

Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization

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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

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(5) and 3.7% at 4 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 intra-uterine 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-Dakroul 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] pre-existing 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 hysterosalpingographic 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.

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 \leq 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) t
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 pre hysterectomy 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 co-workers (Merchant RN, Prabhu SR, Kessel E, unpublished observations) noted in a pre hysterectomy 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 \leq 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.

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