near the limit of detection.

Intraperitoneal placement of 250 mg of quinacrine pellets in cynomolgus monkeys (approximately 15 times the human dose by body weight) has caused death in two of three monkeys." Blood levels in these monkeys were even higher than those for intravascular administration of quinacrine. No deaths occurred among three monkeys that received 125 mg of quinacrine pellets intraperitoneally. These findings are relevant to possible accidental perforation of the uterus in clinical use of the quinacrine pellet method.

COMPLICATIONS

No serious complications or side effects have been reported to date in over 1000 insertions of quinacrine pellets.[5-7] Earlier studies with a liquid slurry of 1500 mg of quinacrine did produce a 2% rate of transient toxic psychosis shortly after quinacrine instillation, but this has not appeared with the 250-mg quinacrine pellet method.[3] An additional aspect of safety is the complications related to pregnancy failures. Of greatest concern in pregnancy failures is the risk of ectopic pregnancy.

Unlike failures of surgical methods, there is no increase in expected rate of ectopic pregnancy among failures of the quinacrine method. In published reports of pregnancy failures after transcervical application of quinacrine as a slurry or as pellets involving 1723 women, there were 125 pregnancies, of which only 1 (0.8%) was an ectopic pregnancy.[5-7,13-15] This rate is not significantly different from the expected rate of 1 in 200 to 300 pregnancies in a noncontracepting population.

The ectopic pregnancy rate reported by Chi and co-workers[16] was 7.7% among 194 failures of surgical sterilization methods followed up for 6 months or more in 23,600 women enrolled in clinical studies at the International Fertility Research Program. This rate is probably conservative in view of other reports of higher rates.",[18]

The pattern of failures for the quinacrine pellet and the surgical methods are quite different. In the case of surgical methods, the intrauterine pregnancy failure rate declines with time since sterilization, whereas the ectopic pregnancy rate remains constant over time.[16] However, in marked contrast, in the case of the quinacrine pellet method, the intrauterine pregnancy failure rate is constant with time since sterilization,[6] whereas ectopic pregnancies are rare.

Both this difference in pattern of failures resulting in intrauterine pregnancy and the absence of increased risk of ectopic pregnancy for the quinacrine method point to a different biologic process involved in at least some failures of the surgical and quinacrine methods of sterilization.

A possible explanation for these differences in ectopic rates is that surgical sterilization method failures that are ectopic involve fistulae formation secondary to endometriosis in the tubal stump.[19] Extensive damage to the tubal muscularis is likely required for this process, because there is a greater probability of ectopic pregnancy among electrocoagulation-method failures.[18,20]

It is likely that fistulae formation is more important in ectopic pregnancy failures than in intrauterine pregnancy failures after surgical methods of sterilization. Fistulae require time to develop, and there is an increase in the number of fistulae found in the medial tubal stump with time. There is also a delay in the appearance of ectopic pregnancies compared with intrauterine pregnancy failures after surgical sterilization.[16] Sperm are more likely to traverse the fistula and fertilize the egg in the distal segment of the tube than the egg is to traverse the fistula, which is necessary for intrauterine pregnancy. Indeed, ectopic pregnancies after surgical sterilization are generally found in the distal tubal segment.[21]

Apparently, if there is recovery from the insult of quinacrine to the fallopian tubes, it is rela-

tively complete or in some women there is a way that the tubes are protected from the insult of exposure to quinacrine. The fact that the intramural fibrosis of the quinacrine method in no way interrupts the continuity of the tubal muscularis and leaves no tubal stump to receive an endometrial implant to start a process of endometriosis may explain the absence of increased risk of ectopic pregnancy in failures of the quinacrine method.

In comparing risks of ectopic pregnancy after surgical versus quinacrine pellet methods of sterilization, the following estimates can serve as a guide. At the end of the first year, surgical methods have an ectopic pregnancy rate of approximately 0.75/1000 procedures, which rises to approximately 2.15/1000 procedures at the end of the second year.[16] For the quinacrine pellet method, which has a uterine pregnancy rate of 31/1000 at 1 year[3] and 4311000 at the end of the second year,[6] the ectopic pregnancy rate is approximately 1/125 pregnancies, or 0.24/1000 sterilizations, at the end of the first year and 0.34/1000 at the end of the second year. These rates are one third and one sixth those of surgical procedures.

In an analysis of 14,910 surgical sterilization procedures, a complication rate of 1511000 has been reported.[22] However, in this large series none of the complications were nearly as serious as ectopic pregnancy. The surgical sterilization morbidity of 2.15 ectopic pregnancies/1000 procedures should have been added to the 15/1000 other lesser early complications of surgical sterilization. The lower ectopic pregnancy rate of the quinacrine pellet method and the virtual absence of reported serious complications of the method to date would make the quinacrine pellet method favorable except that experience with the method is, as yet, too limited.

MORTALITY

The mortality attributable to sterilization depends upon mortality of the sterilization procedure, maternal mortality related to procedure failure ending in abortion or delivery, and the case fatality of ectopic pregnancies among failures of the procedure. There are marked differences in these risks both for surgical sterilization versus nonsurgical quinacrine sterilization and for developing versus developed countries.

Table. 1 illustrates the contrasts in estimated mortality associated with surgical female sterilization and quinacrine nonsurgical female sterilization procedures for Bangladesh and the United States. The surgical procedure mortality estimates are taken from Peterson and co-workers.[23]* We have already estimated the incidence of ectopic pregnancies for the surgical and nonsurgical procedures. The case/fatality rate for ectopic pregnancy in the United States is estimated at 0.08%.[24] Reliable estimates of ectopic pregnancy case/fatality rates do not exist for developing countries. We have applied a rate of 5% for Bangladesh, which is in the same ratio as the reported maternal mortality rates for Bangladesh (570 deaths/100,000 live births)[25] and the United States (7.9 deaths/100,000 live births).[26] This estimate is further supported by the report of Begum,[30] who found a mortality rate of 5.1% among all ectopic pregnancy cases admitted to Dhaka Medical College Hospital in Dhaka, Bangladesh in 1984. The delivery/abortion mortality is calculated by applying the maternal mortality rates to the failures for surgical sterilization, estimated at 0.5%,[22] and for quinacrine nonsurgical sterilization, estimated at 5%.[6]

The contrasts by both method and country are dramatic. One third of attributable surgical sterilization mortality is due to ectopic pregnancy in Bangladesh, whereas this accounts for < 5% of

Table 1. *Estimated Deaths Attributed to Surgical Female Sterilization and Nonsurgical Quinacrine Female Sterilization in Bangladesh and the United States (Per 100,000 Procedures)*

	Surgical sterilization		Nonsurgical sterilization	
	Bangladesh	U.S.	Bangladesh	U.S.
Procedure mortality	19.0	4.0	0.0"	0.0"
Ectopic pregnancy mortality	10.7	0.2	1.7	< 0.1
Delivery/abortion mortality	2.9	< 0.1	28.5	0.4
Attributable mortality	32.6	4.2	30.2	0.4

"Based on limited published reports (see text).

*The estimated rate of surgical sterilization mortality of 0.19/1000 procedures is probably conservative for the Indian subcontinent. Other reports have estimated the rate as five times greater in this region.[27,28] A lower rate of 0.0611000 procedures was reported to the International Project of the Association for Voluntary Sterilization in a survey of their funded projects worldwide that had performed 225,812 female sterilizations.[29] This lower rate probably involves both greater underreporting of deaths from service programs without an active surveillance system and actual lower rates in developing countries with better staffing and facilities.

attributable mortality in the United States. The lower ectopic pregnancy and procedure mortality of the quinacrine method in Bangladesh is offset by the method's higher failure rate and the country's high maternal mortality for abortion and delivery. This offset could, however, be moderated by the provision of safe menstrual regulation services for failures of this method. For the United States, a tenfold reduction in attributable sterilization mortality would be expected with the use of the quinacrine pellet method. These estimates are, of course, based on limited experience to date with the quinacrine pellet method.

The main advantage for a country like Bangladesh in using the quinacrine pellet method, besides its lower cost, is its potential for extension of present sterilization services. If two pregnancies are. prevented by each sterilization procedure, then over 1000 maternal mortalities (roughly twice the maternal mortality rate), would be prevented for each 100,000 quinacrine pellet sterilizations performed as compared to the method's attributable mortality of 30.2/100,000 procedures. For countries with intermediate maternal mortality and ectopic case mortality between that of Bangladesh and the United States, the quinacrine pellkt method has an advantage in terms of reproductive mortality even without consideration of its lower cost or potential for expansion of sterilization services. Again, these projections are based on the limited experience we have with the quinacrine pellet method. But it is also clear from this analysis that the method would have to have a very high procedure mortality in future experience in order to overcome its present apparent favorable risk/benefit ratio in either developing or developed countries.

MULTIPLE QUINACRINE PELLET INSERTIONS

The need for multiple applications of quinacrine for the achievement of a reasonable level of efficacy was demonstrated for the quinacrine liquid slurry formulation." Rates of tubal obstruction, as evidenced by CO_2 insufflation tests, were 54.9% after one instillation and 57.1% after a second instillation 1 month later among those women with tubal patency after one instillation, resulting in a cumulative nonpatency rate of 87.7%" Further evidence for the need of multiple instillations of the quinacrine slurry are the pregnancies occurring between instillations in a three-instillation study." Among 240 women who received a first instillation, 18 became pregnant before the second instillation. An additional 23 women became pregnant before the third instillation. Even after the third instillation, the life-table pregnancy rate was 9.1/100 women at 1 year.[3]

Experience with transcervical insertions of quinacrine pellets is remarkably different. In Zipper and co-workers' first report of 139 women, there was only one pregnancy between the first and second insertion and none between the second and third insertion of quinacrine pellets.[1] The pregnancy rate at 1 year after the third insertion was 3.1.[3] Additional experience confirms both the low pregnancy rate after 1 year and the marked reduction in pregnancies between quinacrine pellet insertions compared with that 01[1] quinacrine slurry instillations.[5-7] The combined experience of Zipper and Guzman-Serani and their co-workers[5, 6] shows that among 454 women entering their quinacrine pellet studies of three monthly insertions, 5 women became pregnant between insertions and l-year pregnancy rates after the third insertion ranged from 0.7/100 women to 4.31100 women. It appears that pregnancy failures between quinacrine pellet insertions would only marginally affect efficacy of the method. The question remains as to what contribution the second and third quinacrine pellet insertions make to efficacy of this method. This question has not been studied. Only a prospective study of one insertion of quinacrine pellets can provide the answer.

The increased efficacy of quinacrine pellets over the quinacrine slurry is probably related to a more prolonged high concentration of quinacrine in the uterine cavity for the pellets. The pellets used in the referenced studies have a 10-minute release time. Prolongation of this release time may be accompanied by a decline in concentration of quinacrine if quinacrine absorption through the endometrium is greater than the release rate. Studies in cynomolgus monkeys of 800-minute and 7-day quinacrine release preparations showed no damage to the fallopian tubes,[31] whereas a quinacrine slurry or lo-minute pellets did damage the tubes of the cynomolgus monkey.[9, 32] It is likely that the most efficacious release rate for quinacrine pellets lies somewhere between 10 and 800 minutes, but it could also be somewhat less than 10 minutes. Prospective stud-

ies in female volunteers are needed to determine the optimal release rate of quinacrine.

The reexamination of the assumption that three monthly insertions of quinacrine pellets are necessary for acceptable efficacy points to an urgent need for a prospective study of one insertion of quinacrine pellets.

CONCLUSIONS

The relative safety and efficacy of surgical methods and nonsurgical quinacrine pellet methods of female sterilization have been reassessed. Although experience with the quinacrine pellet method is limited, it appears to have advantages for both developing and developed countries. Its failure rate at 3 years after three transcervical insertions of 250 mg of quinacrine in pellets is approximately 5%, compared with 0.5% for surgical sterilization. But the method can be delivered in any clinical setting capable of performing an intrauterine device insertion. The absence of increased risk of ectopic pregnancy among quinacrine pellet method failures has been noted. It is estimated that ectopic pregnancy accounts for one third of surgical sterilization mortality in a country like Bangladesh, whereas it accounts for < 5% of sterilization mortality in the United States.

The need for multiple insertions of quinacrine pellets for the achievement of acceptable efficacy has not been demonstrated clinically. A single insertion trial is a high priority for fertility research.

REFERENCES

1. Kessel E, Mumford SD: Potential demand for voluntary female sterilization in the 1980s: the compelling need for a nonsurgical method. Fertil Steril 37:725, 1982
2. Klitsch M: Sterilization without surgery. Int Fam Plann Perspect 8:101, 1982
3. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M: Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 18:275, 1980
4. Bhatt RV, Aparicio A, Laufe LE, Parmley T, King TM: Quinacrine-induced pathologic changes in the fallopian tube. Fertil Steril 33:666, 1980
5. Zipper J, Edelman D, Cole LP, Rivera M: Overview of clinical trials with quinacrine. In Female Transcervical Sterilization: Proceedings of an International Workshop on Nonsurgical Methods. of Female Tubal Occlusion, Chicago, Illinois, June 24, 1982, Edited by GI Zatuchni, JD Shelton, A Goldsmith, JJ Sciarra. Hagerstown, Harper & Row, 1983, p 94
6. Guzman-Serani R, Bernales A, Cole LP: Quinacrine hydrochloride pellets: three-year follow-up on a nonsurgical method of female sterilization. Contracept Deliv Syst 5:131, 1983
7. Raj A, Chakravarty S: Permanent female sterilization by chemical method of transcervical insertion of quinacrine. In Proceedings of the Third International Seminar on Maternal and Perinatal Mortality, Pregnancy Termination and Sterilization, Edited by V Hingorani, RD Pandit, VL Bhargava. New Delhi, New Roxy Press, 1980, p 476
8. Steck EA: Chemotherapy of Protozoan Disease, Vol III. Washington, D.C., Walter Reed Army Institute of Research, U.S. Government Printing Office, 1972, p 23
9. Dubin NH, Strandberg JD, Craft CF, Parmley TH, Blake DA, King TM: Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry, and hematology in cynomolgus monkeys. Fertil Steril 38:741, 1982
10. Dubin NH, Blake DA, DiBlasi MC, Parmley TH, King TM: Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. Fertil Steril 38:735, 1982
11. Wersblem B, deHaseth PL: Quinacrine, a chromosome stain specific for deoxyadenylate-deoxythymidylate-rich regions in DNA. Proc Natl Acad Sci USA 69:629, 1972
12. Dubin NH, Parmley TH, DiBlasi MC, Ghodgaonkar RB, Jiffry MTM, Blake DA, King TM: Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In Female Transcervical Sterilization: Proceedings of an International Workshop on Nonsurgical Methods of Female Tubal Occlusion, Chicago, Illinois, June 24, 1982, Edited by GI Zatuchni, JD Shelton, A Goldsmith, JJ Sciarra. Hagerstown, Harper & Row, 1983, p 60
13. Isrankun D, Phaosavadi S, Neuwirth RS, Richart RM: Clinical evaluation of quinacrine hydrochloride for sterilization of the human female. Contraception 14:75, 1976
14. Mehtaji S, Jadwani K, Goyal V: Chemical sterilization with quinacrine. In Fourth Transaction of Scientific Papers, Edited by S Pachauri. Bombay, India Fertility Research Programme, 1977, p 167
15. Zipper J, Stacchetti E, Medel M: Transvaginal chemical sterilization: clinical use of quinacrine plus potentiating adjuvants. Contraception 12:11, 1975
16. Chi I-c, Laufe LE, Atwood RJ: Ectopic pregnancies following female sterilization procedures. Adv Plann Parent 16:52, 1981
17. Cheng MCE, Wong YM, Rochat RW, Ratnam SS: Sterilization failures in Singapore: an examination of ligation techniques and failure rates. Stud Fam Plann 8:109, 1977
18. Phillips JM, Hulka J, Hulka B, Keith L: American Association of Gynecologic Laparoscopists, 1976 membership survey. J Reprod Med 21:3, 1978
19. Rock JA, Parmley TH, King TM, Laufe LE, Su BC: Endometriosis and the development of tuboperitoneal fistulas after tubal ligation. Fertil Steril 3516, 1981
20. McCausland A: High rate of ectopic pregnancy following laparoscopic tubal coagulation failures. Am J Obstet Gynecol 13897, 1980
21. Qvigstad E, Jerve F: Ectopic pregnancy following tubal sterilization. Int J Gynaecol Obstet 20:279, 1982
22. Mumford SD, Bhiwandiwala PP, Chi I-c: Laparoscopic and minilaparotomy female sterilization compared in 15,167 cases. Lancet 2:1066, 1980

23. Peterson Hb, Lubell J, DeStefano F, Ory HW: The safety and efficacy of tubal sterilization: an international overview. Int J Gynaecol Obstet 21:139, 1983
24. Dorfman SF: Deaths from ectopic pregnancy, United States, 1979 to 1980. Obstet Gynecol 62:334, 1983
25. Chen LC, Gesche MC, Ahmed S, Chowdury AI, Mosley WH: Maternal mortality in rural Bangladesh. Stud Fam Plann 5:334, 1974
26. Advance Report on Final Mortality Statistics; 1982. Monthly Vital Statistics Report 33(9):38, 1984
27. Rosenberg MJ, Rochat RW, Akbar J, Gould P, Khan AR, Measham A. Jabeen S: Sterilization in Bangladesh: mortality, morbidity, and risk factors. Int J Gynaecol Obstet 20:283, 1982
28. Bhatt RV, Pachauri S, Pathak ND, Chauhan L: Female sterilization in small camp settings in rural India. Stud Fam Plann 9:39, 1978
29. Aubert JM, Lubell I, Schima M: Mortality risk associated with female sterilization. Int J Gynaecol- Obstet 18406, 1980
30. Begum SF: Unpublished data
31. Zaneveld LID, Goldsmith A: Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception 30:164, 1984
32. Dubin NH, Parmley TH, Ghodgaonkar RB, Strandberg JD, Rosenshein NB, King TM: Effect of intrauterine administration of tetracycline on cynomolgus monkeys. Contraception 29:561, 1984

Received June 3, 1985.
This study was supported in part by the International Association for Maternal and Neonatal Health, Geneva, Switzerland.
Elton Kessel, M.D., M.P H., International Federation for Family Health, Chapel Hill, North Carolina.
Jaime Zipper, M.D., Hospital Sotero del Rio, Puente Alto, Chile.
Reprint requests: Stephen D. Mumford, Dr.P.H., M.P.H., President, Center for Research on Population and Security, P.O. Box 13067, Research Triangle Park, North Carolina 27709.

Fertility and Sterility 2001;75:830-31.

Quinacrine Hydrochloride Pellets: Three-year Follow-up on a Non-surgical Method of Female Sterilization

1 2

R. GUZMAN-SERANI*, A. BERNALES* and L. P. COLE†

* *Universidad Austral, Valdivia, Chile*
† *Family Health* International

Abstract

The efficacy of three transcervical insertions of quinacrine hydrochloride pellets 1 month apart to produce tubal occlusion was evaluated in 151 women in Valdivia, Chile. Three-year follow-up has been completed for 81 % of the women. The gross life-table pregnancy rate was 4.3 per 100 women at 36 months after the third insertion. The intrauterine insertion of quinacrine pellets can be an effective non-surgical sterilization procedure.

Introduction

The demand for female sterilization far exceeds the ability of most countries to provide services. The development of a rapid, effective, safe method that can be performed by paramedical personnel remains a high priority.

Non-surgical sterilization techniques currently under investigation offer the possibility of such a procedure. Considerable research has focussed on tubal occlusion techniques involving the injection of pharmacologic agents and adhesive materials into the oviduct, either through the hysteroscope or through a blind transcervical delivery system.

For many years, Zipper and associates have evaluated the transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization. Their initial animal studies indicated that quinacrine selectively produced significant morphologic changes in the reproductive tract and caused permanent tubal fibrosis and occlusion in the rat (1). In clinical trials, Zipper **et *al.*** evaluated various doses, concentrations and solvents **for the suspension** as well as different instillation schedules of quinacrine (2,3). Three instillations proved the most effective schedule of quinacrine delivery, but there were still pregnancy rates of almost 10% (4).

Zipper's work led to the development of quinacrine hydrochloride pellets, a delivery system designed to bring the chemical into prolonged contact with the tubal ostia

Contraceptive Delioery Systems: An *International Journal.* ISSN 0143-6112.

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.

through uterine retention. Results of an early study were encouraging: at 1 year after three insertions of 250 mg quinacrine pellets, the cumulative gross life-table pregnancy rate was 3.1 per 100 women (5).

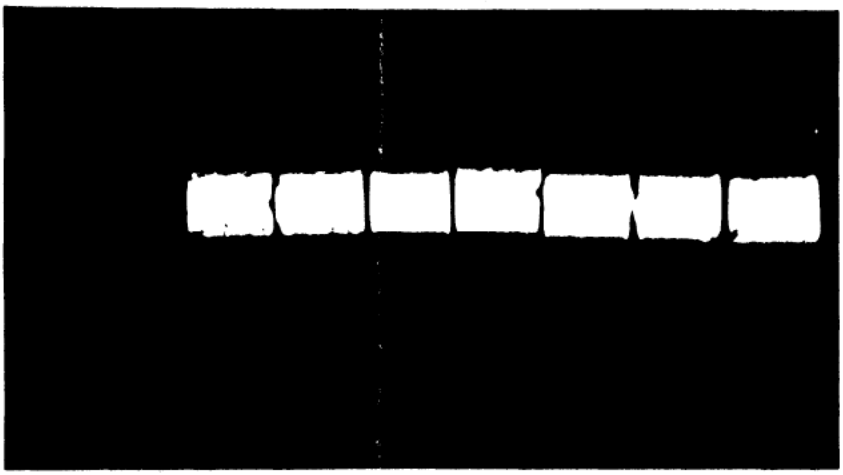
A three-center clinical trial was conducted to further evaluate the efficacy of the yuinacrine pellet method of non-surgical sterilization. Results of this trial have been reported previously (6,7). This paper presents 3-year follow-up data on women at one center who participated in the trial.

Materials and methods

Each yuinacrine hydrochloride pellet is cylindrical and has a diameter of less than 4 mm. The pellets are compacted to contain 10 mg quinacrine per millimeter of length (Figure 1). Insertion is accomplished by placing the pellets in a plastic tube with a push rod positioned behind them. The insertion procedure is essentially the same as that for inserting an IUD (Figure 2).

From March to the end of December 1979, 151 women at an outpatient clinic at the Universidad Austral de Chile School of Medicine, Valdivia, Chile, entered the study after giving informed consent. Seven pellets containing a total of 250 mg quinacrine hydrochloride were to be inserted at admission and again at 1 month and 2 months after admission. Insertions were performed during the proliferative phase of the menstrual cycle in women who had not recently been pregnant (> 42 days since last pregnancy terminated). No additional contraceptives were used. Clinical follow-up was scheduled at 6, 12, 24 and 36 months after the third insertion and at any time when complications or complaints occurred.

Only those women who requested sterilization for family planning reasons and who did not have a history of medical or psychiatric disorders were selected as subjects. If the patient appeared to be unduly nervous or had any pathologic pelvic condition



Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

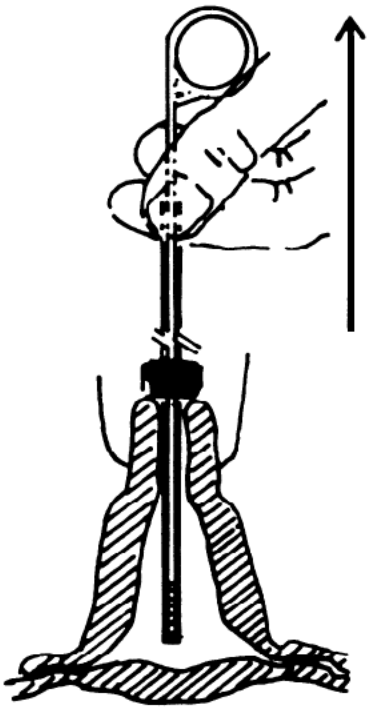


Figure 2 Technique of quinacrine pellet insertion

(except cervicitis), she was excluded from the study and was either scheduled for a surgical sterilization procedure or provided with another method of contraception.

Results

The women entering the study had a mean age of 31.8 years and a mean of 3.3 live births.

Only two women did not complete the scheduled three insertions of quinacrine pellets. One woman had chronic pelvic inflammatory disea se and the second contracted a viral infectious hepatitis after the first insertion.

As reported previously (7) only minor complications ar d complaints often associated with IUD insertion were reported at insertion or between insertions. in most cases, the complications or complaints were of a temporary nature , disappearing within a few hours or a few days after the procedure. Menstrual disturb. ances associated with the quinacrine procedure were also transient.

More than four fifths of the women returned for 36-month follow up. Table 1 shows the quinacrine pellet method to be very effective. The cumulative gross life-table pregnancy rate is 4.3 per 100 women at 36 months. Seven pregnancies have been

Fertility and Sterility 2001;75:830-31.

Table 1 Cumulative gross life table pregnancy rates per 100 women who completed three insertions of quinacrine hydrochloride pellets

	Pregnancy rate	*Follow-up rate*
6 months	0 7 ± 0 7	100.0
12 months	0 7 ± 0 7	99 3
2 months	3 4 ± 1.5	97 2
36 months	4 3 ± 1 7	81 1

reported; they occurred at 4, 15, 18, 19, 24, 34 and 38 months after the third insertion. Four were terminated by an induced abortion procedure, one ended in a spontaneous abortion, and two were carried to term. The term pregnancies occurred 18 and 24 months after the third insertion; the infants were born without any problem.

Follow-up problems were reported by 41 women (27.5 %) in the 36 months since the third insertion (Table 2). Most problems were minor and transitory. Surgery was

Table 2 Events* occurring after three insertions of quinacrine pellets (n = 149)

	No.	%
Pregnancy	7	4 7
Menstrual		
Amenorrhea	1	0 7
Menorrhagia	5	3 4
Dysmenorrhea	7	4 7
Pelvic		
Ovarian cyst	1	0 7
Dysplasia	10	6 7
Episodic pelvic/abdominal pain	2	1.3
Trichomonas	1	0 7
Appendicitis	1	0 7
Transient complaints		
Headaches	2	1.3
Dyspareuniat	14	9 4
Galactorrhea	1	0 7
Total women with one or more events	41	27 5

• Multiple events may by reported for each woman

† These reports were transitory (reported at a single follow-up) for all but three

Fertility and Sterility 2001;75:830-31.

required for seven women, including four conizations of the cervix in women with dysplasia, one appendectomy and one removal of an ovarian cyst. The seventh woman had exploratory surgery because of intermittant and chronic pelvic pain. The genital tract was normal. Both tubes were excised and histological examination showed bilateral closure.

Conclusion

The intrauterine insertion of quinacrine pellets has been shown to be an effective and safe non-surgical sterilization procedure. In general, complications and complaints associated with the procedure were minor and of a transitory nature. By 36 months after the third insertion, seven oft he 149 women had become pregnant. Since all but one of these pregnancies occurred more than a year after the third insertion, recanalization probably occurred in these cases.

There is no doubt that non-surgical sterilization is one of the most important priorities of contraceptive technology. The quinacrine pellet system is a simple, blind method that has great potential in this area.

Acknowledgment

Partial support for this work was provided by Family Health International with funds from the US Agency for International Development.

References

1. Zipper, J., Medel, M. and Prager, R. (1968). Alteration in fertility induced by unilateral intrauterine instillation 0f cytotoxic compoundsjn rats. Am. J. Obstet. Gynecol., 101, 971
2. Zipper, J., Stachetti, E. and Medel, M. (1970). Human fertility con rol by transvaginal application of quinacrine on the fallopian tube. Fertil. Steril., 21, 581
3. Zipper, J., Stachetti, E. and Medel, M. (1975). Transvaginal chemical sterilization. Contraception, 12, 11
4. Zipper, J., Medel, M., Goldsmith, A. et al (1976). The clinical efficacy of the repeated transcervical instillation of quinacrme for female sterilization. Int. J. Gynaecol. Obstet., 14,499
5. Zipper, J., Cole, L. P., Goldsmith, A. et al (1980). Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. Int. J. Gynaecol. Obstet., *18,* 275
6. Zipper, J., Edelman, D., Cole, L. P. and Rivera, M. (1983). Overview of clinical trials with quinacrine. In: Female Transcervical Sterilization: Proceeding:; of an International Workshop on Non-Surgical Methods for Female Occlusion. Chicago, Illinois, June 22-24, 1982, G I. Zatuchni, J. D. Shelton, A. Goldsmith and J. J. Sciarra, eds., Harper & Row, Hagerstown, MD, pp. 94-99
7. Guzrnan-Serani, R., Bernales, A. and Cole, L. P. (1983). Clinical report: quinacrine-fused pellets. In: Female Transcervical Sterilization: Proceedings of an International Workshop on Non-Surgical Methods for Female Occlusion, Chicago, Illinois, June 22-24, 1982, G. I. Zatuchni, J. D. Shelton, A. Goldsmith and J. J. Sciarra, eds., Harper & Row, Hagerstown, MD, pp. 100-104

4. Gentile, G. P. and Siegler, A.M.(1977). The misplaced or missing IUD. Obstet. Gynecol. Surv., 32(IO). 627
5. Heartwell. S. F. and Schlesselman, S. (1983). Risk of uterine perforation among users of intrauterine devices. Obstet. Gynecol. 61, 31-36
6. Kahn, H. S. and Tyler, C. W. (1975). IUD-related hospitalizations in the United States and Puerto Rico. 1973. J. Am. Med. Assoc., 234, 53-56
7. Khan, H.S. andn Tyler, C. W. (1975). Mortalityassociatedwith use of IUDs. J. Am. Med. Assoc., 234, 57-59.
8. Kanagaratnam. K. (1968). Singapore: The National FP Program. Stud. Fam. Plann.. 1(28), 1-11
9. Laufe, L. and McCann, M. (1978). Training: An integral adjunct to the introduction of newer methods of fertility regulation. Int. J. Gynecol. Obstet., 15, 302-306
10. Lippes. J. (1978). Management of the lost IUD: a conservative approach. In: Risks, Benefits and Controversies in Fertility Control. J. J. Sciarra, G. I. Zatuchni and J. J. Speidel. eds., Proceedings of the Workshop, Arlington, Virginia. March 13- 16.1977. Harper & Row, Hagerstown, pp. 404-407
11. Piotrow. P. T. (1979) IUDs - Update on Safety. Effectiveness and Research. Population Reports. Series B. No. 3
12. Prema, K.. Malhotra, U.. Choudhury. S. D. and Saxena, N. C. (1981). Uterine perforations with Copper TIUDs. Contracept. Deliv. Syst.. 2, 327-329
13. Ratnam. S. S. and Tow. S. H. (1970). Translocation of the loop. In: Postpartum Family Planning: A Report on the International Program, G. 1. Zatuchni, ed. McGraw-Hill, New York. pp. 371- 384
14. Rosenfield. A. G. and Castadot, R. G. (1974). Early postpartum and immediate postabortion intrauterine contraceptive device insertion. Am. J. Obstet. Gynecol.. 118, 1104-1114
15. Schwartz. G. F. and Markowitz. A. M. (1970). Serious sequelae of intrauterine contraceptive devices. J. Am Med. Assoc.. 211, 959-960
16. Scott. R. B. (1968). Critical illnesses and deaths associated with intrauterine devices. Obstet. Gynecol.. 31, 322-327
17. Sivard. R. L. (1980' World Military and Social Expenditures 1980, Leesburg, VA. World Priorities Inc. 980. as listed in the World Almanac 1981, New York, NY. Newspaper Enterprise Association, Inc., p. 604. Note: Yugoslavia was used as baseline
18. Soderstrom. R. M. (1978). The wandering IUD: What to do? In: Risks, Benefits and Controversies in Fertility Control, J. J.Sciarra.G.Zatuchniand J. J. Speidel, eds. Harper & Row, Hager stown, pp. 408-412
19. Wolfers. D. (1970). Postpartum Contraception in Singapore. Excerpta Medica Foundation, Amsterdam
20. Zakin. D., Stern, W. Z. and Rosenblatt, R. (1981). Complete and partial uterine perforation and embeddir g following insertion of intrauterine devices. I. Classification. complications. mechanism, incidence and missing string. Obstet. Gynecol. Surv., 36, 335 -353
2). Zakin. D.. Stern. W. Z and Rosenblatt, R. (1981). Complete and partial uterine perforation and embedding following insertion of intrauterine devices. II. Diagnostic methods. prevention, anti management. Obstet. Gynecol. Surv., 36, 401-417

10

Clinical Report: Quinacrine-Fused Pellets

RENE GUZMAN-SERANI

ALFONSO ***BERNALES***

LYNDA PAINTER COLE

In an effort to meet a demand for female sterilization services that far exceeds the current medical care system worldwide, attention has been given to the development of a safe, effective nonsurgical method that can be performed by paramedical personnel.

Zipper and associates have worked in this area for many years and have identified quinacrine hydrochloride as a chemical likely to produce tubal occlusion when placed in the uterus.[2,3,4,5] Zipper's work led to the development of quinacrine hydrochloride pellets, intended to effect a delivery system that would bring the chemical into prolonged contact with the tubal ostia through uterine retention. Results of an early study were encouraging; at 1 year after three insertions of 250 mg quinacrine pellets, the gross life-table pregnancy rate was 3.1 per 100 women.'

The efficacy of transcervical insertions of quinacrine pellets to produce tubal occlusion has been further evaluated in a three-center trial. This chapter reports the results from one of the centers.

MATERIALS AND METHODS

Each quinacrine hydrochloride pellet is cylindrical and has a diameter of less than 4 mm. The pellets are compacted to contain 10 mg quinacrine per millimeter of length. Insertion is accomplished by placing the pellets in a plastic tube with a push rod positioned behind them. The insertion procedure is essentially the same as that for inserting an IUD.

From March through December, 1979, 151 women entered the study, giving informed consent at an outpatient clinic at the Universidad Austral de Chile School of Medicine, Valdivia, Chile. Seven pellets containing a total of 250 mg quinacrine hydrochloride were to be inserted at admission and again at 1 month and 2 months after admission. Insertions were performed during the proliferative phase of the menstrual cycle in women who had not recently been pregnant (>42 days since last pregnancy terminated). No additional contraceptives were used. Clinical follow-up was scheduled at 6, 12, and 24 months after the third insertion and at any time when complications or complaints occurred. In this study, tubal patency was evaluated by hysterosalpingography performed at least 3 months after the third insertion.

Only those women who requested sterilization for family planning reasons and who did not have a history of medical or psychiatric disorders were selected as subjects. If the patient appeared to be unduly nervous or had any pathologic pelvic condition (except cervicitis), she was excluded from the study and was either scheduled for a surgical sterilization procedure or provided with another method of contraception.

Partial support for this work was provided by the International Fertility Research Program, with funds from the U S Agency for International Development

RESULTS

The women entering the study had a mean age of 31.8 years and a mean of 3.3 live births. At admission, 35.1% reported an irregular menstrual cycle. Only two women (1.3%) did not complete the scheduled three insertions of quinacrine pellets. For one woman, chronic pelvic inflammatory disease, which had been missed at admission, was diagnosed before the second insertion; a bilateral salpingectomy was performed. The second woman contracted a viral infectious hepatitis after the first insertion; the hepatitis had a prolonged course, but 6 months later the woman had fully recuperated. Although she is not presently using additional contraception and never received the third quinacrine insertion, she has not become pregnant.

The procedure was deemed safe (Table 10-l); only minor complications and complaints were reported at insertion or between insertions. In most cases, the complications or complaints were of a temporary nature, disappearing within a few hours or a few days after the procedure. Menstrual disturbances associated with the quinacrine procedure were also transient (Table 10-2). Of those women with regular cycles at the time of the first insertions, 35.7% missed one or two cycles in the 3 months it took to complete the procedures; all had returned to menses by the 6-month follow-up visit. Of those with irregular cycles, 37.7% missed one or more cycles, and only one reported amenorrhea at the 6-month follow-up; she was pregnant.

Four-fifths of the women have returned for 24-month follow-up. Table 10-3 shows the quinacrine pellet method to be very effective. The gross life-table pregnancy rate is 4.1 per 100 women at 24 months. Five pregnancies have been reported; they occurred at 4, 15, 18, 19, and 24 months after the third insertion. Three were terminated by an induced abortion procedure, one ended in a spontaneous abortion, and one was carried to term. The term pregnancy occurred 18 months after the third insertion; the infant was born without any problem.

Hysterosalpingographic results for women who completed three insertions of quinacrine pellets are given in Table 10-4. The hysterosalpingograms showed no patency for three women who later became pregnant.

Other than the pregnancies, follow-up problems were reported by eight women (5.4%) in the 24 months since the third insertion. Most problems were minor and transitory, including two cases of menorrhagia, two of head-

TABLE 1 O-l. Complica ions/Complaints Associated With Inser ion of Quinacrine Pellets

	PELLET INSERTIONS					
	1 (N = 151)		2 (N = 150)		3 (N = 149)	
	NO.	%	NO.	%	NO.	%
Complications						
Psycho/emotional reaction	1	0.7	0	0.0	0	0.0
Vomiting	1	0.7	0	0.0	0	0.0
Infectious hepatitis*†	1	0.7	0	0.0	0	0.0
Pelvic inflammatory disease*†	0	0.0	1	0.7	0	0.0
Trichomonas†	1	0.7	2	1.3	0	0.0
Vaginal discharge	1	0.7	1	0.7	0	0.0
Fever	0	0.0	1	0.7	0	0.0
Vaginal bleeding	1	0.7	2	1.3	0	0.0
Vaginal spotting	0	0.0	2	1.3	0	0.0
Total women with one complication or more	6	4.0	9	6.0	0	0.0
Complaints						
Pelvic/abdominal pain						
At insertion	21	13.9	12	8.0	18	12 0
Postinsertion	25	16.6	19	12.7	1	0.7
Headache	2	1.3	1	0.7	0	0.0
Muscle pain	1	0.7	0	0.0	0	0.0
Total women with one complaint or more	43	28.5	32	21.3	19	12.8

*Resulted in discontinuation of procedure.

†Unrelated to quinacrine.

aches, and one each of reduced menstrual flow, irregular cycles, episodic pelvic pain, and an ovarian cyst.

CONCLUSIONS

The results of this study suggest that the intrauterine insertion of quinacrine pellets can be an effective, safe, nonsurgical sterilization procedure. In general, complications and complaints associated with the insertion were minor and of a transitory nature. Only 4.1% of the women had become pregnant by 2 years after the third insertion.

Three women who showed no tubal patency by hysterosalpingogram later became pregnant. The possibility of recanalization seems more likely than that the hysterosalpingogram failed to determine tubal occlusion.

Although no deaths have been reported in studies conducted in conjunction with the International Fertility Research Program, two have been reported following the intrauterine instillation of quinacrine solution by other investigators.*† The cause of these deaths is unknown but may be related to

*Atabrine hydrochloride Product information, Winthrop Laboratories, November 1975

†Chowdhury A Personal communication, August 1976

TABLE 10-2. Amenorrhea Associated With Insertion of Quinacrine Pellets by Menstrual Regularity at Admission

	IREGULAR CYCLE LENGTH REPORTED AT ADMISSION (N = 53)		REGULAR CYCLE LENGTH REPORTED AT ADMISSION (N = 98)	
	NO.	%	NO.	%
At insertion II	17	32.1	22	22.4
At insertion III	14	26.4	24	24.5
At d-month follow-up	1*	1.9	0	0.0
Total women reporting amenorrhea at one or more visits	20	37.7	35	35.7

*Pregnant at time of follow-up.

the rapid absorption of quinacrine. It has been reported that high systemic blood levels of quinacrine from rapid absorption may result in arrhythmias, heart block, impaired cardiac output, hypotension, peripheral vasodilation, and depression of the vasomotor and respiratory centers of the central nervous system.* The pellet method probably decreases the absorption rate, thus reducing the blood level of quinacrine. The decreased absorption rate was part of the reason the pellet method was developed.

A problem with all known blind procedures is that more than one application may be necessary. The quinacrine pellet method used in this study

TABLE 1 O-3. Gross Life-Table Pregnancy Rates for Women Who Completed Three Insertions of Quinacrine Hydrochloride Pellets

	PREGNANCY RATE	FOLLOW-UP RATE
6 months	0.7 ± 0.7	98.0
12 months	0.7 ± 0.7	97.3
24 months	3.8 ± 1.7	82.8

TABLE 10-4. Hysterosalpingographic Results for Women Who Completed Three Insertions of Quinacrine Hydrochloride Pellets

RESULTS	NO. PATIENTS	%
Neither tube patent	121'	81.2
One tube patent	1	0.7
Both tubes patent	0	0.0
HSG not performed	27†	18.1
Total	149	100.0

*Three women became pregnant.

†Two women became pregnant.

*Atabrine hydrochloride Product information, Winthrop Laboratories, November 1975.

requires three insertions. Surgical sterilization procedures, in addition to the demands on medical personnel and clinic resources, require multiple visits from the women. At least two visits are recommended: the visit for surgery and the follow-up visit 7 to 21 days later. Surgical procedures also require anesthesia.

Alternative delivery systems that may reduce the number of quinacrine administrations are being explored, including the use of an IUD vector for better delivery of the quinacrine to the tubal ostia and the development of a sustained-release system that will provide extended exposure of quinacrine to the epithelium.

REFERENCES

1. ZIPPER J, COLE LP, GOLDSMITH A et al: Quinacrine hydrochloride pellets: Preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstet 18:275, 1980
2. ZIPPER J, MEDEL M, GOLDSMITH A et al: The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization Int J Gynaecol Obstet 14:499, 1976
3. ZIPPER J, MEDEL M, PRAGER R: Alteration in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats Am J Obstet Gynecol 101:971, 1968
4. ZIPPER J, STACHETTI E, MEDEL M: Human fertility control by transvaginal application of quinacrine on the fallopian tube Fertil Steril 21:581, 1970
5. ZIPPER J, STACHETTI E, MEDEL M: Transvaginal chemical sterilization Contraception 12: 11, 1975

12

Quinacrine IUDs

LEONARD E. LAUFE

ROBERT G. WHEELER

It is 15 years since Corfman reviewed transcervical oviduct occlusion and chronicled the history of the concept.[2] In 1849 a technique was developed to produce tubal occlusion with the application of silver nitrate to the cornua. Many other agents have since been evaluated for their tubal occlusive capabilities, such as zinc, phenol, chloride, sodium morrhuate, salicylic acid, a mixture of gelatin-resorcinol-formaldehyde, and cyanoacrylates.[4] Richart and others at Columbia University have worked extensively with a variety of these drugs and methods, and currently, they are working exclusively with methyl cyanoacrylate.

Zipper, of Santiago, Chile, has worked extensively with quinacrine and his technique has finally evolved into the quinacrine pellet concept discussed in Chapters 9 and 10.

EVOLUTION OF IUD DELIVERY SYSTEMS

As our interest in the further development of the concept of chemical sterilization with quinacrine was pursued, we realized that we must determine the exact pathologic changes induced by quinacrine. In 1980, Bhatt and associates reported on the quinacrine-induced pathologic changes in fallopian tubes.' This limited study was accomplished by inserting one application of 250 mg quinacrine pellets into the uterine cavity of 23 women awaiting hysterectomies; therefore, 46 tubes were studied. The changes induced by quinacrine were documented, and in about 50% of the cases an obstructive lesion commensurate with tubal closure was induced.

As a result of this study, a concept was developed to provide a better delivery system of quinacrine to attempt to ensure a more accurate application of the drug to the tubal ostia and to reduce the delivery system to a single event. At that time, studies were initiated using the IUD as a vector for delivering quinacrine. Requirements for these studies were that the par-

The authors wish to express their gratitude to the many collaborators in the IFRP network who have contributed data used in the preparation of this chapter Appreciation is expressed to the manufacturer of the No-Gravid device and to the contributors in England, Chile, India, and Bangladesh who participated in these studies

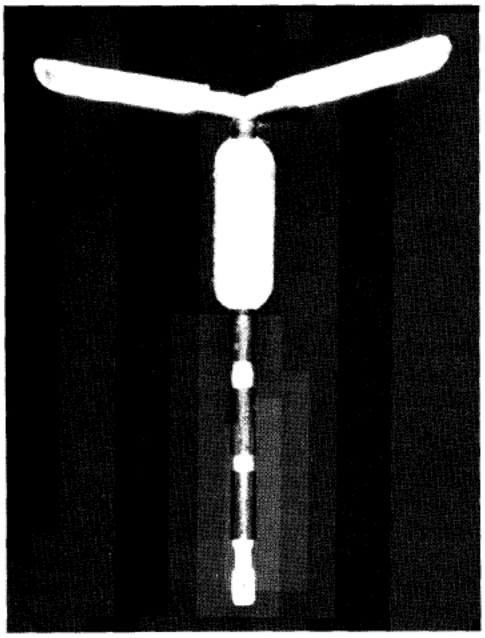


FIG. 12 1. Copper-T 220 with 300 mg quinacrine.

ticipants were awaiting an elective hysterectomy and had no distortion of the uterine body such as myomas and no severe endometrial disturbances. Most of the hysterectomies were in women with prolapse or a premalignant lesion of the cervix. To date, 72 women have been studied. No patient has had any adverse reaction.

In the first five procedures done in Santiago, Chile, a T-vector was inserted, carrying an ethylene vinylacetate (EVA) matrix containing quinacrine. The release rate of the quinacrine from this matrix proved to be extremely limited, and in only one woman could tubal occlusion be demonstrated by hysterosalpingography. Next, a mixture of 80% quinacrine and 20% polyethylene oxide (PEO) was used. PEO is a water-soluble, biocompatible plastic and acts as a binder to hold the quinacrine forms together. The powder mixture was mixed with water to form a very thick paste. The paste was allowed to dry almost completely and was then loaded into a split die and pressed into its final form. The quinacrine/PEO forms were then placed on the arms of the IUD.

The next approach was to add a total dose of 300 mg of the drug to a T-vector, with '75 mg quinacrine at the ends of each of the lateral arms and a central bolus of 150 mg on the stem (Fig. 12-1). The results were erratic, and the central bolus appeared to contribute nothing to the sclerosing effect observed in the tubes. About 50% of the tubes contained a definitive lesion, as with the pellet studies. Results were highly variable. One tube in a given specimen could be totally occluded and the other untouched. The T-vector was next used with the arms upward, as with the original device, but without

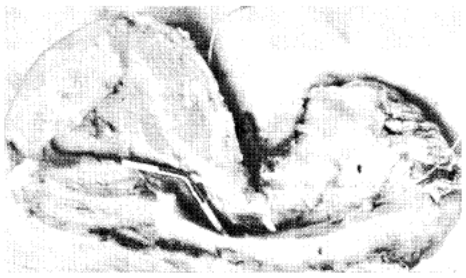


FIG. 12-2. Vaginal hysterectomy specimen with spring device.

the central bolus. In approximately 60% of the tubes, we were able to prod uce definitive sclerosis.

In the next group, instead of flexing the arms of the IUD upward, we bent them downward by redirecting the mold that applied the quinacrine. This improved the closure rate. In the women treated in this fashion, the tubal closure rate was 75%. Considerable emphasis was placed on proper IUD placement, so that the IUD was reaching the fundus and the arms were properly deployed.

Although the results were improved with the configuration in which a "T" with 75 mg quinacrine on each arm was flexed in a downward posture, examination of specimens with the IUD *in situ* showed that it was not properly deployed in all instances.

An attempt was made to design a vector containing a stainless steel spring in the middle to provide outward flexion of the arms.[3] Devices with this design contained no quinacrine, and we asked contributing physicians to insert them in either fresh hysterectomy specimens or when the patient was on the operating table. These devices proved to be inappropriate, in that either the spring was too weak or it could not be inserted high enough in the fundus to obtain proper deployment of the arms to the tubal ostium (Fig. 12-2).

In the hope of finding a better vector, use of the copper-bearing No-Gravid device made in Verona, Italy, was examined (Fig. 12-3). This device, unlike most IUDs, is made of nylon and is relatively rigid; its arms deploy vigorously toward the tubal ostia. The manufacturer of the No-Gravid provided No-Gravid skeletons. Devices were prepared with 100 mg quinacrine per arm (Fig. 12-4). Twelve hysterectomy specimens have been examined.

During surgery, the devices were left *in situ*. Cornual blocks were taken of each specimen and examined prior to opening the uterus. A uterine fundus containing the device is shown in Figure 12-5. This group of specimens provided the most enlightenment. In all six specimens, the devices were properly deployed and each arm was aimed directly at the tubal ostia. In five uteri, there was bilateral tubal closure throughout the intramural portion of the tubes. In the sixth woman, there was absolutely no effect from the quinacrine,

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

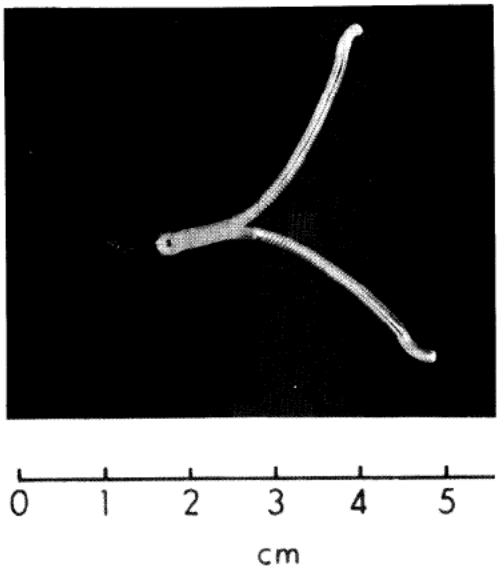


FIG. 12 3. No-Gravid IUD.

and the tubes appeared untouched. The patient had a clinical situation that was unusual. The woman was over 35 years of age and had suffered from extensive menometrorrhagia for the past year. Since a dilation and curettage performed 6 months prior to the IUD insertion revealed no malignancy, she had been treated extensively for 5 consecutive months with high doses of progestational compounds. With this information, we hypothesized that perhaps the extensive use of a progestational compound had made the epithelium resistant to the effect of quinacrine. Another possibility is that her persistent bleeding might have produced rapid dissolution of the quinacrine material and washed it from the uterus.

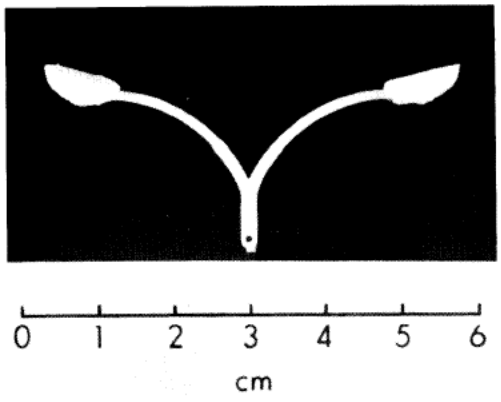


FIG. 12 4. No-Gravid skeleton with 100 mg quinacrine per arm.

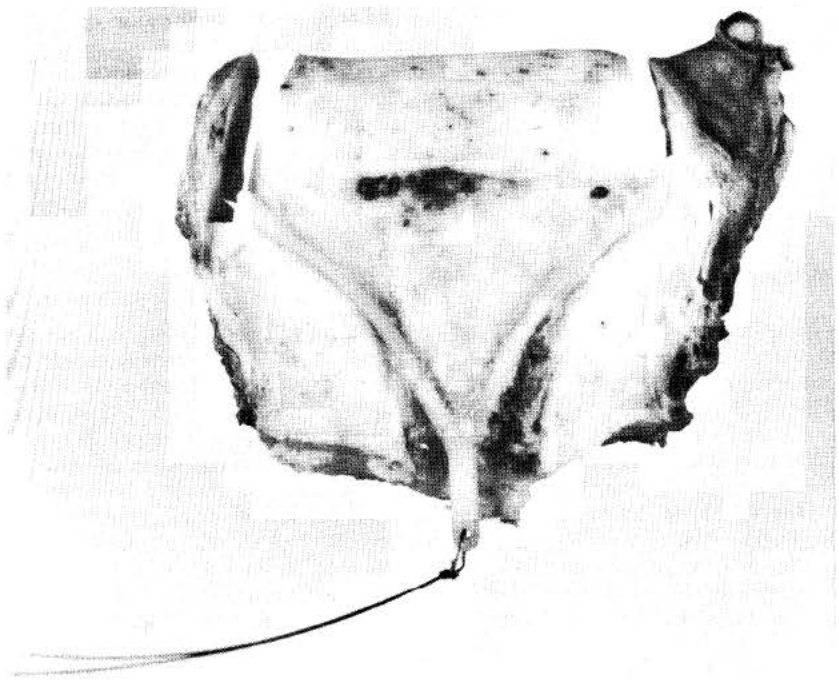


FIG. 12-5. No-Gravid IUD in fixed hysterectomy specimen.

In the early prehysterectomy studies with quinacrine pellets, there was great concern about how the quinacrine acted and whether it operated on the lamina propria in those cases in which the epithelium was intact or had regenerated. One specimen from London, which contained the "T" device, was removed within 10 days of IUD insertion, and we were able to determine that although the epithelium had been damaged it was able to regenerate before sclerosis could occur.

Since the epithelial regeneration of the endometrium and the tubal epithelium is stimulated by estrogen and depressed by progesterone, the next six cases were provided high-dosage progestational therapy 5 days prior to and 5 days following IUD insertion. Megestrol acetate (Megace), 80 mg/day, was used. In these cases ten tubes were found to have definitive large lesions that could only lead to tubal closure. In one tube of one of the specimens, the epithelium was untouched; in one tube of another specimen, there was a mild degree of damage, but whether it would have healed or sclerosed could not be determined.

When these six No-Gravid insertions are added to the first six insertions, definitive tubal lesions are found in 20 of the 24 tubes. If we eliminate the patient with severe dysfunctional bleeding who did not fit the protocol and had received 5 months of intensive progestational therapy, 20 of 22 tubes

have definitive lesions that should provide permanent sterilization of the intramural portions of the tubes.

To construct a confidence interval for the proportion of the fallopian tubes closed, each tube is considered an independent experimental unit. If all 24 tubes are included, the 95% confidence interval for the proportion of closures is 0.66 to 0.98. If the one woman is disqualified on the basis of the arguments presented earlier, the 95% confidence interval for the proportion of closures is 0.79 to 1.00.

DISCUSSION

The results with the No-Gravid device appear most encouraging and the use of the IUD as a vector to deliver quinacrine to the tubal ostium should be pursued. Current plans call for variation on quinacrine delivery to the tube. The IUD vector will remain the same. Sustained-release pellets have been developed that leech the quinacrine out over a period of between 800 and 1200 minutes (13 to 20 hours). These have been fixed to the No-Gravid skeleton (Fig. 12-6) and are being studied in a limited number of volunteers.

One can speculate as to whether a rapid release of quinacrine, such as occurred in the earlier experiments, is more effective than a sustained release at a lower dosage. One can also hypothesize that the mixture of these release systems might be necessary for tubal closure. The sustained 7-day release system, developed by the Southern Research Institute with PARFR support, should also be applied to an IUD and may provide a better closure rate.

The original hypothesis of using an IUD as the vector for quinacrine in-

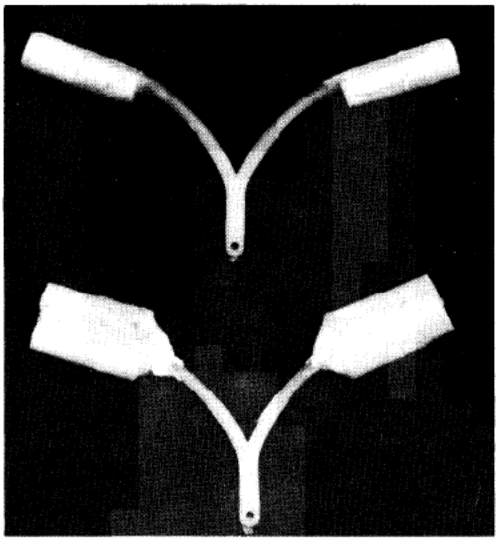


FIG. 12-6. No-Gravid IUD with sustained-release quinacrine pellets.

cluded the idea that the IUD remaining after dissolution of the quinacrine could act as a backup method of contraception. Certainly many variations on this theme are possible. For instance, subsequent to IUD insertion, if the patient wished to have the device removed, a dose of quinacrine pellets could be added at the time of the IUD removal. Patients having the IUD removed could also have a hysterosalpingogram and, if the tubes are patent, could be offered a standard method of surgical sterilization or another quinacrine IUD.

The possibilities are considerable, and we hope that the pursuit of this concept will continue successfully.

REFERENCES

BHATT RV, APARICIO A, LAUFE LE et al: Quinacrine induced pathologic changes in the fallopian tube Fertil Steril 33(6):666–667, 1980

CORFMAN PA: Transcervical oviduct occlusion In Sobrero AJ, Lewit S (eds): Advances in Planned Parenthood Proceedings of the Third and Fourth Annual Meeting of the American Association of Planned Parenthood Physicians International Congress, Series N138, Vol 1, p 183 Princeton, NJ, Excerpta Medica Foundation, 1967

LAUFE LE: Chemical sterilization with an IUD Contraceptive Delivery Systems 2:343–347, 1981

RICHART RM: Female sterilization using chemical agents In Zatuchni GI (ed): Research Frontiers in Fertility Regulation, vol 1, no 5, December 1981 Chicago, Program for Applied Research on Fertility Regulation

FERTILITY AND STERILITY

Vol. 37, No. 6, June 1982
Printed in USA.

Potential demand for voluntary female sterilization in the 1980s: the compelling need for a nonsurgical method

Elton Kessel, M.D., M.P.H.
Stephen D. Mumford, Dr.P.H.

International Fertility Research Program, Research Triangle Park, North Carolina

Voluntary sterilization is the most prevalent method of fertility regulation, and its use is widespread in both developed and developing countries. The estimated number of couples controlling their fertility through sterilization has increased dramatically from 15 million in 1970[1] to 100 million in 1980." The country reporting the highest prevalence of use is the United States, where 31.3% of married women of reproductive age are protected by surgical sterilization or by vasectomy of their husbands.[3] This high prevalence in the United States has been almost stationary over the past few years. The increasing number of surgical procedures required to maintain this prevalence in a slowly growing population is well within the capabilities of the health service delivery system of the United States. Other developed countries have the capability of achieving a similar prevalence within a period of several years.

In the developing world, especially in the most populous countries, the demand for sterilization is steadily rising, the preference being for female sterilization. However, the demand far exceeds the supply of services, which are virtually nonexistent in the rural areas, where most of the women live.

This communication examines the benefits of sterilization and projects the potential demand or need for services. The shortcomings of existing sterilization technology is examined, as well as the hopelessness in meeting the potential demand if existing technology is relied upon. Nonsurgical female sterilization via intrauterine administration of quinacrine appears to stand alone in having the potential to meet the projected demand for female sterilization in the 1980s. The reasons for the belief that chemical sterilization will follow the same technology diffusion path (namely, from developing to developed world) as that for surgical sterilization via minilaparotomy technology are also discussed.

BENEFITS OF STERILIZATION

In the developing world, the risk of maternal and infant mortality is high,' and such risks are greater for high-parity women, even in developed countries.' Maternity is the single greatest cause of death in women of reproductive age in developing countries and is mainly due to high-order pregnancies and births (> 4). High-order births (> 4) in the least developed countries account for a full one-half of all infant deaths, partly because of the large number of such births, but also because of these infants' higher risk of mortality.[6] Estimates of births averted by sterilization indicate that, on the average, the highest two parities are prevented among women with little access to other contraceptive methods.[7] It follows that dramatic improvement in the major health indices is possible through the extension of sterilization services. In most developing countries there is no other feasible health service that could match the positive impact of sterilization on health.

In developing countries (where most of the world's women live), a health service infrastructure necessary to meet the needs of women using temporary fertility regulation methods, including abortion, is lacking. That sterilization is frequently their method of choice is evidenced by the fact that when given the option, tens of millions of women have chosen to be sterilized.

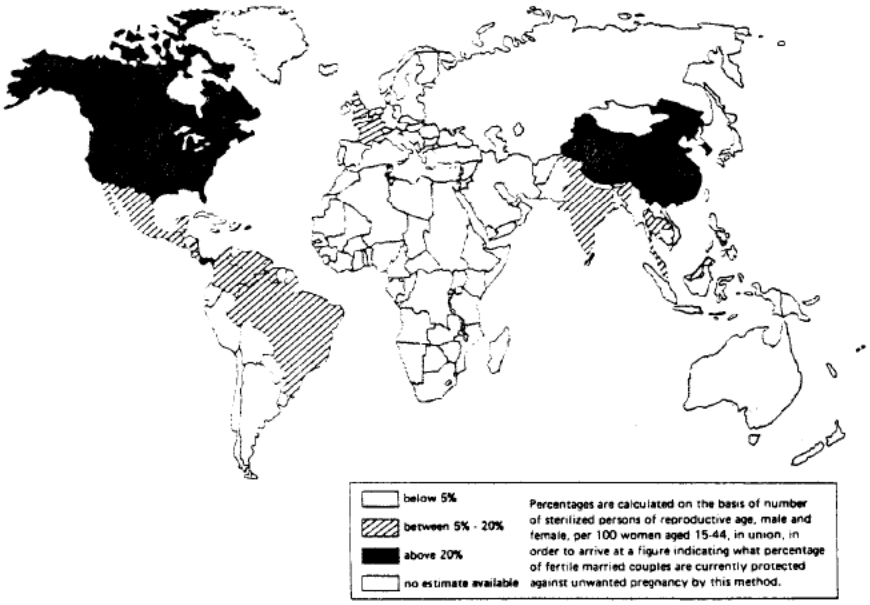


Figure 1
Estimated world prevalence of voluntary sterilization in 1980.

From a socioeconomic point of view, high-parity women tend to belong to the least privileged segments of society, who are, generally, in greatest need of controlling their fertility. Because higher fertility frequently leads to greater poverty and because sterilization is ultimately the most cost-effective of the available methods, it has the most to offer from a socioeconomic standpoint.

Not to be ignored are the disastrous implications of world overpopulation, best summarized in the recent United States Government's heavily documented *Global* 2000 *Report.'* If the dire projections set forth in this report are to be avoided and any nation is to enter the 21st century peacefully and secure, sterilization is certain to play an important role.

ESTIMATE OF THE POTENTIAL DEMAND FOR STERILIZATION IN THE DEVELOPING WORLD (EXCLUDING CHINA) IN THE 1980s

In all countries where sterilization is made readily available, high levels of prevalence occur (Fig. 1). The existing technology will be adequate to meet the demand for sterilization in the slow-growing developed world and in China. Attention will, therefore, be directed to the potential demand for services in the developing world, and all following estimates and statements will exclude China.

The basis for this estimate is the experience with sterilization in the United States, where this service can be considered nearly fully available. The prevalence of sterilization in the United States has plateaued since 1975 at 31.3%[3] of married women of reproductive age. The authors make the assumption that if sterilization were made fully available, the rate of the United States would prevail worldwide. Panama has already achieved a prevalence of 30%; Puerto Rico, in many ways a developing part of the United States, has maintained a prevalence of about 33% for more than two decades; Singapore has already achieved a prevalence of 22%; India and Korea, 20%; and Sri Lanka and El Salvador, 18%.[9]

Also supportive of this assumption is the high proportion of all contraceptors who have chosen sterilization in selective countries: in India, 87%; Nepal, 67%; Piaui State in Brazil, 48%; Dominican Republic, 39%; Tunisia, 35%; and Guatemala, 33%.[9] Mexico experienced the largest increase in voluntary sterilizations reported by any large country in the world, from 13,000 in 1974 to 130,000 in 1977,[10] a lo-fold increase.

Present increases in contraceptive prevalence and the heavy reliance on sterilization by major developing countries point to the reasonableness of the assumption that if sterilization were made fully available, the United States rate of 31.3% would prevail worldwide.[9] Based on this assumption, the estimate of sterilization needs in the 1980s is made in the following manner. The number of women of reproductive age (15 to 44 years of age) in the less developed world, excluding

China, was 488,426,000 *in 1980* and will grow to 647,416,000[11] in 1990. Assuming that 80% of these 647,416,000 women are married, then 517,933,000 married women are in the reproductive age group. In 1980, there were 34,500,000[12] sterilized couples in the less developed world. To achieve the 1975 United States sterilization prevalence of 31.3% of couples in which the wife is aged 15 to 44 years, the number of sterilized couples in the less developed world would need to be 163,150,000 by 1990. The ratio of the estimated number of couples using sterilization by 1990 as compared with the number using this method in 1980 would be 163,150,000: 34,500,000 or about five times the number currently sterilized.

In converting this estimate of prevalence to an estimate of the number of sterilization procedures needed to reach the 1990 prevalence, an additional factor must be considered. A proportion of women protected by sterilization in the 1980s will leave their reproductive years by 1990, requiring additional procedures to reach the projected prevalence. If the average age (35 years) of women who have participated in International Fertility Research Program (IFRP) sterilization studies in developing countries is indicative of the average age of those who will participate in the 1980s, and if there were an equal number of sterilizations performed each year, then the total number of sterilizations would have to be approximately 25% greater than the number needed to reach a 31.3% prevalence by 1990. However, it can be expected that the growth in the number of procedures performed will approximate an exponential rather than a linear growth curve and that the average age of sterilization acceptors will fall. The number of procedures to reach the estimated 1990 prevalence might require an addition of 10% over the prevalence, or approximately 180 million procedures in the 1980s.

OVERVIEW OF EXISTING STERILIZATION METHODS

A wide range of female sterilization methods are available. We can first identify methods with a large experience that definitely show inferior results. Both colpotomy[13] and culdoscopy[14] were widely used in the early 1970s but showed high complication rates, particularly pelvic infection. The tantalum clip,[15] frequently used with culdoscopy sterilization, was the first tubal occlusive clip, but it had an unacceptably high failure rate. Hysteroscopy using an electrocoagulation probe inserted into the ostia has been disappointing in terms of complication and failure rates,[16] although Quinones and colleagues in Mexico have had satisfactory results." Other hysteroscopic techniques are experimental and have little chance of broad use in the 1980s, especially in developing countries. Of the nonexperimental methods, this leaves laparoscopy and minilaparotomy methods for consideration.

Laparoscopic sterilization, techniques have proven to be both safe and effective in the hands of well-trained surgeons in appropriate settings. Laparoscopy may be performed by either a single- or double-puncture approach with the use of any one of several occlusive techniques.

The IFRP has recently analyzed data on 22,115 laparoscopic sterilization procedures from 64 centers in 27 countries using a common protocol.[18] Three tubal occlusive techniques were compared with the use of conventional laparoscopy, namely, electrocoagulation (n = 12,643), tubal ring (n = 7766), and Rocket clip (n = 702). The tubal ring was also used in open laparoscopy (n = 1004). The study centers were generally affiliated with medical schools in urban settings. The findings showed that all techniques were safe and effective and comparable. No one technique was particularly better than any other.

However, evidence is accumulating that shows laparoscopic techniques performed outside major urban centers by less than the most highly-trained surgeons may not be appropriate. Chaturachinda,[19] *in* a study of the use of laparoscopy in rural Thailand, found higher death, complication, and failure rates with laparoscopy than with minilaparotomy.

Of the existing female sterilization methods currently widely used, minilaparotomy with modified Pomeroy occlusion appears to be superior to laparoscopy. The most comprehensive analysis of a comparison of laparoscopy and minilaparotomy in terms of efficacy and safety was made by the IFRP.[20] Studies from 23 countries were utilized to accumulate data on laparoscopy with occlusion by the tubal ring (7053 cases), minilaparotomy with occlusion by the tubal ring (3033 cases), and minilaparotomy with occlusion by the modified Pomeroy technique (5081 cases).

The method failure rate and the complication rate for laparoscopy/ring were twice those for minilaparotomy/Pomeroy (0.60 versus 0.30 and 2.01 versus 0.95 per 100 women, respectively). The authors also note that these laparoscopy pro-

Table 1. Estzmnted Mortality Associated with Maternzty and the Use of Sterilization by Age, Method, and Country Setting[a]

Method and country setting	Age group (yr)					
	15–19	'm-24	25–29	30–34	35–39	40–44
Death due to pregnancy and childbirth (per 100,000 live births,						
Developed countries	11.1	10.0	12.5	24 9	44.0	71.4
Advanced developing countries	*20.0*	*20.0*	*25.0*	*50.0*	1.00.0	150.0
Less-advanced developing countnes	700.0	400.0	500.0	500.0	500.0	800.0
Death due to female sterilization (per 100,000 operations)						
Developed countries	10.0	10.0	10.0	10.0	15.0	20.0
Advanced developing countries	20.0	20.0	20.0	20.0	30.0	40.0
Less-advanced developing countnes	50.0	50.0	50.0	50.0	75.0	100.0

[a]From Green.[22]

cedures were performed by the more experienced senior physicians, while most of the minilaparotomy/Pomeroy procedures were done by less specialized junior physicians, suggesting that if these data had been generated by a randomized comparative trial, the differences in complication and failure rates would have been even greater.

The reports on the safety and efficacy of female sterilization from urban centers of developed and developing countries tell us little about either the risks or feasibility of providing this surgical procedure in rural settings of less developed countries, where the majority of women desiring sterilization reside. Two approaches have been tried in delivering such rural services: camps in which a skilled team from an urban center visits a rural area, and the training of general practitioners in rural centers to perform minilaparotomy. A few carefully conducted studies of a camp experience indicate that early surgical complications may be only slightly higher than in urban settings. However, mortality rates of 40 per 100,000 procedures must be expected.[21, 22] Similar mortality has been reported from stationary rural services in developing countries.[23]

An additional question is whether it is feasible to deliver surgical female sterilization services in rural areas of most developing countries, since most sterilizations are currently performed on women in urban centers. This is an important consideration, since a 5-fold increase in services may require a 20-fold or more increase in rural areas in the balance of this decade.

Camp sterilizations have been most popular in India, where there are many well-trained gynecologists. One of the most impressive achievements was the completion of 5000 voluntary female sterilization procedures in 3 months in rural areas of Gujarat State by a team from Baroda Medical College.[24] If physicians from the more than 100 medical colleges of India were to match this feat, approximately half a million sterilizations could be performed. However, this represents less than 10% of the effort required to reach a prevalence of 15% of female sterilizations for women of reproductive age by 1990 and less than 25% of the female sterilizations needed to maintain such a prevalence, if ever achieved. It is clear that even in India, with its large number of gynecologists, the camp approach is unlikely to achieve the desired prevalence of female sterilization.

The use of general practitioners in fixed rural centers is equally discouraging. No staff of rural health centers in large developing countries has been able to perform a significant number of female sterilizations on a continuing basis. Physician staffing of such centers is generally inadequate and is subject to frequent transfers, usually to urban centers. Training general practitioners to perform a minilaparotomy sterilization procedure is itself a substantial and expensive effort. Motivating them to offer this service in a caring manner to rural women is a significant additional obstacle within the bureaucratic framework of most government rural services.

These are the realities that must be dealt with, despite the fact that female sterilization, even with its increased risks in developing countries, can save women's lives if the service can be delivered. This is demonstrated in Table 1, which shows the comparative maternal and surgical fe-

male sterilization mortality estimates by age of women and development status of the country.[22]

There are currently no plans for a large-scale government effort to train paramedical personnel to perform female sterilization in rural areas. An attempt for paramedical personnel to deliver surgical sterilization services on the scale needed to meet the demand and in the primitive operating conditions that exist would, in our judgment, result in unacceptably high mortality and morbidity rates.

With the exception of the United States, vasectomy has rarely been as widely used as female sterilization (Table 2).[25] Aside from the greater cultural inhibitions to the procedure shown by both providers and consumers, vasectomy, when performed in rural services in the developing world, is associated with significant risks of mortality and morbidity. The same study of stationary rural services mentioned above showed a risk of mortality of 20 per 100,000 procedures.[23] Unless there is a significant advance in techniques of nonsurgical male sterilization, it is likely that most of the sterilizations in the developing world for the balance of this decade will be performed on women.

It is unlikely that the number of sterilizations using the present surgical procedures will increase 5-fold in the less developed countries by the end of this decade in spite of the probable demand and realization of the benefits of the procedure. It is not possible to meet this demand with the sterilization techniques currently used, even with an increase in resources several times the level that can be reasonably expected.

Table 2. *Percentage of Couples* (Wives *Aged 15 to 44) Currently Using Sterilization"*

Region. country, and year	Female	Male
Asia		
Republic of Korea, 1979	14.5	5.9
Thailand, 1978	13.0	3.4
Latin America and Caribbean		
Brazil		
Piaui State, 1979	15.4	0.0
Sao Paulo State, 1978	15.6	0.3
Colombia, 1978	7.4	0.2
Costa Rica, 1978	13.0	0.6
El Salvador, 1978	17.8	0 2
Guatemala, 1978	5.9	0.4
Jamaica, 1979	9.6	0.0
Mexico, 1978	7.4	0.1
Panama, 1979-1980	29.3	0.4
Other		
Tunisia		
Jendouba, 1979	16.1	0.0

"From Contraceptive prevalence.[25]

PROMISING NEW STERILIZATION METHODS

The Erb method[26] uses liquid silicone rubber (Silastic, Dow Corning Corporation, Midland, MI) delivered through a hysteroscope to form a soft plug that conforms to the oviductal lumen. It is currently being tested at several locations in the United States and Europe and may receive United States Food and Drug Administration approval within 2 years. However, the hysteroscopic technique is one of very high technology that requires considerable surgical skill. While this technique may become widely available in the developed world, it can be safely predicted that its use in the developing world will be limited.

Research of immunologic sterilization continues. Talwar et al. have developed a vaccine by linking the beta fraction of human chorionic gonadotropin (hCG) to tetanus toxoid.[27] To date, consistently high titers of antibodies to hCG have not been achieved. This kind of research requires prolonged studies of safety to assure there are no cross-reactions with other tissues or ill effects to future offspring conceived during declining titers of antibodies. Although we believe that immunologic approaches may ultimately offer the near-perfect methods of both temporary and permanent contraception, they are many years away.

Two chemical approaches to female sterilization have advanced to clinical trials: methylcyanoacrylate (MCA) and quinacrine. MCA is a tissue adhesive that can be instilled into the fallopian tubes transcervically as a blind procedure using a specially designed device.[28] The MCA polymerizes in the tubes and causes a local reaction leading to fibrotic occlusion over a period of 3 months, during which time the MCA is degraded and eliminated from the body. In animal studies, no deleterious effects resulted from the spillage of MCA into the peritoneal cavity. At this time, limited clinical trials using hysterosalpingography show that bilateral tubal occlusion is achieved with a single instillation in 80% of cases. Efforts are in progress to improve this rate by the use of drugs to prevent spasm of the tubes or by administration of a second instillation. Larger trials with pregnancy as an end point are also planned.

To date, the MCA method failures have been established using hysterosalpingography, which effectively eliminates the opportunity to measure the proportion of ectopic pregnancies among

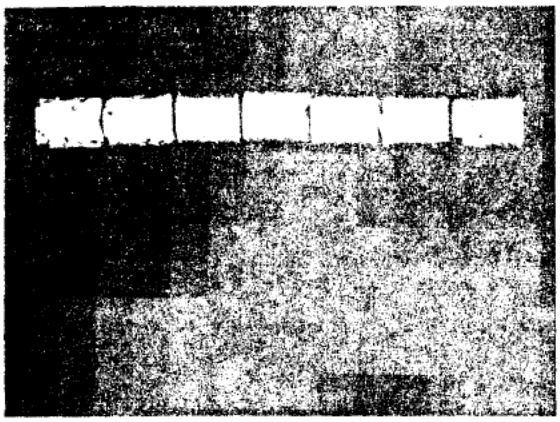


Figure 2
One insertion of quinacrine pellets (250 mg); length in centimeters

pregnancy failures. To document the safety of MCA in terms of ectopic pregnancy will take at least 5 years if a vigorous effort is begun now. Clearly, however, this research should proceed with deliberate speed.

For more than 10 years, Zipper et al. have investigated quinacrine as a method of transcervical female sterilization, using pregnancy rates to determine efficacy.[29] The first studies utilized a liquid slurry of 1.5 gm of quinacrine in water or lidocaine instilled into the uterine cavity with an intrauterine device (IUD) inserter and syringe. Three instillations were required. However, the pregnancy rates, both before completion of the third instillation (12.7%) and after the third instillation (6.1%), were high. Additionally, 2% of the patients experienced cortical excitation at the time of the instillation.

In an effort to overcome these difficulties, Zipper et al. initiated a trial of quinacrine pellets (250 mg)[30] (Fig. 2) inserted through an IUD inserter (Fig. 3) at monthly intervals for three insertions. A 20-mg tablet of sodium thiopental was added to increase viscosity of the uterine fluid in the hope of reducing risk of expulsion of the quinacrine pellets. In this trial, the potentially dangerous side effect, of cortical excitation disappeared, and the 12-month pregnancy rate per 100 women after completion of three applications of quinacrine pellets was reduced to 2.5. It is now presumed that the cortical excitation was caused by accidental intravenous absorption of the liquid slurry as it was administered under pressure, a problem eliminated by the pellet delivery system. Only 1 of the 139 subjects in this study became pregnant before completion of the three insertions.

Three confirming trials[31] of three insertions of quinacrine peilets without sodium thiopental at monthly intervals led to a still further reduction in the pregnancy rate to 1.5 per 100 women at 12 months. It is estimated that the lifetime failure rate will approximate 3 per 100 women. The results of the quinacrine trials are summarized in Table 3.[31]

Tissue damage and fibrosis following intrauterine administration of quinacrine is limited to the cornual area of the uterus and interstitial portion of the fallopian tubes. Ectopic pregnancies have been absent in studies to date among over 200 reported pregnancies in women who have had one or more instillations of quinacrine. In this respect, this method is unique among all carefully studied sterilization procedures. This apparent, safety factor places the quinacrine method several years ahead of the MCA method.

The complications of the quinacrine pellet method are both of low incidence and of less importance in terms of a threat to life, as compared with surgical methods of sterilization.[30] Confirming the findings of the study by Zipper et al., no life-threatening complications have been reported in ongoing quinacrine pellet studies with more than 1500 insertions and more than 5000 woman-months of use.

It is fortunate that there has been wide and chronic use of quinacrine as an antimalarial, es-

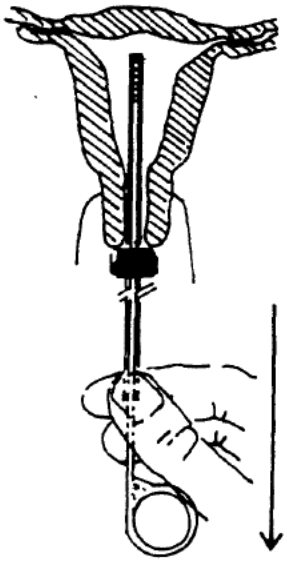


Figure 3
Qumacrine pellet insertion technique using an IUD inserter.

L 7

Table 3. Gross *Life-Table Pregnancy Rates for Women Who Completed Three Administrations of Quinacrine Hydrochloride"*

	6-Month rate	Woman-months	12-Month rate	Woman-months
Quinacrine solution (n = 200)	5.7 ± 2 1	729	9 1 ± 2 6	1375
Quinacrine pellets with sodium thiopental (n = 139)	0 8 ± 0 8	741	2 5 ± 1 4	1422
Quinacrine pellets without sodium thiopental (n = 267)	1.5 ± 0.9	1217	1.5 ± 0.9	2035

"From International Fertility Research Program.[31]

pecially during World War II. The safety of quinacrine is well known for this use, in spite of the fact that the drug is known to combine with deoxyribonucleic acid and to have a positive result in the Ames test. In recent quinacrine toxicology and teratology studies completed at The Johns Hopkins University using rats and cynomolgus monkeys, no chromosomal abnormalities or teratologic defects attributable to quinacrine were found. Quinacrine was widely distributed in body tissues of monkeys after intrauterine administrations, but tissue concentrations were very low after 30 days. Because of the possibility of perforation of the uterus in clinical practice, toxicology studies included purposeful perforation of the monkey uterus. Intraperitoneal administration of quinacrine comparable to the human dose caused no systemic effects but adhesions in one of three monkeys. At ten times the human dose, one of three monkeys had a seizure. At 20 times the human dose, two of three monkeys died and the third had a seizure. At dose levels required for tubal occlusion, these results are reassuring. Like many other drugs, an overdose of quinacrine is dangerous. To establish the risk of serious side effects at recommended intrauterine dosage levels will require larger clinical trials.

Even though first teratologic studies of intrauterine administration of quinacrine show negative results, precautions should nevertheless be taken. Insertions are made in the proliferative phase of the menstrual cycle, which should reduce the risk of pregnancy, but abortion for medical reasons should be recommended for pregnancies conceived before or within 1 month of intrauterine administration of quinacrine. Menstruation is generally unaffected by quinacrine pellet sterilization, although there is occasional transient amenorrhea caused by intrauterine quinacrine. Even in countries where abortion is restricted, it is generally provided following accidental hysterosalpinography in early pregnancy. The same would likely be the case for accidental administration of quinacrine in early pregnancy.

Tietze and Lewit have concluded that use of the condom, with abortion as a backup, is the safest combination of family planning methods currently in use in the United States.[32] Since the lifetime failure rate of the condom far exceeds 3 per 100 women, the quinacrine technique, using abortion as a backup, could possibly replace condom/abortion as the safest family planning method available. It, of course, has both the limitations and advantages of being a permanent method of contraception.

Despite a failure rate higher than that found with surgical sterilization and in light of the low incidence of nonlife-threatening complications, the quinacrine pellet method appears to be ready for large field trials in multiple locations.

The delivery of this nonsurgical sterilization product is virtually comparable to an IUD insertion and offers the opportunity for a wide variety of delivery services. While there are no large-scale government efforts presently planned to train paramedical personnel to perform surgical sterilization in rural areas, an increasing number of countries are training nurse-midwives to perform IUD insertions.[33] It has been demonstrated that large numbers of IUDs can be inserted in rural areas of a developing country in a short period of time. During a 3-year period (1965 to 19681 in India, 2.5 million IUDs were inserted, 82% inserted in women who lived in rural

Table 4 *Hypothetical Example of the Costs of Surgical and Quinacrine Sterilization*

Cost	Surgical sterilization	Quinacrine sterilization
Procedure	$350	3 × 50 = $150
Complications	20	10
Failures	0	0 03 x 500 = 15
Total	$370	$165

areas.[34] The cost of quinacrine sterilization would be comparable to that of three IUD insertions. In the developed world, even including the cost of abortion and surgical resterilization for the increased risk of failure, the cost per completed procedure would be about half that of surgical sterilization. An illustration of financial savings can be seen in Table 4. Assume that the cost of surgical sterilization in a developed country is $350 and the average cost of treatment of complications is $20, the cost of three insertions of quinacrine pellets is $150 and average treatment of complications is $10, and finally 3% of quinacrine sterilizations will require an abortion and surgical sterilization at a cost of $500. Quinacrine sterilization is thus projected to cost half that of surgical sterilization.

While there are several improvements of the quinacrine method currently underway, each will require at least several years to evaluate. The IFRP is currently developing a number of potential improvements.[31,35] The number of insertions of quinacrine pellets may be reduced to one or two by use of an adjuvant to quinacrine. The effect of different release rates of the quinacrine and delivery systems to deploy the quinacrine at the cornual area are under study. If one or more of these potential improvements is documented to be superior to the present three insertions of quinacrine pellets, it can be quickly adopted. It does not appear justifiable to delay use of the existing quinacrine techniques in the hope that improved techniques will prove themselves in later years.

It appears that more accurate and less expensive pregnancy tests and an effective pharmacologic method of early abortion or menstrual regulation to deal with any failures may appear in the 1980s. This will further enhance the acceptability of a permanent method of contraception with a failure rate.

Minilaparotomy is an example of a superior sterilization technique developed and proven in developing countries and transferred to the developed world. We are confident that the quinacrine female sterilization technique will follow the same diffusion path and emerge as a popular method in the developed world in the 1980s. For developing countries, a nonsurgical method of female sterilization is a compelling need. For developed countries, it is a reasonable alternative.

Given the likelihood that only one-fourth to one-third of the potential demand for sterilization in developing countries can be met in the 1980s if surgical sterilization is relied upon, it appears that the quinacrine method of female sterilization offers the best hope for meeting the full demand. Most of the demand in the rural areas, where 80% of developing world woman live, will otherwise simply go unmet. It follows that markedly expanded trials of the quinacrine pellet method is the highest priority for fertility research.

CONCLUSIONS

Sterilization has become the world's most prevalent method of fertility reguiation. The health and socioeconomic benefits of sterilization, especially in developing countries, are achieved by eliminating high-parity births and contributing to slower population growth. An estimate of voluntary sterilization needs in the 1980s in developing countries, excluding China, indicates a demand for approximately 180 million procedures. This represents a 5-fold increase over the number of sterilization procedures presently performed and could mean a 20-fold increase in rural areas. The current state of female sterilization technology has been reviewed. Because of the fragile condition of health care delivery systems in the developing world and the rural residence of the population, it is unlikely that surgical sterilization can meet the projected need.

Progress has been made in the development of the intrauterine administration of quinacrine pellets for nonsurgical female sterilization. In spite of the estimated lifetime failure rate of 3 per 100 women, it is seen as a safe and deliverable method that has potential to meet the expected demand for sterilization in the 1980s.

REFERENCES

1. Ravenholt TR: Prospects for voluntary sterilization. In Voluntary Sterilization: A Decade of Achievement, Edited by ME Schima, I Lubell. New York, The Association for Voluntary Sterilization, Inc., 1980, p 99
2. Stepan J, Kellogg EH, Piotrow PT: Legal trends and issues in voluntary sterilization. Popul Rep [E] No. 6, 1981, p 74
3. Westoff CF, Jones EF: Contraception and sterilization in the United States, 1965-1975. Fam Plann Perspect 9:154, 1977
4. Omran AR: Health risks related to family formation. In Family Formation Patterns and Health, Edited by AR Omran, CC Standley. Geneva, World Health Organization, 1976, p 18
5. Yerushaimy J, Bierman JM, Kemp DH, Conner A, French FE: Longitudinal studies of pregnancy on the island of Kauai, Territory of Hawaii. I. Analysis of previous reproductive history. Am J Obstet Gynecol 71:80, 1956

6. Wyon JB, Gordon JE: A long-term prospective-type field study of population dynamics in the Punjab, India In Research in Family Planning, Edited by CV Kiser. Princeton. Princeton University Press. 1962, p 17
7. Speidel JJ: The role of female sterilization in family planning programs. In Female Sterilization, Edited by GW Duncan. RD Falb, JJ Speidel. New York, Academic Press, 1972. p 89
8. Global 2000 Report to the President: Vol. 4. Washington, DC, U.S. Government Printing Office, 1980
9. Stepan J, Kellogg EH, Piotrow PT: Legal trends and issues in voluntary sterilization. Popul Rep [E] No. 6. 1981, p 76
10. Stepan J, Kellogg EH, Piotrow PT: Legal trends and issues in voluntary sterilization. Popul Rep [El No. 6, 1981, P 75
11. Current Population Reports: Illustrative projections of world population to the 21st century. Special Study Series p-23, No. 79. Washington DC, U.S. Government Printing Office, 1979, p 21. p 27
12. Stepan J, Kellogg EH, Piotrow PT: Legal trends and issues in voluntary sterilization. Popul Rep [E] No. 6, 1981, P 74
13. Brenner WE, Edelman DA: Permanent sterilization through a posterior colpotomy. Int J Gynaecol Obstet 14: 46, 1976
14. Holtrop HR, Goldsmith A, Edelman DA, Porter CW Jr, Sandalls K: Outpatient culdoscopic sterilization: an evaluation. Int J Gynaecol Obstet 14:129, 1976
15. Mroueh AM: Clip sterilization failures. Contraception 16: 19, 1977
16. Richart RM: Complications *of* hysteroscopic sterilization. Obstet Gynecol 44:440, 1974
1'7. Quinones R, Alvarado A, Ley E: Hysteroscopic sterilization. Int J Gynaecol Obstet 14:27, 1976
18. Bhiwandiwala PP, Mumford SD, Feldblum PJ: Comparison of different laparoscopic sterilization occlusion techniques in 24,439 procedures. Am J Obstet Gynecol. In press
19. Chaturachinda K: The use of the laparoscope in rural Thailand. Int J Gynaecol Obstet 18:414, 1980
20. Mumford SD, Bhiwandiwala PP, Chi IC: Laparoscopic and minilaparotomy female sterilization compared in 15,167 cases. Lancet 2:1066, 1980
21. Bhatt RV. Pachauri S, Pathak ND. Chauhan L: Female sterilization in small camp settings in rural India. Stud Fam Plann 9:39, 1978
22. Green CP: Voluntary sterilization: world's leading contraceptive method. Population Report Special Topics Monograph No. 2, 1978, p 57
23. Grimes DA, Peterson HB. Rosenberg MJ, Fishburne JI. Rochat RW, Khan AR, Islam R: Sterilization-attributable deaths in Bangladesh. Int J Gynaecol Obstet. In press
24. The Johns Hopkins Program for International Education in Gynecology and Obstetrics: Dr. Rohit Bhatt of India Relates Experience, JHPIEGO Newsletter. Vol. IV. No. 3, October 1979, p 1
25. Morris *L*, Lewis B, *Powell* DL. Anderson J. Way A, Cushing J, Lawless G: Contraceptive prevalence: a new source of family planning data. Popul Rep [M] No. 5, 1981. p 167
26. Erb RA, Reed TP: Hysteroscopic oviductal blocking with formed-in-place silicone rubber plugs: method and apparatus. J Reprod Med 23:65, 1979
27. Talwar GP, Dubey SK, Salahuddin M, Das C: Antibody response to Pn-β-hCG-TT vaccine in human subjects. Contraception 13:237, 1976
28. Neuwirth RS, Richart RM, Stevenson T, Bolduc LR. Zinser H. Baur H, Cohen J, Eldering G, Rivas GA. Nilsen PA: An outpatient approach to female sterilization with methylcyanoacrylate. Am J Obstet Gynecol 136:951, 1980
29. Zipper J, Medel M, Goldsmith A, Edelman DA, Pastene L, Rivera M: The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization. Int J Gynaecol Obstet 14:499, 1976
30. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M: Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet 18:275, 1980
31. International Fertility Research Program: Network. IFRP, Vol. 2, No. 3, April 1981, p 4
32. Tietze C, Lewit S: Mortality and fertility control. Int J Gynaecol Obstet 15:100, 1977
33. Wortman J: Training nonphysicians in family planning services. Popul Rep [J] No. 6, 1975. p 93
34. Narain G: India: the family planning program since 1965. Stud Fam Plann, 1:(35), 2, 1968
35. Laufe LE, Cole LP: Nonsurgical female sterilization. Int J Gynaecol Obstet 18:333, 1980

Received March 1, 1982.
Reprint requests: Elton Kessel, M.D., Founder/Senior Consultant, International Fertility Research Program, Research Triangle Park, North Carolina 27709.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

PERMANENT FEMALE STERILISATION BY CHEMICAL METHOD TRANSCERVICAL INSERTION OF QUINACRINE

ARCH RAJ,* F.R.C.O.G.
and
DR. SAKHRUP CHAKRAVARTY, M.B.B.S., D.G.O.**

Introduction :

India is one of the first countries to introduce voluntary sterilisation as part of its national family planning programme. The attitude towards female sterilisation is quite favourable but still the methods exceed the abilities of our country, So Research work are on demand for different technology which can be applied outside the hospital setting, by paramedical personnel, and which equipments that is simple to use, low-costing and easy to maintain. It appears that trans cervical approach of chemical or mechanical blocking methods of tubes may answer to the problem.

Various chemical agents have been used for permanant tubal blockage by transcervical approach, amongst which Quinacrine has been considered to be the best. Quinacrine as a chemosterilant is an occlusive agent that acts on the intramural portion of the tube; a granulamatous reaction is produced probably by Quinacrine-DNA binding. Quinacrinc does not affect the endometrium because of the presence of Zinc. Quinacrine pellets when deposited in the uterincavity get slowly absorbed and produce the desired blockage of intramural portion of the tube by prolonged contact.

In this paper the results of a preliminary study with quinacrine pellets have been presented.

Materials and Methods :

Each Quinacrine hydrochloride pellet has a cylindrical shape with a diameter of less than 4 mm. and each pellet contains 50 mgm. of Quinacrine. Two pellets i.e. 100 mg. of quinacrine hydrochloride are deposited in the uterine cavity with the use. of Cu-T introducer. The tube with the pellets is passed through the cervical canal as a blind procedure and pellets are deposited into the upper segment of the uterine fundas.

Insertions are performed during the proliferative phase of the menstrual cycle, for three consequtive methods at one month interval. Hystero-salpingogram has been performed after 2 months of the last insertion. Histopathological studies of the tube have been carried out after inserting quinacrine pellets in gynaecological cases-who have undergone hysterectomy-at different period of intervals.

* Asstt. Prof. (G.S.O.) Dept. R.G. Kar. M.C.H.
** Hon. Sr. House-Staff R.G. Kar. M.C.H.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

In all cases except the gynaecological group additional contraceptive measures are advised for first two months, either oral pills or Condoms according to the patient's choice.

In the present series, MTP cases and few puerperal cases are included, when 250 mgm. of pellets have been used for 1st insertion. Follow up studies are scheduled at 6 months and 12 months interval or at any time when complication occur.

Patients' Profile :

Patients who desire for permanent contraceptive measure and do not suffer from any medical disorder are selected for trial. The series consist of interval cases, post abortal and puerperal cases and also few gynaecological cases for histopathological studies.

Total 131 cases for trial

Table I :

Total no. of cases (including all)	Total no. cases drop out after 1st dose	No. of Gynae. cases under study	Total no. of cases on trial	No. of intrerval cases total	No. of post abortal cases (total)	No. of puerperal cases (total)
131	22	6	103	55	46	2

Drop out cases after 1st insertion are excluded from the list.

Table II. Age group and parity of patient on trial

Different age group of patients :	Number of cases
25 years-30 years	54
31 years-35 years	26
36 years-40 years	14
40 years +	9 (including 6 gynaecological cases)

Table III. Parity of patients on trial

Parity of patients on trial :	Number of cases
P_2 :	6
P_2 + :	22 (abortion cases)
P_3 + :	35
P_4 + :	40

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Table IV. Socio Economic and Educational status

All belong to low socio-economic group except 2 cases who belong to middle socio-economic status.

All literate-except 2 cases of high education group.

Results :

Table I 'shows that the total no. of cases on trial in this series are 131. But 22 cases did not turn up after the 1st insertions and also 6 gynaecological cases are not taken into account.

Table V.

Total no. of cases on trial	Course complete (including HSG report showing Bilateral block)	No. of cases completed doses of quinacrine	No. of drop out cases after 2nd insertion.
103	50	43	10

Table Vi. 83—Follow up cases (those who have completed the schedule method)

Total no. of follow up cases after 1 year or more after last insertion	Total no. of follow up cases 6 months after last insertion	No. of cases turned up for Rpt. H.S.G.	No. of cases H.S.G. done report—persistance of Bilateral block after 1 year	Waiting for H.S.G.
14	16	11	4	7

Table VII. Result of Histopathological Examination of tubes in Gynaecological cases-after pre-hysterectomy insertion of Quinacrine

Total no. of Gynae. cases	H.P. report after 7 days of insertions no. of cases - 2	H.P. report after 3 wks of insertions no. of cases - 2	H.P. report after 2 insertion no. of cases - 1	H.P. report after two months of 2 insertion - 1
6	Report showed-no change in intramural portion of tube	Report showed inflammatory reaction with exudation at intramural portion of tube	No. tubal portion found in the specimen	Report showed fibrosis at the intramural portion of tube causing occlusion of the tubal cavity

Table VIII

Total no. of cases 3 insertion completed	H.S.G. done 50 cases report	H.S.G. not done
83	Bilateral block in all 50 cases	23 cases after 3rd doses

TABLE IX : Complication

Complication	Number of cases
Psychosis	nil
Menstrual disturbances (a) Menorrhagia (b) Prolonged menstrual cycle	3 cases (no treatment required) 2 cases-responded by Hormone with drawl treatment
Pregnancy	1 case within 1 yr. of followup.
Pelvic pain	Nil.
Vague complaints headache, weakness palpitation	3 cases-no treatment required.

Summary and Conclusion

The preliminary results obtained from the present study indicate that quinacrine pellets are quite effective in producing tubal blockage. The patients' acceptability toward the method are quite encouraging. In the present study 100 mgm. of quinacrine pellets are used as a test of response to Indian women.

Literature shows Zipper has performed various clinical series of quinacrine instillation both with solution and pellets by transcervical approach. He claim better results by pellets.

Davidson has reported similar results by single dose instillation of quinacrine and used oral contraceptive as an adjunctive method.

Isvangkun, et al have noted that one installation produces bilateral tubal occlusion in only about half the patients.

Ben it has demonstrated increasing rates of tubal occlusion with successive instillation.

Quinone has reported a high failure rate in a small series of patients receiving hysteroscopic instillation of quinacrine.

In the present series 83 cases had 3 consequitive insertions and only one case of failure within 1 yr. of follow up. Hyterosalpingographic report of 50 cases show bilateral tubal block at the isthmic portion of the tube.

Bhatt, R, et al has shown quinacrine induced pathological changes in fallopian tube. Our histopathological changes show quinacrine pellets require prolonged contact with the tube and repeated insertion showed better results. Complications and/or side effects that can be attibuted to the quinacrine pellet, produce either at the time of insertion or between insertions apear to be infrequent or minor. Menstrual disturbances such as menorrhagia, occured in 3 cases who do not require any treatment. 2 cases had prolonged menstrual cycle, responded well by hormone withdrawal treatment. Follow up studies are carried on, only 14 cases have completed 1 yr. and one became pregnant within 1 yr.

Conclusive remarks are awaited till long term followup have been carried out. Regarding reversibility of tubes-it is is expected that as the isthmical portion of the tubes are affected it will be easier to reinsert the healthy portion into the uterus.

In near future. it may be popular method which could be applicable to women of rural areas of India, if mobile camp can be organised for this method either by the Government or some voluntary organisations. Only disadvantage is that it is a time consuming procedure and at least three insertions are required for blockage of the tubes.

Acknowledgement

This work has been supported by Dr. B. Mullick of International Fertility Research Programme, who supplied the quinacrine pellets.

References

1. Benoit A, Melancon, J., Gagnon, M. :-Chemically induced tubal occlusion in the human female using intra uterine instillation of quinacrine, contraception 12 : 95, 1975.
2. Bhatt R.V., Pathak, N.D., Chauhan, L.N., Shah, D.S. and Bukapatamm, V.V. : A. study of transcervical instillation of quinacrine before hysterectomy to test tubal blockage. India Fertility Research Programme, Bombay, p. 171, 1977.
3. Davidson, O.W- and Wilkins C. Chemically induced tubal occlusion in the human female following a single instillation of quinacrine. Contraception 7 : 333-339, April, 1973.
4. Isvangkun, C. Phaosvadi, S., Neuwirth, R.S., and Richar, R.M. :— Clinical evaluation of quinacrine hydrochloride for sterilisation of the human female, Contraception 14 : 75, 1976.
5. Mehtaji, S. Jadwani, K., and Goyal, V. : Chemical sterilisation with quinacrine, Fourth Transaction of Scientific papers, India Fertility Research programme, Bombay, p.p. 167, Sept., 1977.
6. Quinones, R. Alvarado, A. and Lcy, E.-Hysteroscopic sterilisation Int. J. Gynae. Cal 14- 27-34, 1976.
7. Zipper, J. Stacchetti, E. and Medel, M.: Transaginal chemical sterilisation : – Clincical use of quinacrine plus potentiating adjuvants, Contraception 12:11,1975.
8. Zipper J, Medel M. Goldsmith A, Edelman DA, Pastene L, Rivera M :-The clinical efficiency of repeated transcervical instillation of quinacrine for female sterilisation. Int. J. Gynaecol Obstet 14 (6) : 499, 1976.
9. Zipper, J : IFRP Medical Advisory Committee. June, 1978

Int J Gynaecol Obstet 1980;18(4):275-9.

Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization

J Zipper, L P Cole, A Goldsmith, R Wheeler, M Rivera

- PMID: 6109672
- DOI: 10.1002/j.1879-3479.1980.tb00496.x

Abstract

The efficacy of transcervical insertions of quinacrine hydrochloride pellets to produce tubal occlusion has been evaluated in a study of 139 women in Santiago, Chile. At one year, the pregnancy rate was 3.1%, an acceptable rate for a nonsurgical method of female sterilization.

PIP: 139 volunteers seeking permanent sterilization were treated with 3 transcervical insertions of quinacrine hydrochloride pellets to produce tubal occlusion. The procedure is essentially the same as inserting an IUD. Pregnancy rate at 1 year was 3.1%, and results showed this method to be more effective than the quinacrine solution method, which entails a higher risk of transient toxic psychosis.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

CHEMICAL FEMALE STERILIZATION USING QUINACRINE PALLETS

ROHIT V. BHATT* MD, DCH
KOKILA M. JARIWALA**, MD, DGO
POURU BHIWANDIWALA***, MD.
LEONARD LAUFE****, MD.

It is generally accepted that surgical method of female sterilization is a very effective method of contraception. However, it is difficult to provide service for female sterilization in the remote rural areas. There may be fear of surgery in the minds of some women The surgical operation needs qualified medical persons and the number of such persons may not be adequate for the number of such procedures to be performed. Therefore, development of simplified non-surgical sterilization procedures that can be performed by paramedical personnel remains a high priority for countries with limited surgical facilities and trained personnel. Quinacrine has been tried for producing tubal blockage. Zipper states that transcervical instillation of Quinacrine hydrochloride solution has been associated with an unacceptably high pregnancy rate (25.5%). Bhat *et al* reported on the tubal blockage after instillation of Quinacrine hydrochloride solution in prehysterectomy cases. The instillations were made 4 weeks and 8 weeks before hysterectomy. Now quinacrine hydrochloride pallets have been developed in an effort to produce a delivery system that would bring the chemical into prolonged contact with the tubal ostia and thus increase the probability of successful tubal blockage. The Quinacrine pallets would dissolve slowly in the uterine cavity which would minimise the risk of rapid intravascular absorption. Zipper claims that quinacine acts as a powerful obstructive agent in the epithelium of the intramural region without altering the histology of the endometrium. Hagenfeldt has shown that human endometrium is rich in zink and it is this zink content of the endometrium which gives protection from quinacrine. The purpose of the present study is to evaluate the efficacy of quinacrine pallets in producing tubal blockage.

Material and Methods

The study consists of 80 women who agreed to have chemical method of contraception. These women wanted to control their fertility. They were told about the quinacrine pallets and possible risks and failure rate were also communicated. Women with pelvic pathology were not included in the study. Women with history of psychiatric disorders were also excluded. The pallets were inserted in the proliferative phase of the menstrual cycle. The pallets containing 250 mg. of quinacrine hydrochloride were deposited in the uterine cavity with the use of modified Cu-T-200 IUD inserter. The insertions were done on an out-patient basis without any premedication. They were observed for 2-3 hours before allowing them to go home. Total three insertions were made at the interval of 4 weeks. All these women were sexually active. They were not allowed to use any other contraceptive during this time. Women were

*Professor and Head Dept. Obst. Gynaecology, Medical College and S.S Cr. Hospital, Baroda.

**Research Assistant.

***International Fertility Research Program. RTP, North Carolina, USA.

scheduled for followup 6 months and 12 months after the: third insertion of the pallets.

Results

Socio-demographic data is given in table I. The average age of these patients was 31.4 years and average parity was 4.1. We could not perform more than one instillation in 2 cases because of subsequent pregnancy.' Discomfort in the first 48 hours was the main complaint. However the discomfort was slight and occured in 14 cases.' The other women had no discomfort. The pattern of menstrual cycle is shown in table II. Menstrual irregularity a.id scanty menses were observed in 6 to 12 percent of the cases. The prolonged cycle was the cause of concern to the women because of the fear of pregnancy. However, they were relieved of the anxiety when they were told that the pregnancy test was negative. The pregnancies are reported in Table III. Total 4 pregnancies resulted during the followup which varied from 10 to 14 months. Out of the four pregnancies, one occured after 1st instillation and one occurcd after second instillation of quinacrine. Two pregnancies resulted after all the three instillations. All these pregnancies were terminated by suction evacuation. There is no ectopic pregnancy in this series so far.

TABLE I. Socio-Demographic Data

Age in yrs.	N o .	School yrs. completed	Education Wife No.	Husband No.
15—19	0	0	22	8
20-24	0	1—6	25	18
25-29	7	7—12	29	40
30-34	72	13+	4	4
35+				
Residence			Total live births	
Urban	*62*		One	0
Rural	*18*		Two	*2*
Religion			Three	26
Hindu	*76*		Four	'34
Muslim	*3*		Five	15
Parsi	1		Six	3
Christian	0			

Discussion

The study shows that the pallet has more convenience of insertion as compared to the quinacrine solution. However four pregnancies during early followup is disturbing. Even if we exclude two pregnancies which occured before all the three instillations were complete, two occured even after three instillations. Bhatt *et al (1980) have* shown that quinacrine can induce tubal fibrosis with subsequent tubal occlusion. However, the erratic distribution of pathological lesions is note worthy. There is no doubt the quinacrine produces fibrosis and tubal blockage. What is not well understood is the optimal dosage

TABLE II. Menstrual Cycle Data

	After Ist Instillation	After 2nd Instillation	After 3rd Instillation
Pattern of Menstrual Cycle			
Normal	45	39	44
Shorter	14	17	12
Longer	16	20	20
Irregular	01	02	02
Amenorrhoea	04	01	00
	(One Pregnant)	(One Pregnant)	
Menstrual Flow			
Normal	72	70	68
Scanty	04	07	10
Profuse	00	01	00
Average Duration of Flow			
Same	70	68	72
Longer	02	06	00
Shorter	04	04	06

TABLE III. Pregnancy

After 1 instillation	...	1
After 2 instillation	...	1 2
		4

TABLE IV

	Lap. Ster. F. Ring	Lap. Ster Clip	Lap. Ster. Cautry	Mini Lap. Ster.
Technical failure	0.6%	0.9%	0.5%	Nil
Technical difficulties	2.7%	31.3%	—	—
Surgical difficulties	6%	8.5%	8.7%	10%
Surgical complications :				
(a) Immediate	1.3%	4.7%	8%	1.3%
(b) Late	—		—	6.7%
Complaints (pain)	52.7%	42.7%	10.16%	10%
Failure rate	0.2%	0.9%	0 2%	0.1%

and the mode of delivery of quinacrine. This is only a preliminary report and these women would be followed for two years to gather more information.

References

1. Bhatt, R.V., Pathak, N.D., Chauhan, L.N., ***et al.*** Proceedings of the India Fertility Research Program, 1978.

2. Bhatt, R.V., Aparacio, A., Davidson, O.'Laufe, L., King, T. Fertility and Sterility, 33 : 666-667; 1980.

3. Hagenfeldt cited by Zipper, J. in Female Sterilization. Ed. Duncan, G., Falib, RID. J.J. Academic Press, New York & London, 1972, page 231.

4. Zipper, J., Medel, M., Gold smith, A. et ***al.*** Int. J.' Gynaecol Obstet 14-499-552; 1976.

5. Zipper, J., Prager, Ruth., Medel, M. Fertility & Sterility, 24; 48-53; 1973.

Proceedings

of

THE THIRD INTERNATIONAL SEMINAR

on

Maternal and Perinatal Mortality

Pregnancy Termination and Sterilization

New Delhi, India

3rd to 5th October 1980

Editors :

VERA HINGORANI
F.R.C.O.G., F.A.M.S., F.A.C.S.,
F.I.C.S., Hon. F.A.C.O.G.

R. D. PANDIT
M.D., F.A.C.S., F.I.C.S.

V. L. BHARGAVA
M.D.

Printed by Prof. Vera Hingorani, Head Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, at New Roxy Press, South Extension-1, New Delhi-1 1004, and published by her for the Federation of Obstetric and Gynaecological Societies of India, Purandare Griha, 3 1 /C, Dr. N.A. Purandare Marg, Bombay-400007.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT. PLEASE REFER TO ORIGINAL)

Nonsurgical Female Sterilization

Leonard E. Laufe[1, 2] and Lynda P. Cole'
[1] *International Fertility Research Program, Research Triangle Park, North Carolina, USA*
[2] *Duke Medical Center, Durham, North Carolina, USA*

ABSTRACT

Laufe LE, Cole LP (International Fertility Research Program, Research Triangle Park, NC, and Duke Medical Center, Durham, NC, USA). Nonsurgical female sterilization.

Int J Gynaecol Obstet 18: 333-339, 1980

The development of a safe, effective nonsurgical method of female sterilization that can be performed by paramedical personnel remains a high priority. The method should haze a blind delivery system and require only one application. Methyl cyanoacrylate and quinacrine hydrochloride are the two most promising chemical agents. Quinacrine has evolved from instillations of a solution to the development of pellets to the use of an IUD vector. By using an IUD vector to deliver the quinacrine, tubal occlusion can be achieved with a reduction in total dosage and with one insertion instead of the three necessary with the solution and pellet methods.

BACKGROUND

The importance of the development of a nonsurgical method of female sterilization cannot be overstated. Such a method would give access to sterilization to the women who most need it, those living in areas of the world where medical resources are at a premium or nonexistent. For greatest impact, the nonsurgical method should be inexpensive and simple, preferably a one-insertion, blind transcervical procedure that is highly effective (a failure rate of <5.0%) and can be performed by paramedical personnel.

Nonsurgical sterilization techniques currently under investigation offer the possibility of such a procedure. Considerable research has focused on tubal occlusion techniques involving the injection of pharmacologic agents and adhesive materials into the oviduct, either through the hysteroscope or through a blind transcervical delivery system. Corfman (3) reported that, in 1849, Froriep developed a technique of tubal occlusion by applying silver nitrate at the cornua. Since then, the effect of such agents as zinc, chloride, phenol, salicylic acid, sodium morrhuate, gelatin resorcinol-formaldehyde and cyanoacrylate have been investigated (5, 10). There is much anecdotal information on the use of other compounds, such as creosote, but the long-term adverse effects were disastrous. Recently, there have been reports from China on the use of phenol and mucilage (9). The above-mentioned caustic solutions produce occlusion of the tubes in a varying proportion of patients. Material escaping through the tubes into the peritoneal cavity could cause coagulation of tissue proteins and irritation of the peritoneum. Hypermenorrhea and amenorrhea are other potential side effects.

METHYL CYANOACRYLATE

Methyl cyanoacrylate (MCA) is a tissue adhesive that produces irreversible occlusion of the fallopian tube by causing an inflammatory response, tissue necrosis and fibrosis; the material biodegrades in 4-5 months. Stevenson (12) reported that tubal occlusion occurred after one application via a balloon catheter in all patients in whom MCA reached the interstitial and isthmic portions of the tube (70% of the cases); no recanalizations were found after three years of follow-up. MCA has been delivered by hysteroscope and a balloon and cannula that accurately deliver a measured amount of the substance to the tube (11). The equipment is well-designed for developed countries or major medical centers but requires trained personnel since time is a critical factor in the procedure due to the rapid polymerization of the activated mixture.

QUINACRINE HYDROCHLORIDE

Quinacrine hydrochloride is a well-known drug according to Goodman and Gilmore (6). Human and animal data are extensive. It has been used safely as an antimalarial agent in hundreds of thousands of persons. Few people have experienced side

effects from the drug even when daily doses of 100 mg were taken for more than a year. Those side effects that have been reported were mild. Quinacrine taken orally has proved to be safe in all stages of pregnancy. While enormous doses may be lethal, large doses taken in attempted suicide have proved nonfatal. Quinacrine hydrochloride is approved for intrapleural or intraperitoneal use in patients with cancer, with a maximum dose of 1 gm per instillation every two days for five instillations. Drug reactions include fever, pleural or peritoneal pain, paralytic ileus, dyspnea and disorders of the central nervous system, such as hallucinatory agitation. Reactions are usually infrequent and transient and disappear quickly (6).

DELIVERY SYSTEMS

Quinacrine instillations

For over a decade, Zipper and associates have evaluated the transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization. Their initial animal studies (15) indicated that quinacrine selectively produced significant morphologic changes in the reproductive tract and caused permanent tubal fibrosis and occlusion in the rat. The clinical trials, Zipper et al (16, 17) evaluated various doses, concentrations and solvents for the suspension as well as instillation schedules of quinacrine. None of the patients used adjunctive contraceptives. All instillations were performed during the proliferative phase of the menstrual cycle. Three instillations proved the most effective schedule of quinacrine delivery, but there were still pregnancy rates of almost 10%. Other investigators substantiated the findings (1, 4, 7, 8).

Zipper felt the quinacrine instillation schedule was unsatisfactory since it resulted in an unacceptably high rate of pregnancy. The injection of the solution was dependent on generating pressure in the syringe reservoir to deliver the drug to the uterine fundus. Because of the varying degrees of pressure that could occur. there was occasional rapid intravascular absorption, which produced transient toxic psychosis (characterized by a sudden increase in motor and psychomotor activity; auditory and visual hallucinations, delusions and the occasional presence of ideas of reference; gradual clouding of the sensorium; disorientation; amnesia for recent events; and confabulation [6]). This method also requires that the solution be prepared immediately prior to insertion.

Quinacrine pellets

Zipper suggested that quinacrine hydrochloride pellets be developed to avoid rapid instillation and pressure and to prolong the contact of the drug with the tubal ostia, thus increasing the probability of successful occlusion. Because the quinacrine pellet exerts no pressure within the uterine cavity, the risk of rapid intravascular absorption may be reduced.

Each quinacrine hydrochloride pellet is cylindrical and has a diameter of less than 4 mm. The pellets are compacted to contain 10 mg of quinacrine per millimeter of length. Insertion is accomplished by placing the pellets in a plastic tube with a push rod positioned behind them (Fig. 1). The insertion procedure is essentially the same as that for inserting an IUD.

Zipper and colleagues conducted a study of the efficacy of three transvaginal insertions of 250 mg of quinacrine pellets preceded by a single pellet of 20 mg of sodium thiopenthal (13). Sodium thiopenthal, which is hydroscopic, was used to increase the viscosity of the uterine fluid in an attempt to improve the intrauterine retention of the quinacrine.

Insertions were performed during the proliferative phase of the menstrual cycle. The procedure was repeated at one month and two months after the first insertion. Only those women who requested sterilization for family planning reasons and who

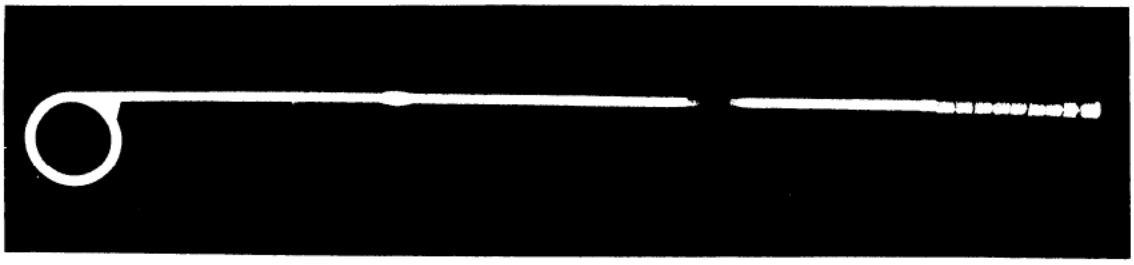


Fig. 1. Modified Cu-T IUD inserter loaded with quinacrine pellets.

Table 1. Life-table pregnancy rates per 100 women completing three administrations of quinacrine solution and quinacrine pellets.

Months Since Treatment	Quinacrine Solution ($N = 124$)[a]			Quinacrine Pellets ($N = 124$)[b]		
	Woman-Months	Rate	SE	Woman-Months	Rate	SE
6	726	5.7	2.1	741	0.8	0.8
12	1372	9.1	2.6	1422	2.5"	1.4
24	2317	10.9	2.9			

[a] *Of the 140 patients completing three instillations of quinacrine solution, 124 returned for one or more follow-ups.*
[b] *Of the 12 7 patients completing three insertions of quinacrine pellets, 1 24 returned for one or more follow-ups.*
[c] *p = 0.05.*

did not have a history of psychiatric disorders were selected as subjects. No adjunctive contraceptives were used.

A comparison of results from studies conducted by Zipper show that the pellet method is an improvement over the solution method (14) (Table I). However, the procedure still requires three administrations of quinacrine before it is effective, thus, falling short of the ultimate goal of an effective, blind, one-insertion procedure.

The erratic performance of the quinacrine pellets in occluding the tubes is probably caused by the uneven distribution of the quinacrine to the tubal ostia. Alternate systems to deliver the drug more accurately to the tubal ostia have been explored.

Quinacrine IUDs

A mixture of 80% quinacrine and 20% polyethyleneoxide was molded over a Copper-T (Cu-T) vector (Fig. 2). The mixture goes into solution within four hours after insertion. These intrauterine devices (IUDs) were inserted in 25 menstruating women awaiting hysterectomy for uterine prolapse. A slight yellowish vaginal discharge was noticed up to 24 hours postprocedure. Extirpated uteri were examined to determine the presence of sclerosing lesions in the intramural portion of the tubes. The first eight Cu-Ts inserted had 75 mg of quinacrine at the end of each arm and a bolus of 150 mg on the stem. In an effort to determine whether the bolus contributed to occlusion, the next 17 Cu-Ts inserted had only 75 mg of quinacrine per arm. These IUDs produced results equal to those produced by the IUDs with the larger dose. As with quinacrine pellets, the IUDs were not uniformly effective in delivering the quinacrine to the uterotubal junction. The erratic occlusion seemed to be a function of the correct placement of the IUD. The IUDs were inserted with the arms bent upward. Fig. 3 shows that the arms of the Cu-T were not correctly placed adjacent to the uterotubal junction. Currently, the

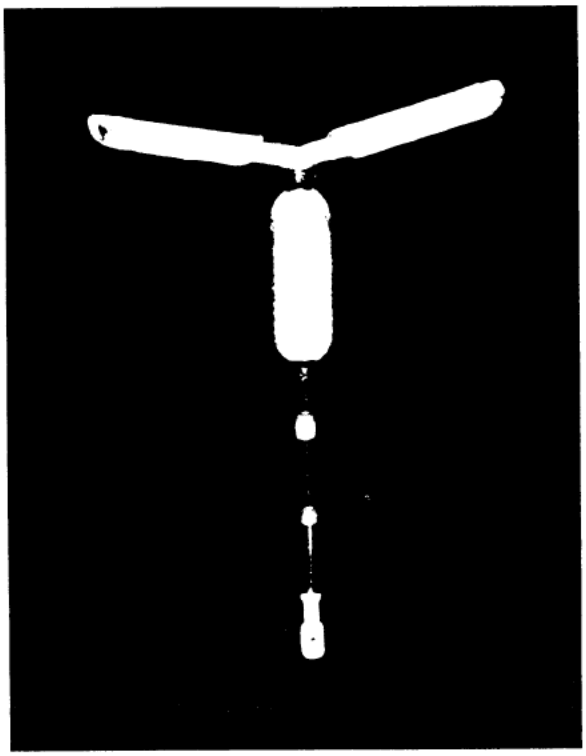


Fig. 2. Cu-T IUD with quinacrine.

International Fertility Research Program, Research Triangle Park, NC, USA, is investigating T-vector IUDs with and without copper that have the arms bent downward.

Other IUD vectors are also being explored, including an Ypsilon-shaped IUD and the spring-activated system illustrated in Fig. 4. The spring-activated system consists of a 2-cm, tightly coiled stainless steel spring attached at each end of a polyethylene rod 2 mm in diameter. The quinacrine is placed at the terminal end of each rod. After the

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT. PLEASE REFER TO ORIGINAL)

Fig. 3. Quinacrine-loaded CU-T IUD incorrectly placed in the uterine cavity.

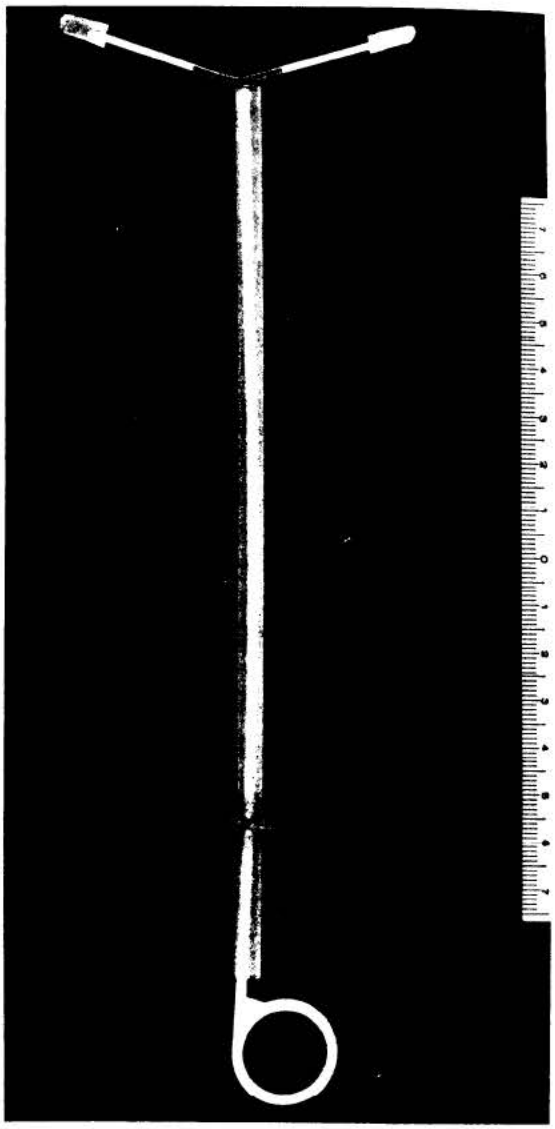


Fig. 4. Spring-activated IUD with quinacrine.

uterus has been sounded, a device with an arm length of 1 cm less than the uterine cavity depth would be inserted. Release of the quinacrine would be completed within four hours so that, even if the IUD is expelled after that time, the drug will have been delivered. If the IUD is not expelled, there is backup contraception for any method failures.

PATHOLOGIC EFFECTS OF QUINACRINE

Studies were initiated to study the pathologic effects of quinacrine on the fallopian tube. Twenty-three menstruating women who required hysterectomies for uterine prolapse voluntarily accepted a single intrauterine insertion of 250 mg of quinacrine pellets. Hysterectomies were performed one month postinsertions and the intramural portions of the tubes were examined. In more than 50% of the tubes, a definite sclerosing lesion of the tubal lumen was identified. The lesions observed appeared to be limited to the intramural portion of the tube. There seems to be no doubt that quinacrine can induce tubal fibrosis and occlusion (2).

The changes identified were easily divided into three groups: (a) no identifiable damage to the fallopian tube (Fig. 5); (b) subepithelial hyalinization and scarring with involvement of both the lamina propria and the muscularis of the tube (Fig. 6); and (c) destruction of the epithelium of the tube, as well as the changes seen in group (b) (Figs. 7 and 8).

CONCLUSION

The use of quinacrine hydrochloride as a method of nonsurgical female sterilization has evolved from

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT. PLEASE REFER TO ORIGINAL)

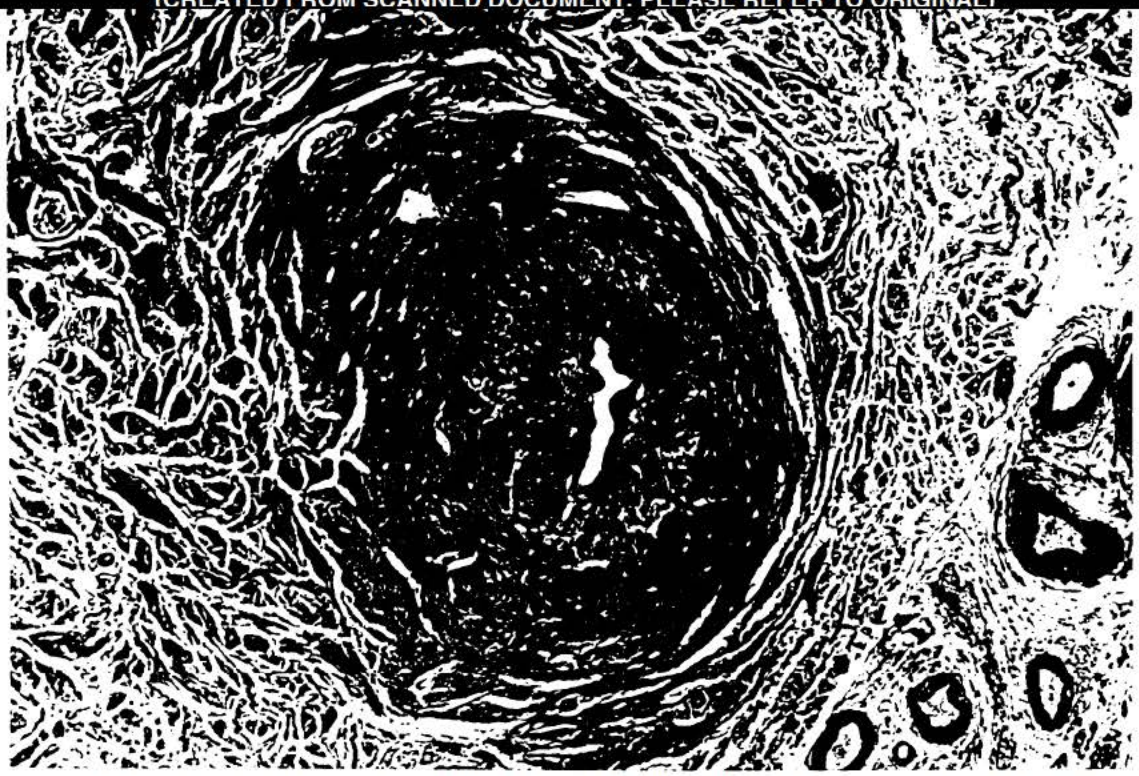


Fig. 5. Cross section showing no identifiable damage to the fallopian tube. Source: Bhatt et al (2).

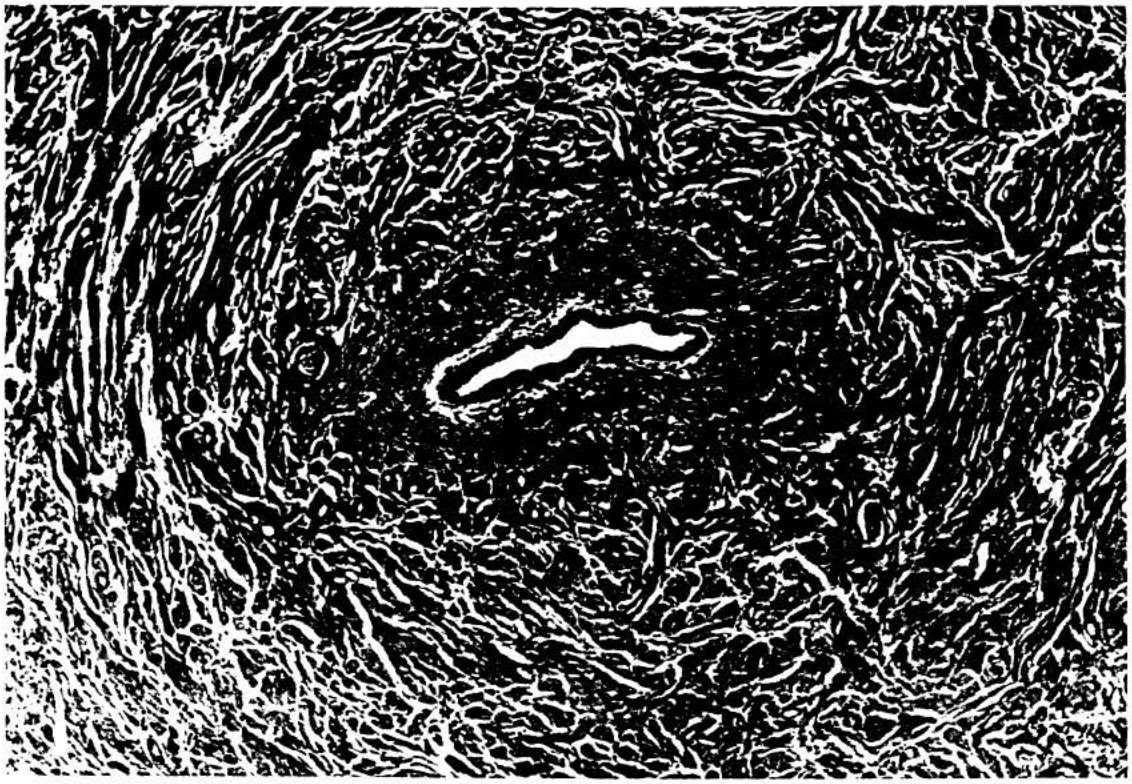


Fig. 6. Cross section showing subepithelial hyalinization and scarring involving both lamina propria and th muscularis of the tube. Source: Bhatt et al (2).

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.

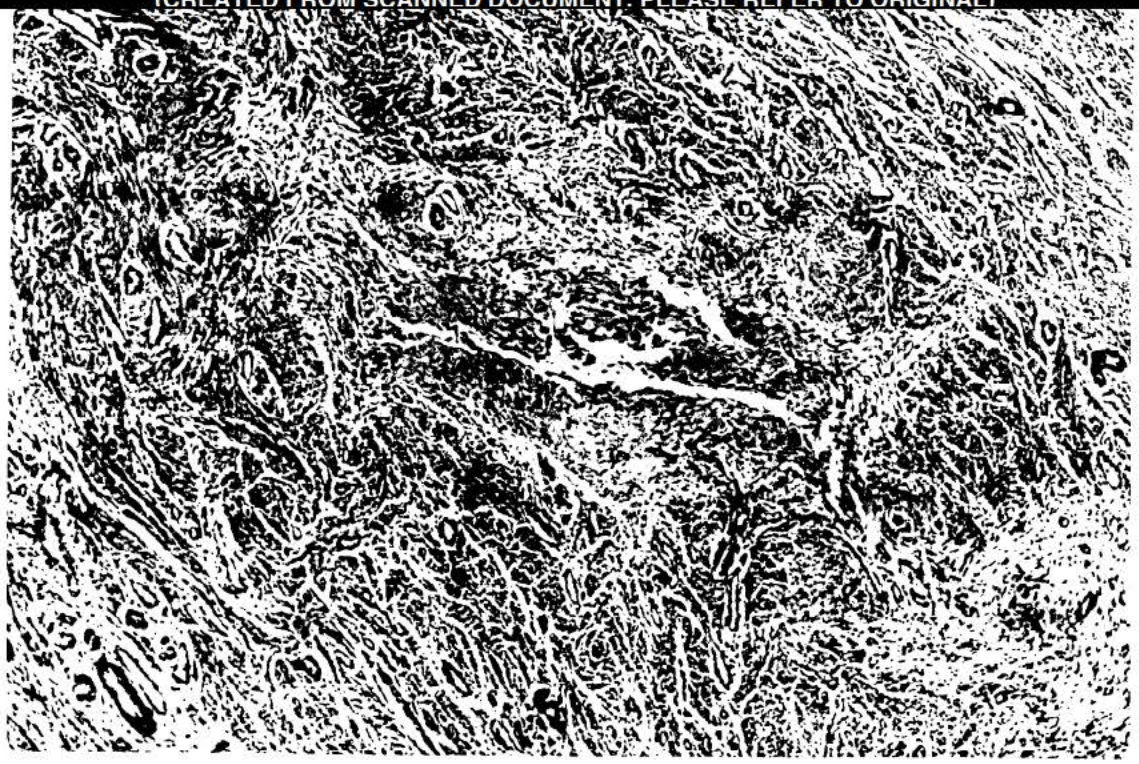


Fig. 7. Cross section showing destruction of the epithelium of the tube, as well as the changes seen in Fig. 6.

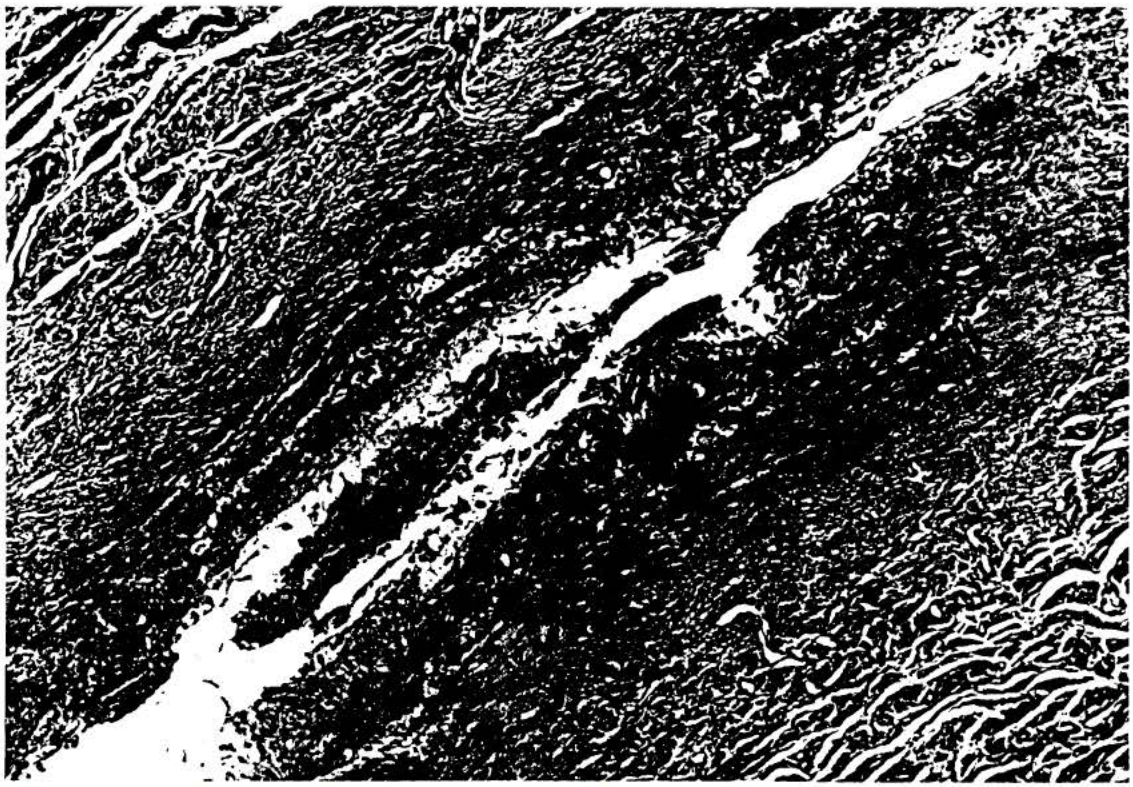


Fig. 8. Longitudinal section through lumen showing destruction of the epithelium and lamina propia.

instillations of a solution to the development of pellets to the use of an IUD vector. The advantage of the IUD delivery system is that tubal occlusion may be produced with a reduction in total dosage and with only one insertion instead of the three necessary with the solution and pellet methods. The IUD also provides backup contraception for any method failures.

There is no doubt that nonsurgical sterilization is one of the most important priorities of contraceptive technology. It has a longstanding history. Tubal occlusion can be accomplished by the transcervical application of chemical agents to the tubal ostia. Current research is focusing on the delivery of MCA and quinacrine, but other agents, as yet not tested, may also be promising.

ACKNOWLEDGMENT

Partial support for this work was provided by the International Fertility Research Program with funds from the US Agency for International Development.

REFERENCES

1. Benoit A, Melancon J, Gagnon M Chemically induced tubal occlusion in the human female using intrauterine instillation of quinacrine Contraception 12 95, 1975
2. Bhatt R Aparicio A Davidson 0 et al: Quinacrine-induced pathologic changes in the fallopian tube Fertil Steril 33: 666, 1980
3. Corfman PX: Transcervical oviduct occlusion In Advances in Planned Parenthood, Proceedings of the Third and Fourth Annual Meeting of the American Association of Planned Parenthood Physicians International Congress Series N 138 (ed AJ Sobrerg, S Lewit), Vol 1, p 183 Excerpta Medica Foundation Princeton NJ, 1967
4. Davidson 0, Wilkins L: Chemically induced tubal occlusion in the human female following a simple instillation of quinacrine Contraception 7:333, 1973
5. Falb R, Grode GA, Pavkov KL Adhesive blockage of the fallopian tube in female sterilization In Female sterilization (ed GW Duncan, R Falb, JJ Speidel), p 31 Academic Press New York, 1972
6 Goodman LS, Gilmore A (eds): The Pharmacologic Basis of Therapeutics, 4th ed, p 1081 The McMillan Co, New York, 1970
7. Israngkun C, Phaosavadi S, Neuwirth R et al: Clinical evaluation of quinacrine hydrocholoride for sterilization on the human female Contraception 14:75, 1976
8 Mehtaji S, Jadwani J, Goyal V: Chemical sterilization with quinacrine *In* Fourth Transaction of Scientific Papers, India Fertility Research Program, Bombay, September 1977, p 167 India Fertility Research Program, Bombay, India, 1978
9 Research Group of Tubal Occlusion by Drugs (Zhorgshan Medical College): Sterilization by occlusion of the fallopian tubes with mucilage phenol Chin J Obstet Gynecol 14 79, 1979
10. Richart RM, Neuwirth RS, Taylor HC: Experimental studies of fallopian tube occlusion *In* Human Sterilization (ed RM Richart, DJ Praeger), p 360 Charles C Thomas, Springfield, IL, 1972
11 Sciarra JJ: Current research in male and female sterilization *In New* Advances in Sterilization (ed ME Schima, I Lubell), p 198 Association for Voluntary Sterilization, New York, 1976
12 Stevenson TC: Methyl cycanoacrylate (MCA) for tubal occlusion *In* Advances in Female Sterilization Techniques (ed JJ Sciarra W Droegemueller, JJ Speidel) p 2 16 Harper and Row, Hagerstown MD, 1976
13 Zipper J, Cole LP, Goldsmith A et al: Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization Int J Gynaecol Obstet 18 275, 1980
14 Zipper J, Medel M, Goldsmith A et al: The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization Int J Gynaecol Obstet 14 499, 1976
15. Zipper J, Medel M, Prager R: Alteration in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats Am J Obstet Gynecol 101 97 1, 1968
16. Zipper J, Stachetti E, Medel M: Human fertility control by transvaginal application of quinacrine on the fallopian tube Fertil Steril 21 581, 1970
17 Zipper J, Stachetti E, Medel M Transvaginal chemical sterilization Contraception 12 11, 1975

Address for reprints:

Information Coordinator
International Fertility Research Program
Research Triangle Park, NC 27709
USA

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Chemical Sterilisation with Quinacrine

SHIRIN MEHTAJI, MD
Grant Medical College & Cama and Albless Hospital
Bombay

K. JADWANI, MD., DGO
Institute of Research and Reproduction
Bombay

V. GOYAL, MD., DGO
Institute of Research and Reproduction
Bombay

I. INTRODUCTION

Surgical sterilisation is one of the most important methods of fertility control in India. There is a need to study non-surgical methods of tubal occlusion. Several chemical agents are presently being tried in experimental animals but only a few can be used in humans. The ideal chemical should be effective, inexpensive, easily available and easy to administer. Most chemicals used for sterilisation are either sclerosing agents which act by destroying the inner lining of the fallopian tube and causing subsequent fibrosis or agents which solidify within the tube and act by forming a plug and bringing about tissue adhesiveness.

Drugs such as ethanol, fomaldehyde and silver nitrate cause tubal acclusion but cannot be used because of their toxicity. Silastic S. 5392, S. 521 and inethyle-2-cyanoacrylate (M.C.A.) act by causing tissue adhesiveness. They are highly effective but the process of application has not, so far, been established for these chemicals.

In 1961, Zipper first used quinacrine for blocking the tubal lumen. Quinacrine was used in 800 women; 638 study subjects were observed for 14,677 women months. Five dose schedules and drug combinations were used. Tubal occlusion was reported for 69 .O percent of the cases. The most effective combination was quinacrine and xylocaine with or without epinephrine which resulted in tubal occlusion in 94 percent cases after two instillations.1

Quinacrine ($C_{33}H_{30}ClN_3O$–HCL–$2H_2O$) acts by causing granulation of the tubal epithelium by binding the endothelial cells with DNA. It has no action on the endometrial lining. When instilled into the uterus, quinacrine caused

Histologic changes in the fallopian tubes after lower dose of transcervical quinacrine insertion.

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

occlusion in rats but not in rabbits. The genital tract of the rabbit has a high concentration of zinc which protects it from damage. Hagenfedt showed that while the human endometrium is rich in zinc the zinc content is much less in the tubal epithelium and so blockage of the tubes occurs following quinacrine instillation.*

II. MATERIALS AND METHODS

Trials with quinacrine were conducted at the Cama and Albless Hospitals at Bombay under the auspices of the Indian Council of Medical Research. Quinacrine was used in 98 cases. Women with 3 or more living children and atleast one male child who requested permanent limitation of family size but did not accept surgical sterilisation were included in the study. Women who requested sterilisation after medical termination of pregnancy were accepted soon after bleeding stopped and women with lactational amenorrhoea were included within 6 weeks after delivery.

Subjects

All the study subjects were married with proven fertility and in the 22 to 40 years age group. Half of the subjects in the study were Hindus; 45 .O percent were Muslims and 5 .O percent were Christians. While 65.0 percent of the women were menstruating regularly, 13.0 percent had lactational amenorrhoea and 13.0 percent were postabortal cases.

Physical examination was conducted to exclude pelvic pathology. Atropine was administered intramuscularly half an hour before the procedure. After cleansing the external gentalia and vagina, a freshly prepared suspension of 1 mg of quinacrine in 3-4 ml was instilled transcervically, very slowly, without using any pressure through a cannula or a No. 8 Foley's catheter. The patient's vital signs were monitored before and after the administration of the drug and pain and reflux were noted. The patient reported for examination after one week. The second dose of quinacrine was instilled after four weeks or following the next menstrual period.

III. RESULTS AND DISCUSSIONS

About 60.0 percent of the women used some contraception during the 6 month period before quinacrine instillation. Oral pills were used by 37.0 percent and injectable or implants by 15 .O percent of the study subjects. If the patient had an IUD before quinacrine instillation, the drug was instilled with the IUD inside. The duration of contraceptive use varied between 2 months and 5 years.

In this series, 35 women did not use any additional contraceptive after the first instillation; as pregnancies occurred before tubal blockage could be confirmed subsequent cases were provided additional contraceptive methods after quinacrine instillation. The patients continued to use the contraceptive method until blockage

Fertility and Sterility 2001;75:830-31.
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

of the tubes was confirmed by hysterosalpingography. While 83 .O percent women used oral pills, 10 .O percent used conventional contraceptives and 40.0 percent used long acting injectables.

Tubal Occlusion Following Quinacrine Instillation :

Bilateral tubal block occurred in 70 (82.3 %) study subjects. Tubal occlusion occurred after two instillations in 65 (76.5 %) cases and after three instillations in 4 cases. In one case tubal block occurred after one instillation only. This woman refused a second instillation but used oral combination pills after the first instillation. Hysterosalpingography was performed 6 months after quinacrine instillation and showed tubal blockage. Three of the four cases who required three instillations had lactational amenorrhoea, they used oral pills as an additional contraceptive.

Side Effects and Complications :

No side effects were observed during or after quinacrine instillation. There was one case of mild pelvic peritonitis and one patient developed a skin rash. Another reported fever and pelvic pain which subsided without any specific treatment. No other complications' were observed. Menstrual cycles were regular for most of the women. Zipper reported 2 cases who experienced excitation of central nervous system and were treated with intravenous barbiturates. In his series, amenorrhoea for 3 months was reported in 7 cases; four patients developed intrauterine adhesions and 4 developed chemical vaginitis after quinacrine instillation. Cervical cytology was normal in all cases.

Pregnancies

In this series, 70 women were followed for 680 months. Pregnancies occurred in 2 cases at 2 months and 8 months after tubal occlusion was confirmed by hysterosalpingography. It is interesting to note that there was no spill in the peritonial cavity. Both were intrauterine pregnancies.

To prevent reflux various cannulae and catheters have been used. The drug was instilled under direct vision via the hysteroscope by Alvarodo and Quinones; their failure rate was, however, very high (62.0 %) and so this method was abandoned.

Reversibility after quinacrine has been tried in animal experiments by the administration of estrogen and progesterone 1 to 28 days after quinacrine instillation.

IV. CONCLUSIONS

Quinacrine sterilisation is a simple method; the drug is inexpensive, the equipment is simple and the method can be used on an out-patient basis. No anaesthesia is necessary and hospitalisation is not required. There is no need for

specialised personnel or sophisticated equipment. If this method proves to be effective it could be popular. Even though the success rate is not as high as with surgical procedures this method of tubal occlusion deserves large scale trials with careful follow-up.

ACKNOWLEDGEMENT

We wish to thank the Superintendent of the Cama and Albless Hospitals for allowing us to present these data and Dr. K. Jadwani for conducting this study.

REFERENCES

1 Zipper, J., Stacchetti, E., and Medel, M. Transvaginal Chemical Sterilisation. Clinical Use of Quinacrine Plus Potentiating Adjuvants, Contraception. 12 (1): 11-21, July 1975.

2. Hagenfeldt quoted by Zipper, J., and Insunza, S.: Pharmacological Agents that Potentiate or Inhibit the Occulsive Action of Quinacrine in the Rabbit Tube and Rat Uterus. In: Female Sterilisation Eds. Duncan, G., Falib, R.D., and Spiedel, J.J. Academic Press, New York and London, 1972.

3. Zipper, J., Prager, R., and Medel, M. Biological Changes Induced by Unilateral Intrauterine Instillation of Quinacrine in the Rat : Reversion through Use of Estrogen and Progesterone. Fertility and Sterility. 24 (1): 48-53, January 1973.

7. **Snowden,** R. and Williams, M. The use effectiveness of the Dalkon Shield in the United Kingdom. Contraception **7:91-104** (1973)

8. **Cooper,** D., Israel, **R.** and Mishell, D. Randomized comparative study of the Copper **T** 300, Dalkon Shield and Shell Loop in parous women. Obstet Gynecol **45:569-573** (1975)

9. Davis, H.J. The Shield intrauterine device: A superior modern contraceptive. Am J Obstet Gynecol **106:455-456** (1970)

10. Ostergard, D.R. and Broen, E.M. The Dalkon Shield: A clinical evaluation. Contraception **4:313-317** (1971)

CLINICAL EVALUATION OF QUINACRINE HYDROCHLORIDE FOR STERILIZATION OF THE HUMAN FEMALE*

Charanpat Israngkun, **M.D.,** Sukhit Phaosavadi, M.D.
Robert S. Neuwirth, M.D., and Ralph M. **Richart,** M.D.

From the Department of Obstetrics-Gynecology
St. Luke's Hospital Center, New York City
Chulalongkorn University, Bangkok, and
Columbia University, New York City

Reprint Requests: Robert S. Neuwirth, M.D.
Director of Obstetrics-Gynecology
Woman's Hospital
St. Luke's Hospital Center
114th Street and Amsterdam kvenue
New York, N.Y. 10025

Abstract

Sixty women seeking sterilization were treated with 1 gm of quinacrine in 7 ml of sterile water applied via a Kahn cannula with an olive tip held against the cervix. The tubal closure rate by hysterosalpingogram and/or pregnancy was 44%. In view of the need for multiple applications of this drug and some of the potential problems of the method as yet not clarified, widespread clinical trials are not warranted. **However,** further testing may resolve the current limitations and risks of the method to yield a useful clinical technique.

Accepted for publication May 24, 1976

***This** work was undertaken as part of the contraceptive development **research** program **sponsored** and coordinated by the International **Committee** for Contraceptive Research of the Population Council.

Introduction

The successful transcervical application to the Fallopian tubes of a chemical agent which will consistently produce tubal closure without producing serious side-effects has long been a goal of investigators interested in human fertility and its regulation. Although a number of chemical agents have been identified which will close tubes in experimental animals and in humans, an acceptable system for their safe delivery has been elusive.

The, ideal system would be simple, inexpensive and could be used by non-specialist physicians or paramedical personnel on an office or out-patient basis. The original description by Zipper et al.(1) and subsequent description(2) of the use of quinacrine hydrochloride as a uterine lavage to produce tubal closure were encouraging in that the delivery system was extremely simple and inexpensive, but were discouraging because even after two instillations, the failure rate was high. Due to the design of the delivery system, it was not clear whether the failures were related to a lack of the quinacrine tube-closing ability, the delivery of an inadequate drug dosage, or to a failure to deliver the drug to the tube.

As part of an effort to determine why the failures occurred, we undertook a study of tubal closure in patients in whom high concentrations of quinacrine were delivered to the uterine cavity, using an olive-tipped Kahn cannula to increase the likelihood of tubal application.

Materials and Methods

Sixty women of reproductive age who wished to be sterilized were recruited from the Family Planning Clinic of Chulalongkorn University Hospital in Bangkok and were offered the opportunity to participate in this study. Most had been using a variety of contraceptive methods for varying periods of time prior to their being treated in this study. Patients were included only if they were in good health, and each was screened through a medical history and physical examination prior to treatment. They were in all phases of the menstrual cycle, except menstruation. None was thought to be pregnant on the basis of the screening.

The patients were placed on an examining table, a pelvic examination performed, a speculum inserted and the cervix exposed. The uterus was sounded and a Kahn cannula introduced into the uterine cavity, generally without the need for cervical dilatation. A rubber olive was adjusted against the cervix and a pre-filled 10 ml syringe locked on. The contents of the syringe were injected at a uniform rate over a clocked 20-second period and the syringe and cannula held in place for an additional clocked 40 seconds. Following the quinacrine application, the cannula was removed and the cervix and vagina inspected for evidence of reflux, the volume of which was estimated by the operator. The study was conducted with an observer-recorder present at all times in addition to the operator to ensure conformity with the protocol.

The material which was instilled into the uterine cavity was made up immediately prior to each procedure and consisted of 1 gm of quinacrine HCl suspended in 7 ml of sterile water. Due to the dead space in the Kahn cannula, the actual amount delivered varied between 645 mg and 860 mg. In one patient only 3 ml was delivered due to leakage, and one had 7 ml delivered because 8 ml of water was erroneously used to make up the suspension. Postprocedure contraception was one injection of 150 mg depomedroxyprogesterone acetate intramuscularly.

The patients were recalled one month following the procedure, interviewed, examined and blood withdrawn for a determination of hemoglobin, white blood count, total bilirubin and blood urea nitrogen. Four months following the procedure, hysterosalpingograms were performed to determine tubal patency.

Patients who became pregnant during the study were offered a therapeutic abortion and all failures were offered alternate sterilization procedures.

Results

The rates of tubal closure are summarized in the Table.

TABLE

TUBAL CLOSURE BY HYSTEROSALPINGOGRAM

Four months following one instillation of Quinacrine Hydrochloride:

Patients undergoing instillation	60	
Lost to follow-up	8	
Pregnant at/or before hysterogram	6	(2 underwent x-ray)
Patients undergoing hysterogram	48	
Bilateral tubal patency on x-ray	22	(46%)
Unilateral tubal patency on x-ray	3	(6%)
Bilateral tubal closure on x-ray	23	(48%)
Failure rate by x-ray and/or pregnancy	56%	

Of the forty-eight patients who had hysterograms, 48% had bilaterally blocked tubes, 6% had unilateral blockage, and,

in 46% both tubes were patent. In six patients or 12% of the fifty-two with follow-up, pregnancy occurred'prior to the hysterosalpingogram. Some of these pregnancies may have occur--red prior to treatment as previous contraception was of variable reliability, and the procedures were performed in all phases of the cycle but menstruation. There were no adverse patient reactions, either during the procedure, immediately thereafter, or up to the time of hysterosalpingography. All blood counts and chemistries were within normal limits.

Closure rates were tabulated for the various types of contraception reported by the patients just prior to the instillation of quinacrine. No significant correlations were found. The closure rate of women using systemic steroidal contraception was not different than those using local forms or none. The DMPA administered following the procedure may have an effect on the quinacrine action, but the study cannot evaluate this question.

Fifteen patients who were treatment failures at sixteen weeks underwent an alternative procedure for sterilization. Seven had hysteroscopic tubal cauterization performed and eight underwent laparoscopic sterilization. At laparoscopy, no abnormal findings were noted, and tubal cauterization with transection was done. In the hysteroscopy group, two patients were noted to have fine adhesions in the cornual regions of the endometrial cavity. The findings in the other five were normal.

Discussion

The data confirm the findings of **Zipper(3)** and Davidson and **Wilkins(4)** that quinacrine exerts an occlusive effect on the tube. The toxicity in this limited series was nil which also confirms their reports. Indeed, the rate of tubal closure in this trial was not significantly different from that reported by Zipper(3) (43.6%) after one instillation. Thus, this technique of application of quinacrine did not augment effectiveness for a single application.

Filling of the endometrial cavity with the quinacrine suspension as described by Davidson(4) rather than the lavage teehnique employed by Zipper(3) is more likely to deliver the quinacrine to the interstitial tube'. Unfortunately, we are unable to determine from our data the specific relationships between quinacrine delivery to the Fallopian tube and the subsequent status of the tube. However, Alvarado et **al.(5)** have reported a series of cases in which a quinacrine suspension was placed in the Fallopian tube under direct hysteroscopic control. The closure rates were low although the concentrations of quinacrine used by Alvarado were in the same range as those employed by Davidson(4) and by us. The technique they reported does not rule out the possibility that the quinacrine was washed from the tube following the intratubal injection. Nevertheless, **Alvarado's(5)** experience and the published data do suggest that quinacrine is a weak tubal sclerosing agent which will require multiple applications as Zipper has reported, to produce the desired effect in a significant percentage of yomen.

A sterilization technique requiring multiple treatments raises an obstacle to the ultimate applicability of such a method. In order to be acceptable the method cannot expose the patient who does not get the follow-up for whatever reason to an increase in life threatening risk. Such a situation was recently reported by Israngkun(6) following hysteroscopic tubal cautery without follow-up hysterography where the rate of ectopic pregnancy was inordinately high. The ectopic pregnancy rate following quinacrine treatment is unclear. Zipper(3) did not report any ectopic pregnancies in his series. More recently, he has described two ectopic pregnancies in his patients, but believes the ectopic pregnancy rate is not elevated over normal(7). On the other hand, the pathological data reported by Davidson(4) and Alvarado(5) suggest that partial tubal damage is a real possibility. Therefore, the ectopic pregnancy rate must be carefully established in a well followed group in order to clarify this important question.

Recently, Joseph and **Kincl(8)** have reported enteromegaly in rats treated with intratubal quinacrine leading to death in some animals. This effect is similar to findings initially described by Keeler et **al.(9)** following intraperitoneal injection in rats. This effect has not been seen by **Zipper(10)** in rats or humans. In our laboratory(preliminary tests in a small group of rhesus monkeys treated intraperitoneally with 1 gm of quinacrine suspension instilled into the pelvis at laparotomy demonstrated no local effect at sacrifice six weeks later. Obviously, the enteropathy question will have to be clarified, but it is of sufficient significance to merit caution for clinical application.

In view of the relatively low tubal closure rate after one treatment, even with the technique described which increases the likelihood of direct tubal application, the promise of quinacrine is limited unless some other method is found to augment the effect. The risks of accidental intravascular injec-"on of quinacrine via the uterine veins, the new adverse anim'l data reported by **Joseph(8)**, and the undetermined ectopic pregnancy risk in a large treated population, limit the wide-'pread clinical applicability of this method at this time.

REFERENCES

1. Zipper, J., Medel, M. and Prager, R. Alterations in Fertility Induced by Unilateral Intrauterine Instillation of Cytotoxic Compounds in Rats. American Journal Obstetrics and Gynecology 101, 971 (1968).

2. Zipper, J., Medel, M., Pastene, L. and Rivera, M. Intrauterine Instillation of Chemical Cytotoxic Agents for Tubal Sterilization and Treatment of Functional Metrorrhagia International Journal Fertility, 14,280 (1969)

3. Zipper, J. Stachetti, E., and Medel, M. Human Fertility Control by Transvaginal Application of Quinacrine on the Fallopian Tube. Fertility and Sterility 21, 581 (1970).

4. Davidson, O.W. and Wilkins, C. Chemically Induced Tubal Occlusion in Human Female Following a Single Instillation of Quinacrine. Contraception 7:333 (1973).

5. Alvarado, A., Quinones, R. and Aznar R. Tubal Instillations of Quinacrine under Hysteroscopic Control. Hysteroscopic Sterilization, International Medical Book Corp 381 Park Avenue, So., New York City.

6. Israngkun, C. Presented at the Third Meeting of the American Association of Gynecological Laparoscopists. Anaheim, California (November 1974).

7. Zipper, J. Personal Communication to the Population Council. (September 1974).

8. Joseph, A.A. and Kincl, F.A. Toxic and Antifertility Effects of Quinacrine Hydrochloride in Rats. American Journal Obstetrics and Gynecology 119, 978 (1974).

9. Keeler, R, Richardson, H. and Watson, A.J. Enteromegaly and Steatorrhea in the Rat Following Intraperitoneal Quinacrine. Laboratory Investigation 15, 1253 (1966)

10. Zipper, J. Personal Communication (April 1974).

11. Neuwirth, R. and Richart, R. Unpublished Data.

Plasma Levels of d-Norgestrel, Estradiol and Progesterone During Treatment with Silastic Implants Containing d-Norgestrel

E. Weiner and E.D.B. Johansson

Department of Obstetrics and Gynecology, University Hospital, Uppsala, Sweden

ABSTRACT

Six silastic capsules, each containing approximately 30 mg d-norgestrel, were inserted subcutaneously in 5 women. During treatment the plasma levels of d-norgestrel, estradiol and progesterone were determined by radioimmunoassay.

The highest levels of d-norgestrel in plasma were found initially. Decreasing levels in plasma were found during the first 60 days of treatment in most of the patients. Thereafter, the d-norgestrel concentrations were found to be fairly constant. Individual variations in the levels of d-norgestrel were observed.

The concentrations of d-norgestrel in plasma did not inhibit the baseline levels nor the surges of estradiol in plasma, but ovulation was inhibited in most of the patients. Dvulatoy pattern of progesterone was restored within 50 days after removal of the capsules.

The calculated lifetime of the capsules suggest a contraceptive efficacy of at least 5 years.

Accepted for publication May 24, 1976

Int J Gynaecol Obstet 1976;14(6):499-502.

The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization

J Zipper, M Medel, A Goldsmith, D Edelman, L Pastene, M Rivera

- PMID: 20347
- DOI: 10.1002/j.1879-3479.1976.tb00093.x

Abstract

The safety and efficacy of the repeated transcervical instillation of quinacrine hydrochloride in a suspension of 5 ml of 2% Xylocaine was evaluated in 200 patients. All instillation procedures were performed during the proliferative phase of the menstrual cycle: the second instillation was made in the first menstrual cycle following the initial instillation and the third and last instillation at 6 months after the first. None of the patients used any adjunctive contraceptives. Follow-up visits were scheduled at 6-month intervals after the last instillation. The potentially serious complications following the instillation were four cases of cortical exitation, and one case of acute adnexitis. The second instillation was not performed for 16.0% and the third instillation was not performed for 16.7% of the patients, for medical and/or personal reasons. Fifty-one pregnancies were reported, 41 (80.4%) before completion of the three instillations. The results of this study show that the instillation schedule used is unsatisfactory for widespread use. Additional studies are currently being conducted to evaluate the use of an adjunctive contraceptive up to the time of the third instillation in order to reduce the high pregnancy rate.

Transvaginal chemical sterilization: Clinical use of quinacrine plus potentiating adjuvants

- J. Zipper
- E. Stacchetti
- M. Medel

DOI:https://doi.org/10.1016/S0010-7824(75)80031-X

Abstract

Six years of experience with the use of transvaginal quinacrine as an obliterating agent of the intramural portion of the fallopian tube are presented. Fifteen different forms of treatment using various dosages of quinacrine, alone as well as a combination of quinacrine with several other pharmacological agents were studied. The purpose of these studies was to increase the rate of tubal obstruction, with 1 or 2 instillations of solution. The total experience is based on 638 patients who received treatment according to a prefixed plan. There was a total of 14,677 women months of observation and 437 patients were diagnosed as having tubal obstruction with CO_2 insufflation. Out of this group of 437, 50 pregnancies were observed, none of them ectopic, for a Pearl Index of 4. 10. The most effective treatment regimen, quinacrine + xylocaine, with and without epinephrine, after the second instillation had an obstruction rate of 94%. Most of the pregnancies in obstructed patients occurred in the first year and appeared to be due to incomplete obstruction of the oviduct.

CHEMICALLY INDUCED TUBAL OCCLUSION IN THE HUMAN FEMALE FOLLOWING A SINGLE INSTILLATION OF QUINACRINE

Oscar W. Davidson, M.D.
Carolyn Wilkins, M.D., Ch.B.

Department of Obstetrics and Gynecology
University of Miami Medical School

ABSTRACT

In a case study of ten fertile women receiving a single intrauterine instillation of a suspension of Quinacrine, the six patients who did not have a hysterectomy 5 to 6 days later were found to have non-patent tubes when tested at least three weeks post-instillation. Five of these patients were using oral contraception prior to, during, and after treatment. Of the remaining four patients who underwent surgery within one week of instillation, three were found to have lesions suggesting tubal inflammation; none of these patients were using any-kind of contraception.

Accepted for Publication March 15, 1973

INTRODUCTION

A simple method of sterilization has concerned physicians for many years. In particular, methods have been sought that could be used by paramedical personnel in developing countries. The intrauterine instillation of tubal occluding agents is a possible solution to this problem. Zipper has observed that Quinacrine has an occlusive effect on the intramural portion of the human fallopian tubes and that this effect appears to be permanent. However, he found it necessary to use two instillations of Quinacrine to obtain an occlusion rate of 84.3 percent as tested by tubal insufflation and pregnancy exposure (1). In this report we have studied tubal changes following a single instillation of Quinacrine as determined by tubal insufflation, hysterosalpingography and/or surgical pathology.,

METHODS

All patients included in this study were volunteers who had requested sterilization. In three of these, bilateral vaginal tubal ligation was attempted but could not be completed for technical reasons. In the remaining seven patients vaginal tubal ligation was contraindicated, thus (see Table I) vaginal hysterectomies were indicated and the patients agreed to participate in this study in the interim. When possible, tubal patency was proved prior to instillation either by tubal insufflation or hysterosalpingogram (see Table I). Quinacrine was instilled in early or mid-cycle and was given in the out-patient department. One gram of Quinacrine (Atabrine Winthrop) was suspended in 6 ml of sterile water for injection and instilled into the uterine cavity via a flexible polyethylene cannula inserted through the cervix. In patients with a large cervical os, a perforated rubber stopper was fitted 1-1/2 inches behind the tip of the cannula to prevent reflux of the suspension. Since the capacity of the cannula is about 2 ml, only 4 ml (approximately 680 milligrams) of Quinacrine entered the uterus. Injection time was approximately one minute and the cannula was held in place for one or two minutes following injection to prevent reflux. However upon removal of the cannula, in most cases, some suspension was seen to reflux into the vagina.

Patients were kept under observation for at least an hour following the procedure. Follow-up was scheduled for the next month although some patients underwent surgery earlier (see Table III). In four patients, only pathological studies were done, two had clinical and pathological studies and the remainder have been under clinical follow-up to the present time (Table II). Methods of interim contraception can be seen in Tables II and III.

TABLE I

CASES INCLUDED IN THIS STUDY

CASE #	AGE	PARITY	REASON FOR INCLUSION	PATENCY PROVEN PRIOR TO INSTILLATION
1. (LB)	39	3013	failed vaginal tubal ligation	not done
2. (BC)	30	5025	obesity	not done
3. (SC)	32	2112	only right tube vaginally ligated	Rubin-pos.
4. (DG)	23	5006	vaginal hysterectomy	not done
5. (VP)	34	1132	vaginal hysterectomy	not done
6. (RR)	34	4024	only right tube vaginally ligated	Rubin-pos.
7. (DR)	29	3023	vaginal hysterectomy	not done
8. (EB)	42	4004	obesity	Rubin-pos.
9. (ME)	37	4014	obesity	HSG-pos.
10. (MK)	21	3033	obesity	HSG-pos.

TABLE II

PATIENTS RECEIVING CLINICAL, FOLLOW-UP

CASE	OCCLUSION PROVED BY	TIME FROM INSTILLATION
2. (BC)*	Rubin -neg Pathology (see Table III)	5 months 6 months
3. (SG)	Rubin -neg Rubin -neg HSG -neg	1 month 3 months 7 months
6. (RR)	HSG -neg	7 months
8. (EB)	Rubin -neg HSG -neg	1 month 1 month
9. (ME)*	Rubin -neg Pathology (see Table III)	3 weeks 10 weeks
0. (MK)	Rubin -neg	3 months

All patients except #6 were taking oral contraceptives prior to, during and after treatment with Quinacrine.

*These patients underwent vaginal hysterectomies at 6 and 2-1/2 months post-instillation.

TABLE III

PATHOLOGICAL FINDINGS

CASE #	BIRTH CONTROL	TIME FROM INTERVAL INSTILLATION	PATHOLOGY OF FALLOPIAN TUBES
1. (LB)	none	5 days	L-no pathological changes R-focal obliteration of the lumen
2. (BC)*	O.C.	6 months	L-mild peritubal chronic inflammatory reaction R-narrowing with focal denudation of the mucosa
(DG)	none	6 days	L and R-focal acute exudative inflammatory isthmic portions
5. (VP)	none	6 days	L and R- no pathological changes
7. (DR)**	none	5 days	L-mild perisalpingitis R-no pathological changes
9. (ME)*	O.C.	10 weeks	L and R-segmental inflannnatory stenosis of isthmic portions

*See footnote in Table II.

O.C. = combination oral contraceptives

**Received only 200 mg Quinacrine.

RESULTS

All 6 women followed clinically showed tubal occlusion following a single instillation of Quinahrine (Table II). Of the four women who were operated within one week of instillation; histological examination showed one with pathological changes in both tubes, two had changes in one tube only and one showed no changes (see Table III). Two other patients who had hysterectomy 2.5 and 6 months after instillation, upon histological examination were found to have gross pathological changes confirming their previous clinical findings of tubal occlusion. Pathological changes were confined to the intramural portion of the tube Up to date no side effects or pregnancies have been observed in this group of ten patients. *There were* no changes in the menstrual pattern after treatment. There was no intermenstrual bleeding or menorrhagia.

DISCUSSION

The outstanding finding in this study was that the tubes of the patients who were examined at least three weeks following a single Quinacrine instillation were found to be occluded. Most of these women were using oral contraceptives prior to, during and after treatment. Of the patients examined within one week of instillation (none of them were using oral contraceptives), the tubal lesions varied from none to marked pathological changes. Zipper (1) used an endometrial cannula for instillation which did not occlude the cervix. We used a polyethylene cannula and made certain that no reflux occurred during instillation. Thus, higher intrauterine pressure was probably accomplished during the procedure and probably the Quinacrine suspension went through both fallopian tube openings.

It is also possible to speculate on the role of combination oral contraceptives as a potentiating agent in the action of Quinacrine. It was observed by Mahgoub et al.(3) that injected progestins cause a "stasis and supression" of the epithelial cells in the epithelium of the fallopian tube. Also, a decrease in tubal motility in vitro was obtained by the use of oral contraceptives by Jakobovits et al.(4). Both these observations suggest that oral contraceptives may have some potentiating effect by allowing a longer contact between the super-saturated solution of Quinacrine and the tubal epithelium. Since it is thought that the mechanism of action of Quinacrine as an occlusive agent is dependent upon its binding with DNA, we may speculate that the action of oral contraceptives may allow a longer contact with this epithelium, thus increasing chances of penetration into the cell and subsequent binding to DNA. It has also been stated that this binding can be inhibited by an increase in zinc concentration (2). It is not known at the present time whether oral contraceptives have any effect on the zinc concentration in the epithelium of the human fallopian tube. In conclusion, our observations differ slightly from Zipper on the following points: (a) all patients with an interval longer than three weeks between a single instillation and testing had evidence of tubal occlusion; (b) most of our patients were using oral contraceptives at the time of instillation* (c) while Zipper used an endometrial cannula for instillation'which does not completely occlude the cervix, we believe our technique of preventing cervical reflux during the procedure results in a higher intrauterine pressure which allows Quinacrine to enter both utero-tubal junctions in a single instillation. It must be realized that these preliminary findings are limited to a small number of women. The results obtained, however, justify further clinical investigation.

ACKNOWLEDGEMENTS

These studies were supported by The Population Council Contract No. M71.138/ICCR/RA-3.

REFERENCES

1. Zipper, J., Stachetti, E. and Medel, M.: Human fertility control by transvaginal application of Quinacrine on the fallopian tube. Fertil. Steril. 21:581, 1970.

2. Zipper, J. and Insunza, S.: Pharmacologic agents that potentiateor inhibit the occlusive action of Quinacrine on the rabbit tube and rat uterus. Female Sterilization. Duncan, G., Falb, R.D., and Speidel, J., (eds.). J. Academic Press, New York and London, 1972.

3. Mahgoub, S.El., Karim, M., Ammar, R.: Long-term effects of injected progestogens on the morphology of human oviducts. J. Reprod. Med. 8:288, 1972.

4. Jakobovits, A., Gecse, A., Piukovich, L., Szontagh, F., and Karady, I.: Effect of 19-norsteroids on the motility of human fallopian tubes. Int'l. J. Fertil. 15:36, 1970.

Section 4: Animal Studies (1945 - 2015)

1. Haseman, J.K., Growe, R.G., Zeiger, E., McConnell, E.E., Luster, M.I., Lippes, J., 2015. A critical examination of the mode of action of quinacrine in the reproductive tract in a 2-year rat cancer bioassay and its implications for human clinical use. Regul. Toxicol. Pharmacol. 71, 371-378.

2. McConnell, E.E., Lippes, J., Growe, R.G., Fail, P., Luster, M.I., Zeiger, E., 2010. An alternative interpretation of, "A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats" Regul. Toxicol. Pharmacol. 56, 166–173.

3. Cancel, A.M., Dillberger, J.E., Kelly, C.M., Bolte, H.F., Creasy, D.M., Sokal, D.C., 2010. A lifetime cancer bioassay of quinacrine administered into the uterine horns of female rats. Regul. Toxicol. Pharmacol. 56, 156–165.

4. Cancel, A.M., Smith, T., Rehkemper, U., Dillberger, J.E., Sokal, D., McClain, R.M., 2006. A one-year neonatal mouse carcinogenesis study of quinacrine hydrochloride. Int. J. Toxicol. 25, 109–118.

5. Jensen, J.T., Rodriguez, M.J., Liechtenstein-Zabrak, J., Zalany, S., 2004. Transcervical polidocanol as a nonsurgical method of female sterilization: a pilot study. Contraception 70, 111–115.

6. McClain, R.M., Keller, D., Casciano, D., Fu, P., MacDonald, J., Popp, J., Sagartz, J., 2001. Neonatal mouse model: review of methods and results. Toxicol. Pathol. 29 (Suppl. l), 128 -137.

7. Fail, P.A., Martin, P., Sokal, D.C., 2000. Comparative effects of quinacrine and erythromycin in adult female rats: a non-surgical sterilization study. Fertil. Steril. 73, 387–394.

8. Flammang, T.J., von Tungeln, L.S., Kadlubar, F.F., Fu, P.P., 1997. Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Regul. Toxicol. Pharmacol. 26, 230-240.

9. Sutapa, R., Evaluating the Genotoxicity of Quinacrine in Mammals using the Sister Chromatid Exchange Test. (1996). Dissertations, Theses, and Masters Projects. William & Mary. Paper 1539626041.

10. Zaneveld, L.J., Goldsmith, A., 1984. Lack of tubal occlusion by intrauterine quinacrine and tetracycline in the primate. Contraception 30, 161–167

11. Dubin, N.H., Pharmley, T.H., Diblasi, M.C., Ghodgaonkar, R.B., Jiffry, M.T.M., Blake, D. A., King, T.M., 1983. Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 60-70.

12. Blake, D.A., Dubin, M.C., Diblasi, M.C., Parmley, T.H., Stetten, G., King, T.M., 1983. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni, G.I., Shelton, J.D., Goldsmith, A., Sciarra, J.J. (Eds.), Female Transcervical Sterilization. Harper and Row, Philadelphia, pp. 71–88.

13. Dubin, N.H., Blake, D.A., DiBlasi, M.C., Parmley, T.H., King, T.M., 1982a. Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. Fertil. Steril. 38, 735–740.

14. Dubin, N.H., Strandberg, J.D., Craft, C.F., Parmley, T.H., Blake, D.A., King, T.M., 1982b. Effect of intrauterine and intravascular quinacrine administration on histopathology, blood chemistry, and hematology in Cynomolgus monkeys. Fertil. Steril. 38, 741–747.

15. H. Chandra, H., Malaviya, B., 1981. Toxic Effects of Quinacrine Hydrochloride in Rhesus Monkeys. Contraception. 24, 269-274.

16. Fitzhugh, G., Nelsok., A.A., Calvery, H.O., 1945. The chronic toxicity of quinacrine (Atabrine). Journal of Pharmacologic Experimental Therapy, 85, 207-221.

Section 5: In Vitro and In Silico Studies

1. Tice, R.R., 2022. In Silico Approaches In Carcinogenicity Hazard Assessment: Current Status and Future Needs. Computational Tox 20, 100191.

2. Chapman, K.E., Wilde, E.C., Chapman, F.M., Verma, J.R., Shah, UK., Stannard, L.M, · Seager, A.L., Tonkin, J.A., Rowan Brown, M., Doherty, A.T., Johnson, G.E., Doak, S.H., Jenkins, G.J.S. 2021. Multiple-endpoint in vitro carcinogenicity test in human cell line TK6 distinguishes carcinogens from non-carcinogens and highlights mechanisms of action. Archives of Toxicology. 95, 321–336

3. Clarke J.J., Sokal D.C., Cancel A.M., Campen D.B., Gudi R., Wagner V.O., San R.H., Jacobson-Kram D., 2001. Re-evaluation of the mutagenic potential of quinacrine dihydrochloride dihydrate. Mutat Res/Genetic Toxicol Environ Mutagen 494(1):41–53

4. Tice, R.R., Cavender, F.L., Carson, B.L., Haneke, K.E., 1999. Is Quinacrine a Human Carcinogen?

5. Tice, R.R., Griffith, J., Recio, L., June 22, 1990. An Evaluation of the Mutagenicity and Carcinogenicity of Quinacrine. Unpublished report of Family Health International; 32pp.

Epilogue

Prior to being elected President of ISAF in June of 2019, Don Collins, Jr. served on the Board of ISAF since October 2010. Prior to that in January of 2007, the FDA halted, then repeatedly in subsequent decades, denied any further discussion of a phase III clinical trial of QS in the United States. Junior is proud to follow in his father's footsteps. See a letter to Guttmacher Donald Collins, Sr. wrote on April 20, 2018, to Rebecca Wind.

"My connection with Guttmacher goes back to my days in the late 1960's early 1970's when I was working as a foundation executive. At that time, I was able to help Fred Jaffe and Jeannie Rosoff who headed a research department within PPFA headquarters obtain an initial grant so they could hold an informational conference at HEW. Following that initial successful conference which Fred arranged at HEW, Guttmacher subsequently got started as a separate entity at the suggestion of Al Moran, then Executive Director of PPNYC. Brilliant idea. Along the way I had the honor and pleasure of developing a warm friendship with Alan Guttmacher; what a great exemplar for family planning.

My own career in family planning evolved from serving for 6 years on the National Board of PPFA to helping obtain original funding for the beginnings of PSI, IFRP (aka Family Health International, now FHI360), IPAS, Population Institute, and others. I enjoyed years of service on the Family Health International board with Sharon Camp, Malcolm Potts, Fred Sai and many others.

I founded ISAF in 1976 to enhance women's access to contraceptives. ISAF then coproduced an advocacy film entitled "Whose Choice?" which aired in prime time on TBS on September 21, 1992. Subsequently, as the enclosed informational sheet notes, the TV film was updated and reoffered to many audiences.

In 1994 ISAF began to concentrate on getting FDA approval for a method of permanent female sterilization known as quinacrine sterilization or QS. The outcry from some sources was highly negative without any solid evidence of coercive use or its causing cancer.

After years of carefully documented evidence presented in prestigious juried journals, it is now clear that QS does not cause cancer and that its widespread approval by regulatory authorities would be a logical next step.

Unfortunately, the US FDA refused, after years of exhaustive ISAF presentations, to address the evidence ISAF presented and summarily rejected our continuing request to conduct a Phase III trial on December 16, 2018.

A very brief story of QS history was recently summarized by ISAF's Project Director, Dr. Jack Lippes, whose famous Lippes Loop was used by millions of women. He has long believed in the powerful potential of QS to help millions of women worldwide.

A copy of The European Journal of Contraception & Reproduction's February 2017 journal paper on its favorable findings on QS is enclosed.

If Guttmacher decided to do a careful research study of our evidence on this method, we can supply all the background information, including the potential downside opinions of those who have attacked without information the safety and efficacy of the method.

I am convinced that your history of scientific integrity would prevail regardless of the attitudes of QS' enemies.

You of course may decide that the public relations downsides of truth telling about QS make such a careful study one you would not wish to undertake. Either way I would appreciate your reply."

Cordially,
Donald A. Collins
President and Treasurer

Enclosures:

Jack Lippes Brief Essay on QS, July 2017

"In 1983, the Center for Disease Control (CDC) of the United States Public Health Service recorded 108 deaths occurring between 1977-1981 associated with surgical tubal ligations (TL). The case fatality rate was reported as 3.6 per 100,000. (May 20,1983/32(19);249-50)

Eager to obtain more recent data, my enquiry, "How many TL deaths occurred between 2009 and 2016," provided a surprise. The CDC no longer collected data on TL deaths. Of course, TL deaths still occurred. We just don't know how many. All such TL deaths are tragic. But today such deaths are especially tragic because we know that they can be prevented by providing Quinacrine sterilization in place of TL. No death has ever been reported with QS in the over 150,000 procedures using the pellet method.

Quinacrine Sterilization (QS) is a simple non-surgical procedure where a small (252 mg.) dose of the drug Quinacrine(Q) is inserted into the uterine cavity of a women who has chosen to be sterilized. Quinacrine pellets dissolve and the drug reacts with the lining of the oviduct scarring the oviduct. This procedure is repeated a month later. The small resulting scar prevents conception and the woman may never become pregnant again. In

Vietnam where 50,000 women chose and received QS, all procedures were performed by nurses, nurse practitioners or midwives. It was and is not necessary for a physician to be present during a QS procedure.

The cost between QS and TL is astounding. In Vietnam where 50,000 women elected and received QS, the cost was one dollar per case. On the other hand, TL can cost $5,000 for each case. In the US there are about 750,000 TLs performed annually. If QS were substituted for TL lives would be saved and the American health care budget would be reduced by more than 3 billion dollars. Furthermore, complications that sometimes occur with surgery would also be prevented by QS. The FDA bases its opposition to QS on a rat study where the rats had Quinacrine placed in their uteri and developed cancer. Because the rats were so overdosed, this rat study lost any validity.

Then in February of 2017 the Degge Group published an epidemiological study of QS. It was a 16-year retrospective review of 20,000 women in Vietnam. Half of these women received QS while the other half used an IUD or had a TL.

There was no difference in the incidence of cancer between the 2 cohorts. When you are in possession of both animal and human data the animal data becomes superfluous.

Every TL death leaves survivors in pain, i.e. husbands, children and siblings are left grieving. Is it possible for these survivors to sue the FDA for negligence in not approving QS. Women who suffered non-fatal injuries from their attempted TL may similarly sue the FDA. Where does this end???

The FDA which has rejected QS should approve QS and thereby save women's lives and reduce the health budget of the US."

This book is written to document accomplishments through almost half a century of QS science and to encourage health ministers to continue to help women and mothers everywhere by adopting the QS method saving lives and changing markets which now have women undergoing surgery or paying for contraception for 15 – 20 years beyond any childbearing desire they might have.

Melissa Haussman's 2013 book, Reproductive Freedom and the State; Getting the Birth Control, RU-486, and Morning-After Pills and the Gardasil Vaccine to the U.S. Market, in this one sentence, "For example, as noted by Hollander, Pfizer's Viagra was approved in less than six months of its application to the FDA on March 27, 1998."

Contrast Viagra's approval with this Brief History of the Abortion Pill in the U.S. from WebMD. Thank goodness for Peg Yorkin, President Clinton, and other brave souls.

“Sept. 28, 2000 -- The road toward FDA approval for the abortion pill RU-486, or mifepristone, has spanned two decades and been cluttered with at-times bitter, contentious battles between those against abortion rights and pro-choice advocates. But as of Thursday, medical abortion with RU-486 is now an option for American women.

To date, more than half a million women in Europe have undergone medical abortions with RU-486, as have thousands of women in the U.S. as part of clinical trials.

‘A combination of complex business and political issues contributed to the long time it has taken to bring this product to the market,’ says Sandra Waldman, spokesperson for the Population Council, a nonprofit group marketing the drug in the U.S.

‘I think RU-486 offers more options to women, but it won't solve all of our abortion access problems,’ says Tina Hoff, director of Public Health Information and Communication at the Henry J. Kaiser Family Foundation in Menlo Park, Calif. ‘There are still issues to overcome including whether or not insurance will cover the cost of abortion with RU-486, whether RU-486 can be administered by non-physician providers, and how doctors will accommodate the [time] that it takes to expel the fetus,’ she tells WebMD.

To illustrate the long, embattled road toward approval, WebMD has put together a timeline of the milestones and roadblocks in the fight to approve RU-486, both here and abroad:

1980 -- Researchers at Roussel-Uclaf, a French pharmaceutical company, develop mifepristone (RU-486).

1983 -- The FDA issues a testing permit to the Population Council, a nonprofit group, to conduct trials of mifepristone as an early abortion method.

1988 -- RU-486 is approved in France, but distribution is halted in response to protests. The French Minister of Health intervenes and orders the company to return the drug to the market. Anti-abortion rights groups then threaten to boycott Hoechst A.G. (Rousell-Uclaf's parent company).

1989 -- In response to pressure from the Bush Administration and others, the FDA bans the importation of RU-486 for personal use. Hoechst says it won't market or distribute the drug outside of France to appease groups against abortion rights.

1990 -- Leading scientists testify before Congress that the FDA import ban has hindered research on the broad medical benefits of RU-486, including treatment for some cancers, HIV, and uterine tumors, and for inducing labor.

July 1992 -- An American woman named Leona Benten issues the first direct challenge to the FDA import ban when U.S. Customs seizes the drug from her as she returns from Europe. However the U.S. Supreme Court refuses to hear her case or order the FDA to overturn the ban.

Jan. 1993 -- President Clinton asks the FDA to re-examine its import ban.

Sept. 1993 -- The Institute of Medicine suggests that an expedited new drug application be submitted to the FDA for the use of RU-486 as a method of early abortion.

1994-1995 -- Roussel-Uclaf gives the Population Council the U.S. patent rights for RU-486. Clinical trials involving 2,100 women begin.

March 1996 -- The Population Council submits a drug application to the FDA for RU-486 as an early abortion method.

July 1996 -- An advisory arm of the FDA recommends approval of RU-486 as a safe and effective early nonsurgical method of abortion.

Sept. 1996 -- The FDA issues an "approvable letter" for RU-486 for early abortion, when used with misoprostol, a drug that causes uterine contractions to expel the embryo. The letter states that the two-drug combination is safe and effective when used under close medical supervision but notes that additional information is needed on the manufacturing process and labeling before a final decision is made.

Feb. 1997 -- A major roadblock: The European manufacturer responsible for producing RU-486 in the U.S. cancels its contract with the Population Council -- delaying the drug's introduction in the U.S. indefinitely.

April 1997 -- A study in The New England Journal of Medicine shows that RU-486, when used in combination with a type of drug called a prostaglandin (misoprostol), medically terminates 92% of pregnancies when taken within 49 days of conception.

June 1998 -- An amendment to a bill is passed that bans the FDA from using funds to test, develop, or approve any abortion drug.

Sept. 1998 -- The Clinton administration opposes the amendment.

Oct. 1998 -- The ban is deleted from the bill.

Feb. 2000 -- The FDA postpones approval of RU-486 until certain questions about the manufacturing and distribution of the drug are answered.

Sept. 28, 2000 -- RU-486 is approved by FDA as a method of early medical abortion."

June 24, 2022 – U.S. Supreme Court Dobbs decision overturns Roe v. Wade.

May 2, 2023 -- Abortion medication is illegal in 13 states where near-total abortion bans went into effect in 2022.

The QS journey is a similar one, rife with even more focused politics and government corruption bent on killing the best method of female sterilization (the most used contraceptive method) forever. We must not let that happen.

About the Authors

Dr. Stephen D. Mumford is the founder and President of the Center for Research on Population and Security. He has his doctorate in Public Health. His principal research interest has been the relationship between world population growth and national and global security. He has been called to provide expert testimony before the U.S. Congress on the implications of world population growth.

Dr. Mumford has decades of international experience in fertility research where he is widely published. In 1981, he received the Margaret Mead Leadership Prize in Population and Ecology. He has been recognized for his work in advancing the cause of reproductive rights by the Feminist Caucus of the American Humanist Association, and has addressed conferences worldwide on new contraceptive technologies and the stresses to the security of families, societies and nations that are created by continued uncontrolled population growth. He has written extensively on the pivotal role of the Catholic hierarchy in thwarting efforts to tackle the world's burgeoning population.

In 1974, President Richard Nixon requested the authoritative interagency study that came to be known as NSSM 200 (National Security Study Memorandum 200). The NSSM 200 report states: "There is a major risk of severe damage [from continued rapid population growth] to world economic, political, and ecological systems and, as these systems begin to fail, to our humanitarian values." However, the implementation of NSSM 200 recommendations that were already approved by President Ford was blocked by the swift action of the Vatican. As CIA Director, George H.W. Bush was in the position most concerned with such a grave threat to the United States and global security. Just days after leaving his post at the agency, he told Dr. Mumford, author of *Population Growth Control* (1977), "I agree with everything you are saying here," referring to the book, "and I can assure you the folks at the CIA agree with you too."

As president of the Center for Research on Population and Security, Dr. Mumford continues his work of more than four decades as lead scientist in the development and evaluation of contraception methods and advancing the cause of reproductive rights. Collaborating with health providers and scientists in more than 20 countries, his office is in North Carolina where he makes his home. His wife of 40 years, a Chinese immigrant and leading cancer researcher, focuses much of her investigation on environmental cancers affecting large populations of poor women.

In addition to his books on biomedical and social aspects of family planning, as well as scientific articles in more than a score of journals, Dr. Mumford's major works include American Democracy and the Vatican: Population Growth and National Security (Amherst, New York: Humanist Press, 1984), The Pope and the New Apocalypse: The Holy War Against Family Planning (Research Triangle Park, North Carolina: Center for Research on Population and Security, 1986), and The Life and Death of NSSM 200: How the Destruction of Political Will Doomed a U.S. Population Policy (Research Triangle Park, North Carolina: Center for Research on Population and Security, 1996).

The following is a sampling of some of the articles, excerpts and presentations by Dr. Mumford that we feature on this site. There is a much wider selection available here.
How far is the Vatican willing to go to insure its survival?
Why the Catholic Church has survived for 2000 years while all other tyrannies have failed
The Catholic Church and Sex
How the undemocratic activities of the Catholic Church silences critics
Catholicism – both a religion and an ambitious, arrogant political institution
The Roman Catholic hierarchy: a cabal of power that moves under the guise of benevolence
Postponing Self-Destruction of the Catholic Church
Overcoming Overpopulation: The Rise and Fall of American Political Will
What happened to American political will to deal with the overpopulation problem?
The Vatican's Role in the World Population Crisis: The Untold Story
Vatican Control of World Health Organization Policy: An Interview with Milton P. Siegel
NSSM 200, the Vatican, and the World Population Explosion
Eight kinds of power the Vatican exercises to control Catholics
Why The Pope Can't Change The Church's Position On Birth Control: Implications For Americans

Don Collins, Jr. is a senior technical sales manager, a business development manager, consultant, and senior engineering manager in the computer industry and holds 65 patents. His R&D teams had more than a million products installed worldwide. He has founded and served on the boards of nonprofits for more than a decade, is President of ISAF a 501(c)(3), holds his B.S. from Temple University, and his M.S. in Electrical Engineering from NTU. He is an author and speaker.

About the Book

QS is a nonsurgical permanent contraceptive (NSPC) method only for women who wish to have no more children. Following counseling and uncoerced written consent of and by candidates for QS, followed by a prescribed waiting period (if required), QS is given in two doses of quinacrine as seven pellets each 36 mg (total dose 252 mg), during the proliferative phase of the menstrual cycle (days 6 to 12 after the onset of menstruation), 28 days apart, using a modified Copper-T intrauterine device (IUD) inserter which is advanced to the fundus, then, using the Hieu method, the inserter is withdrawn 0.5 cm, and the plunger is advanced so that the pellets are all expelled at the top of the uterus "blind." Alternate contraception must continue for 3 months following the first insertion allowing time for a woman's immune system to respond and occlude both of her fallopian tubes.

Since 1976, approximately 200,000 cases using this pellet QS method have been performed in 53 countries, including the U.S. with no reported deaths. This book assembles and reviews all available evidence from almost 50 years found in 941 references consolidated to 107 unbiased peer reviewed and published human, in vivo, in vitro, and in silico studies (summarized in tables) to support that QS is safe (with no increase in ectopic pregnancy, hysterectomy, or cancer) and better than 97% effective when women follow the prescribed QS 2-insertion method based upon 47,101 women in 42 studies from 1977 to 2010 including 107,548 women years of follow-up.

Thank you to those hundreds of thousands of satisfied women who were not coerced and who preferred the QS method over surgical tubal ligation. Those women would not have been served, those hundreds of publications proving the safety and efficacy of nonsurgical permanent contraception (NSPC) for women (QS) and this book (written to provide evidence for the future approval of QS) would never have happened without more than a thousand doctors, researchers, healthcare providers, and others who recognized the value to women of QS and who acted to improve women's lives.

Dr. Stephen D. Mumford is the founder and President of the Center for Research on Population and Security. He has his doctorate in Public Health. His principal research interest has been the relationship between world population growth and national and global security. He has been called to provide expert testimony before the U.S. Congress on the implications of world population growth.

QS is a nonsurgical permanent contraceptive (NSPC) method only for women who wish to have no more children. Following counseling and uncoerced written consent of and by candidates for QS, followed by a prescribed waiting period (if required), QS is given in two doses of quinacrine as seven pellets each 36 mg (total dose 252 mg), during the proliferative phase of the menstrual cycle (days 6 to 12 after the onset of menstruation), 28 days apart, using a modified Copper-T intrauterine device (IUD) inserter which is advanced to the fundus, then, using the Hieu method, the inserter is withdrawn 0.5 cm, and the plunger is advanced so that the pellets are all expelled at the top of the uterus "blind." Alternate contraception must continue for 3 months following the first insertion allowing time for a woman's immune system to respond and occlude both of her fallopian tubes.

Since 1976, approximately 200,000 cases using this pellet QS method have been performed in 53 countries, including the U.S. with no reported deaths. This book assembles and reviews all available evidence from almost 50 years found in 941 references consolidated to 107 unbiased peer reviewed and published human, in vivo, in vitro, and in silico studies (summarized in tables) to support that QS is safe (with no increase in ectopic pregnancy, hysterectomy, or cancer) and better than 97% effective when women follow the prescribed QS 2-insertion method based upon 47,101 women in 42 studies from 1977 to 2010 including 107,548 women years of follow-up.

Thank you to those hundreds of thousands of satisfied women who were not coerced and who preferred the QS method over surgical tubal ligation. Those women would not have been served, those hundreds of publications proving the safety and efficacy of nonsurgical permanent contraception (NSPC) for women (QS) and this book (written to provide evidence for the future approval of QS) would never have happened without more than a thousand doctors, researchers, healthcare providers, and others who recognized the value to women of QS and who acted to improve women's lives.

ISBN 9798869839183

90000

9 798869 839183