

Randomized trial of one versus two transcervical insertions of quinacrine pellets for sterilization

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Objective: To determine the relative effectiveness of single vs. two transcervical monthly insertions of 252 mg of quinacrine for female sterilization.

Design: Controlled clinical study.

Setting: Family planning clinics of 6 academic centers.

Patient(s): Sexually active reproductive-age women requesting sterilization.

Intervention(s): At each of six centers 70 and 30 women were randomly assigned to receive either one or two, respectively, monthly transcervical insertions to the fundus of 252 mg of quinacrine and 75 mg of diclofenac as pellets and they were followed for 1 year.

Main Outcome Measure(s): Complications, side effects, and pregnancy failures.

Result(s): There were no serious complications and side effects were transient and easily treated. There were 3 (7.4%) pregnancy failures in the single insertions group and 2 (1.1%) in the two insertions group, but with marked center variation.

Conclusion(s): Quinacrine sterilization using two monthly insertions of 252 mg of quinacrine appears safe and reasonably effective. (Fertil Steril 2002;77:1065-8. © 2002 by American Society for Reproductive Medicine.)

Key Words: Quinacrine sterilization, sterilization failures, sterilization complications, nonsurgical sterilization

The quinacrine method of nonsurgical female sterilization involves transcervical insertion of quinacrine pellets in the proliferative phase of the menstrual cycle, using a modified copper T IUD inserter (1). Quinacrine causes inflammation of the endometrium and epithelial lining of the proximal tube, which is dose related (2). At a dose of 252 mg (seven pellets of 36 mg each) the endometrium recovers but an occluding scar is produced at the intramural tube, which takes up to 3 months to form in some women (2). This has led to a recommendation of continuing contraception for an additional 3 months. Efficacy can also be improved by administration of a second insertion a month later and by careful placement of the pellets at the fundus (3). There is some evidence that the

intrauterine addition of 75 mg of diclofenac can both improve efficacy and reduce side effects (4).

The safety of quinacrine use has recently been reviewed (5). There is extensive experience in using oral quinacrine as an antimalarial at much higher doses than needed for sterilization. Toxicology studies for intrauterine use were completed at Johns Hopkins University in the early 1980s, leading to approval by the United States Food and Drug Administration of a prehisterectomy trial (6). Long-term follow-up of quinacrine sterilization acceptors in Chile found no increased risk of cancer (7). These studies lead us to conclude that if there is an increased risk of carcinogenicity or teratogenicity with quinacrine sterilization, this risk

must be low. Such risks must be compared to potential benefits of this method for Indonesian women.

MATERIALS AND METHODS

The objective of this trial was to confirm the safety and effectiveness as reported by other investigators (1, 3, 4) of single and repeated transcervical insertion of quinacrine pellets and to determine acceptability of this method by women in several areas of Indonesia.

The study design was dictated by practical limitations and our special interests. Several previous trials indicated a pregnancy failure rate of approximately 3 per 100 women at 1 year for two or three insertion studies (1, 3, 8). Single insertion trials indicated a doubling of this failure rate (3), but there was wide variation among studies in different centers. A new insertion technique suggested lowering of failure rates (3) possibly to approximately 2 per 100 women at 1 year for a two-insertion protocol and 4 per 100 women for a one-insertion protocol. If this difference were to be acceptable for practical reasons of simplicity and lower costs-financial and medical-we would need a sample size in each center of 1,286 subjects for a single-sided test with alpha of 0.05 and power of 90%.

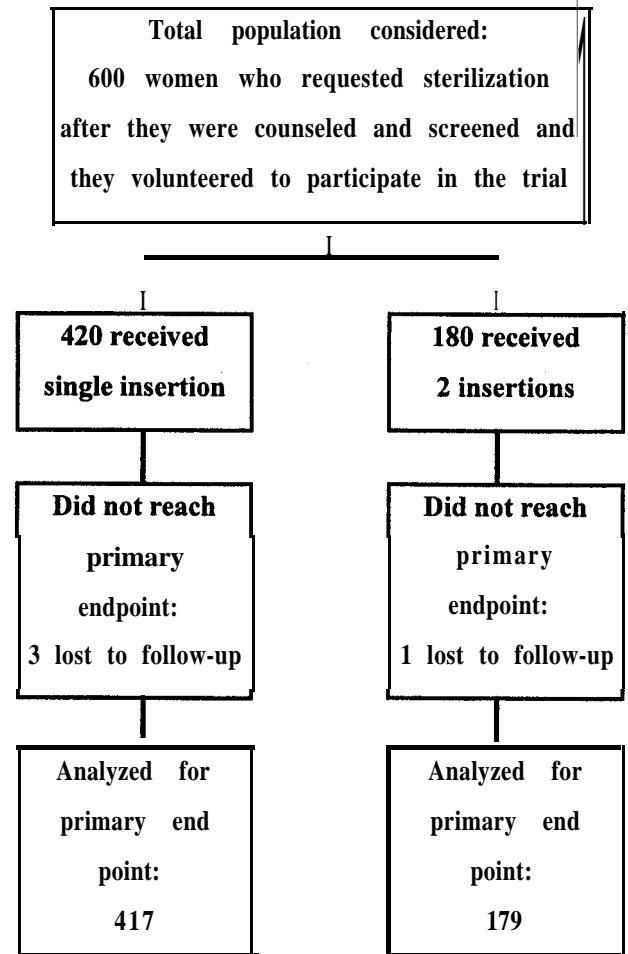
Because of financial and administrative constraints, this was not possible. We were particularly interested in possible center variation in efficacy and, as less was known about single insertion efficacy, we chose a study design using six centers with 100 subjects each divided into a group of 70 for single insertion and 30 to receive two insertions. An expanded trial of 600 women was planned based on results of this initial trial. The trial profile is shown in Figure 1.

A single clinic with clinical trial experience was chosen from Bandung, Denpasar, Jakarta, Semarang, Surabaya, and Yogyakarta. The senior author, who had previous experience with the method (9), served as principle investigator, with responsibility for training of the six clinical investigators. The protocol chosen, which was approved by the Ethics Committee of the National Family Planning Coordinating Board, compared single and two insertions in the proliferative phase of the menstrual cycle of 252 mg of quinacrine (seven pellets of 36 mg each) with a dissolution time of 30 minutes (Sipharm, Sisseln, Switzerland) and 75 mg of diclofenac (three pellets of 25 mg each) with a dissolution time of 10 minutes. Each clinic recruited 100 volunteer subjects, 70 to receive a single insertion and 30 a repeat insertion in 1 month by random allocation.

Presterilized inserters and pellets were prepared by Kimia Farma, Bandung, Indonesia. Random assignments were kept in opaque envelopes by patient order number. Insertions were made using an aseptic technique that is also used for intrauterine device (IUD) insertions. Following the recommendation of Hieu et al. (3), the loaded inserter was advanced to the fundus and then withdrawn 0.5 cm. Holding

FIGURE 1

Trial profile.



Agoestina. Quinacrine female sterilization trial. Fertil Steril 2002.

the inserter sheath fixed, the inserter plunger was slowly advanced to deposit all pellets at the fundus.

Subjects were generally healthy, sexually active, menstruating women, 25-40 years of age with two or more living children, the youngest being at least 2 years old, who requested sterilization and agreed to volunteer for the study that would include follow-up visits at 3, 6, and 12 months. Their medical history and physical examination revealed no uterine abnormalities, abnormal uterine bleeding, pelvic inflammatory disease, severe cervicitis, or pregnancy. Their hemoglobin was ≥ 10 g/dL and they were at least 6 weeks postpartum. We carefully explained to them the advantages and disadvantages of this method, and the fact that it was under investigation and irreversible.

Nurse midwives, who were familiar with patient histories, provided initial counseling and screening. Health criteria for

TABLE 1

Age, education, number of living children, obstetric, menstrual, and sexual history of 600 women receiving single and repeat insertions of 252 mg of quinacrine and 75 mg of diclofenac.

Characteristics/events	Single insertion (n = 420)	Two insertions (n = 180)
Mean age (y)	34.2	33.3
Mean education (y)	6.5	6.1
Living children	3.1	3.1
Age of youngest child (y)	3.9	3.6
Mean sexual intercourse (last 4 wk)	4.4	4.3
Menstrual cycle (d)	28.9	28.7
Menstruation (d)	4.9	5.0
Last pregnancy (%)		
Live birth	99.0	97.2
Perinatal death	0.7	2.2
Spontaneous abortion	0.2	0.6

Agoestina. Quinacrine female sterilization trial. *Fertil Steril* 2002.

admission to the trial were the same as for surgical sterilization, to which was added absence of uterine cavity distortion. A consent form was signed by each subject, who agreed to return for follow-up visits at 3, 6, and 12 months after quinacrine insertions and to use a provided oral contraceptive for three cycles after the last insertion. These women were encouraged to visit the clinic for any serious complaint. A standard clinical record recommended by the International Federation for Family Health was completed at each visit. The 600 subjects were admitted between March 1993 and September 1995.

Data entry and data analysis were conducted in the Center for Biomedical and Human Reproduction Research and Development of the National Family Planning Coordinating Board-Indonesia, by means of computer package programs SPSS/DE and SPSS PC-plus (SPSS Inc., Chicago, IL). t Test was used to find mean difference, and the proportion test was done with χ^2 . Life table analysis was carried out to study failure and continuation rates.

RESULTS

Subjects randomized to receive one or two insertions were similar in age, education, and number of living children, as well as having similar obstetric, menstrual, and sexual histories (Table 1). Previous contraceptive use was none, 22.3%; IUD, 29.5%; oral contraception, 29.5%; injectables, 22.8%; Norplant, 5.5%; condom, 2.7%; coitus interruptus, 1.6%; and diaphragm, 0.2%. These percentages were similar for single and two-insertion subjects.

Follow-up was complete except for two women lost to monitoring for the 12-month visit in Semarang and two in Denpasar, one of whom moved to Sumatra before the 12-month visit.

TABLE 2

Cumulative life-table pregnancy failure rates per 100 women after transcervical insertion of quinacrine (252 mg) with diclofenac (70 mg).

Period (mo)	One insertion			Two insertions			P
	At risk (No.)	Failure rates	SE	At risk (No.)	Failure rates	SE	
3	418	0.48	0.34	177	0.00	0.00	<.05
6	408	1.62	0.88	177	0.00	0.00	<.01
12	367	4.69	1.26	176	1.12	0.79	<.01

SE = standard error.

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There were no significant differences between the single or two-insertion groups from baseline to 12-month visit for reported frequency of sexual intercourse (mean range 4.3-4.8 per 4 weeks), length of menstrual cycle (mean range 28.7-29.2 days), or menstrual period (mean range 4.9-4.4 days). Reported mild dysmenorrhea decreased from 14% before admission to 4.9%, 2.4%, and 1.9% at 3-, 6-, and 12-month follow-up visits, respectively. No serious complications were reported. Side effects reported up to 3 months included fever, lower abdominal pain, and leucorrhea occurring in less than 2% in each case and similar for single and two-insertion cases and virtually zero at 6- and 12-month visits. The method was well accepted when offered to clinic clients requesting sterilization.

The cumulative life-table pregnancy rates for the single and two-insertion groups are shown in Table 2 and the distribution of pregnancy failures by center in Table 3. In Table 2, the number of women at risk in the life-table analysis at 12 months reflects the number of women who were in the model at 365 days or later. A few women made their 12-month visit before 365 days from the insertion procedure day, and thus are not included in the number of

TABLE 3

Pregnancy failure by clinic center at 12-month visit for 70 single insertion and 30 two insertion procedures per center.

Center	Single insertion		Two insertions	
	No.	(%)	No.	(%)
Jakarta	1	(1.4)	—	—
Bandung	2	(2.8)	—	—
Semarang	4	(5.7)	—	—
Yogyakarta	5	(7.1)	—	—
Surabaya	8	(11.4)	—	—
Denpasar	11	(15.7)	2	(6.7)
Total	31	(7.4)	2	(1.1)

Agoestina. Quinacrine female sterilization trial. *Fertil Steril* 2002.

women at risk at 12 months. Of the 33 pregnancy failures, 15 were terminated by menstrual regulation, one ended in a spontaneous abortion, and the rest were carried to term resulting in healthy infants, except for a single case of esophageal atresia where the infant died. The mean age of the 33 patients with pregnancy failure was 32.5 years, which is only marginally lower than that for all of the patients (Table 1). For this major malformation the estimated date of conception was 6 months after the last quinacrine insertion when no quinacrine should be present in any tissue (10). Strictly speaking, the 12-month rates are actually 9-month rates as all subjects were advised to use an additional contraceptive for 3 months from last insertion.

DISCUSSION

Indonesia's family planning program began in 1970 with 40,000 contraceptive acceptors and has reached 18 million today for a prevalence of more than 50% of married couples. Despite this success, there are shortcomings in the health status of Indonesia and its family planning program, in particular. Maternal mortality was reported in 1994 as 326 per 100,000 live births (11) and female surgical sterilization remains at a low 2.9% (11). On the other hand, a well-trained staff of paramedics can perform IUD insertions in both urban and rural areas.

The potential for quinacrine sterilization to increase contraceptive prevalence and contribute to other efforts to lower maternal mortality led the National Family Planning Coordinating Board to conduct a clinical trial of this method. Quinacrine sterilization appears to be a reasonable option for well-informed women at increased risk of a surgical complication, estimated at 1.7% of women in the United States undergoing laparoscopic sterilization (12), and for those without access to surgical sterilization. The financial implications for a developing country like Indonesia also need to be considered.

The addition of diclofenac transcervically was based on an early report (4) showing possible increased efficacy, but a recent report (13) on the addition of 55.5 mg of ibuprofen showed no effect on efficacy. The addition of diclofenac or ibuprofen is not part of the present recommended protocol for quinacrine sterilization (14).

This is the first reported randomized trial of single vs. two insertions of quinacrine pellets for sterilization. It confirms previous studies showing a higher failure rate for single insertion. A marked center effect was experienced with a high proportion of pregnancy failures in a single center. Although all investigators received practical training in the standard insertion technique, it is possible that a variation in the placement of pellets occurred at this center. The absence of failures for two insertions in the other five centers is encouraging but needs a larger series for confirmation.

In conclusion, this method appears to be safe and effective

based on this limited trial when two insertions are given. Our data appear to confirm that of the large Vietnam field trial (3). The higher failures in Denpasar may relate to insertion of pellets below the fundus. Our lower failure rate for two insertions compared to the Vietnam trial may be due to more consistent insertion of pellets at the fundus, as also suggested by Bairagi and co-workers (15). The recent report by Mullick and his colleagues (16) of high efficacy with a single insertion when 150 mg of medroxyprogesterone is given i.m. needs early confirmation.

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