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Quinacrine sterilization of 1997 women in Daharpur, Midnapore, West Bengal, India: a comparison of 3 protocols

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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.
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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].

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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.

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