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Quinacrine sterilization (QS) in a private practice in Daytona Beach, Florida: a preliminary report

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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

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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.

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