

## Four-year follow-up of insertion of quinacrine hydrochloride pellets as a means of nonsurgical female sterilization\*

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*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 third administrations. 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.*  
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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<sup>1</sup> 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.

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,<sup>2</sup> 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.,<sup>2</sup> 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

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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 diffi-

culties 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 <sup>a</sup>
		%
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

<sup>a</sup>Follow-up rate is defined as the percentage of women not pregnant who returned for a follow-up visit.

**Table 2. Complications and Complaints<sup>a</sup> 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
Leukorrhoea	4	5.0

<sup>a</sup>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 leukorrhoea, 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.<sup>3</sup> 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.<sup>2</sup>

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.<sup>2, 4, 5</sup>

Chandra and Malaviya<sup>6</sup> 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.<sup>7</sup> 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."<sup>7</sup>

**Table 3. Menstrual Pattern Data Before and After Sterilization**

	Before procedure (N=89)	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 adhere 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.

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