

## Clinical Report: Quinacrine-Fused Pellets

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In an effort to meet a demand for female sterilization services that far exceeds the current medical care system worldwide, attention has been given to the development of a safe, effective nonsurgical method that can be performed by paramedical personnel.

Zipper and associates have worked in this area for many years and have identified quinacrine hydrochloride as a chemical likely to produce tubal occlusion when placed in the uterus.<sup>2,3,4,5</sup> Zipper's work led to the development of quinacrine hydrochloride pellets, intended to effect a delivery system that would bring the chemical into prolonged contact with the tubal ostia through uterine retention. Results of an early study were encouraging; at 1 year after three insertions of 250 mg quinacrine pellets, the gross life-table pregnancy rate was 3.1 per 100 women.

The efficacy of transcervical insertions of quinacrine pellets to produce tubal occlusion has been further evaluated in a three-center trial. This chapter reports the results from one of the centers.

### MATERIALS AND METHODS

Each quinacrine hydrochloride pellet is cylindrical and has a diameter of less than 4 mm. The pellets are compacted to contain 10 mg quinacrine per millimeter of length. Insertion is accomplished by placing the pellets in a plastic tube with a push rod positioned behind them. The insertion procedure is essentially the same as that for inserting an IUD.

From March through December, 1979, 151 women entered the study, giving informed consent at an outpatient clinic at the Universidad Austral de Chile School of Medicine, Valdivia, Chile. Seven pellets containing a total of 250 mg quinacrine hydrochloride were to be inserted at admission and again at 1 month and 2 months after admission. Insertions were performed during the proliferative phase of the menstrual cycle in women who had not recently

Partial support for this work was provided by the International Fertility Research Program, with funds from the U.S. Agency for International Development.

been pregnant (>42 days since last pregnancy terminated). No additional contraceptives were used. Clinical follow-up was scheduled at 6, 12, and 24 months after the third insertion and at any time when complications or complaints occurred. In this study, tubal patency was evaluated by hysterosalpingography performed at least 3 months after the third insertion.

Only those women who requested sterilization for family planning reasons and who did not have a history of medical or psychiatric disorders were selected as subjects. If the patient appeared to be unduly nervous or had any pathologic pelvic condition (except cervicitis), she was excluded from the study and was either scheduled for a surgical sterilization procedure or provided with another method of contraception.

### RESULTS

The women entering the study had a mean age of 31.8 years and a mean of 3.3 live births. At admission, 35.1% reported an irregular menstrual cycle. Only two women (1.3%) did not complete the scheduled three insertions of quinacrine pellets. For one woman, chronic pelvic inflammatory disease, which had been missed at admission, was diagnosed before the second insertion; a bilateral salpingectomy was performed. The second woman contracted a viral infectious hepatitis after the first insertion; the hepatitis had a prolonged course, but 6 months later the woman had fully recuperated. Although she is not presently using additional contraception and never received the third quinacrine insertion, she has not become pregnant.

The procedure was deemed safe (Table 10-1); only minor complications and complaints were reported at insertion or between insertions. In most cases, the complications or complaints were of a temporary nature, disappearing within a few hours or a few days after the procedure. Menstrual disturbances associated with the quinacrine procedure were also transient (Table 10-2). Of those women with regular cycles at the time of the first insertions, 35.7% missed one or two cycles in the 3 months it took to complete the procedures; all had returned to menses by the 6-month follow-up visit. Of those with irregular cycles, 37.7% missed one or more cycles, and only one reported amenorrhea at the 6-month follow-up; she was pregnant.

Four-fifths of the women have returned for 24-month follow-up. Table 10-3 shows the quinacrine pellet method to be very effective. The gross life-table pregnancy rate is 4.1 per 100 women at 24 months. Five pregnancies have been reported; they occurred at 4, 15, 18, 19, and 24 months after the third insertion. Three were terminated by an induced abortion procedure, one ended in a spontaneous abortion, and one was carried to term. The term pregnancy occurred 18 months after the third insertion; the infant was born without any problem.

Hysterosalpingographic results for women who completed three insertions of quinacrine pellets are given in Table 10-4. The hysterosalpingograms showed no patency for three women who later became pregnant.

Other than the pregnancies, follow-up problems were reported by eight women (5.4%) in the 24 months since the third insertion. Most problems were minor and transitory, including two cases of menorrhagia, two of head-

TABLE 1 O-1. Complications/Complaints Associated With Insertion of Quinacrine Pellets

	PELLET INSERTIONS					
	1 (N = 151)		2 (N = 150)		3 (N = 149)	
	NO.	%	NO.	%	NO.	%
Complications						
Psycho/emotional reaction	1	0.7	0	0.0	0	0.0
Vomiting	1	0.7	0	0.0	0	0.0
Infectious hepatitis†	1	0.7	0	0.0	0	0.0
Pelvic inflammatory disease*†	0	0.0	1	0.7	0	0.0
Trichomonas†	1	0.7	2	1.3	0	0.0
Vaginal discharge	1	0.7	1	0.7	0	0.0
Fever	0	0.0	1	0.7	0	0.0
Vaginal bleeding	1	0.7	2	1.3	0	0.0
Vaginal spotting	0	0.0	2	1.3	0	0.0
Total women with one complication or more	6	4.0	9	6.0	0	0.0
Complaints						
Pelvic/abdominal pain						
At insertion	21	13.9	12	8.0	18	12.0
Postinsertion	25	16.6	19	12.7	1	0.7
Headache	2	1.3	1	0.7	0	0.0
Muscle pain	1	0.7	0	0.0	0	0.0
Total women with one complaint or more	43	28.5	32	21.3	19	12.8

\*Resulted in discontinuation of procedure.

†Unrelated to quinacrine.

aches, and one each of reduced menstrual flow, irregular cycles, episodic pelvic pain, and an ovarian cyst.

CONCLUSIONS

The results of this study suggest that the intrauterine insertion of quinacrine pellets can be an effective, safe, nonsurgical sterilization procedure. In general, complications and complaints associated with the insertion were minor and of a transitory nature. Only 4.1% of the women had become pregnant by 2 years after the third insertion.

Three women who showed no tubal patency by hysterosalpingogram later became pregnant. The possibility of recanalization seems more likely than that the hysterosalpingogram failed to determine tubal occlusion.

Although no deaths have been reported in studies conducted in conjunction with the International Fertility Research Program, two have been reported following the intrauterine instillation of quinacrine solution by other investigators.\*† The cause of these deaths is unknown but may be related to

\*Atabrine hydrochloride. Product information, Winthrop Laboratories, November 1975.

†Chowdhury A: Personal communication, August 1976.

TABLE 10-2. Amenorrhea Associated With Insertion of Quinacrine Pellets by Menstrual Regularity at Admission

	IRREGULAR CYCLE LENGTH REPORTED AT ADMISSION (N = 53)		REGULAR CYCLE LENGTH REPORTED AT ADMISSION (N = 98)	
	NO.	%	NO.	%
At insertion II	17	32.1	22	22.4
At insertion III	14	26.4	24	24.5
At d-month follow-up	1*	1.9	0	0.0
Total women reporting amenorrhea at one or more visits	20	37.7	35	35.7

\*Pregnant at time of follow-up.

the rapid absorption of quinacrine. It has been reported that high systemic blood levels of quinacrine from rapid absorption may result in arrhythmias, heart block, impaired cardiac output, hypotension, peripheral vasodilation, and depression of the vasomotor and respiratory centers of the central nervous system.\* The pellet method probably decreases the absorption rate, thus reducing the blood level of quinacrine. The decreased absorption rate was part of the reason the pellet method was developed.

A problem with all known blind procedures is that more than one application may be necessary. The quinacrine pellet method used in this study

TABLE 1 O-3. Gross Life-Table Pregnancy Rates for Women Who Completed Three Insertions of Quinacrine Hydrochloride Pellets

	PREGNANCY RATE	FOLLOW-UP RATE
6 months	0.7 ± 0.7	98.0
12 months	0.7 ± 0.7	97.3
24 months	3.8 ± 1.7	82.8

TABLE 10-4. Hysterosalpingographic Results for Women Who Completed Three Insertions of Quinacrine Hydrochloride Pellets

RESULTS	NO. PATIENTS	%
Neither tube patent	121†	81.2
One tube patent	1	0.7
Both tubes patent	0	0.0
HSG not performed	27†	18.1
Total	149	100.0

\*Three women became pregnant.

†Two women became pregnant.

\*Atabrine hydrochloride. Product information, Winthrop Laboratories, November 1975.

requires three insertions. Surgical sterilization procedures, in addition to the demands on medical personnel and clinic resources, require multiple visits from the women. At least two visits are recommended: the visit for surgery and the follow-up visit 7 to 21 days later. Surgical procedures also require anesthesia.

Alternative delivery systems that may reduce the number of quinacrine administrations are being explored, including the use of an IUD vector for better delivery of the quinacrine to the tubal ostia and the development of a sustained-release system that will provide extended exposure of quinacrine to the epithelium.

#### REFERENCES

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