

## The Clinical Efficacy of the Repeated Transcervical Instillation of Quinacrine for Female Sterilization

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### ABSTRACT

Zipper, J., Medel, M., Goldsmith, A., Edelman, D., Pastene, L. and Rivera, M. (Dept. of Physiology & Biophysics, School of Medicine, University of Chile, Santiago, and Dept. of Obstetrics & Gynecology, Hospital Sotero del Rio, Puente Alto, Chile, and International Fertility Research Program, Research Triangle Park, North Carolina 27709, USA). *The clinical efficacy of the repeated transcervical instillation of quinacrine for female sterilization.*

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The safety and efficacy of the repeated transcervical instillation of quinacrine hydrochloride in a suspension of 5 ml of 2% Xylocaine was evaluated in 200 patients. All instillation procedures were performed during the proliferative phase of the menstrual cycle: the second instillation was made in the first menstrual cycle following the initial instillation and the third and last instillation at 6 months after the first. None of the patients used any adjunctive contraceptives. Follow-up visits were scheduled at 6-month intervals after the last instillation. The potentially serious complications following the instillation were four cases of cortical excitation, and one case of acute adnexitis. The second instillation was not performed for 16.0% and the third instillation was not performed for 16.7% of the patients, for medical and/or personal reasons. Fifty-one pregnancies were reported, 41 (80.4%) before completion of the three instillations. The results of this study show that the instillation schedule used is unsatisfactory for widespread use. Additional studies are currently being conducted to evaluate the use of an adjunctive contraceptive up to the time of the third instillation in order to reduce the high pregnancy rate.

### I. INTRODUCTION

Although female sterilization is the most effective method of contraception for women who

desire no additional children, the procedure requires the use of elaborate surgical facilities and instruments, and highly trained medical personnel. Therefore the development of simplified, non-surgical sterilization procedures that can be performed by paramedical personnel remains a high priority for countries with limited surgical facilities and trained personnel.

The only non-surgical sterilization procedure that appears clinically useful is the transcervical instillation of quinacrine hydrochloride (6). Other non-surgical procedures such as the infusion of various scarifying and necrosing agents, tissue glues, and tubal plugs have been abandoned because they are ineffective or are not sufficiently developed to determine their safety and effectiveness (8).

Animal studies (9) indicated that quinacrine selectively produced significant morphological changes in the reproductive tract and caused permanent tubal fibrosis and tubal occlusion in the rat. Zipper and associates (10) have since performed clinical trials with quinacrine in which various doses, concentrations, solvents for the suspension, and instillation schedules of quinacrine were evaluated. These trials demonstrated that the instillation of quinacrine can produce relatively low pregnancy rates for patients who have two or three instillations. In a smaller series Davidson (4) reported similar results for women who were administered one instillation of quinacrine and who used oral contraceptives as an adjunctive method. Israngkun (5) reported that one instillation of quinacrine produced bilateral tubal occlusion in only about half the patients and Davis (2) demonstrated

Table I. Age and parity distributions

	No.	%
<i>Age (years)</i>		
20-29	77	38.5
30-39	107	53.5
40 and over	16	8.0
Median		31.3
<i>Parity</i>		
0-3	83	42.1
4-5	78	39.6
6 and over	36	18.3
Median		3.8

that rates of tubal occlusion increased with successive instillations.

To evaluate the safety and efficacy of one quinacrine dose schedule, 200 consecutive patients were studied.

## II. METHODS AND MATERIALS

From August 1974 to December 1975, 300 women underwent elective sterilization by the transcervical administration of quinacrine hydrochloride according to the same protocol: all subjects were scheduled for three instillations which were performed during the proliferative phase of the menstrual cycle. The second instillation was performed during the first menstrual cycle after the first instillation and the third instillation was performed during the sixth menstrual cycle after the first instillation. At 6 and 12 months after the third quinacrine instillation, patients were scheduled for a follow-up history and physical examination.

### *Procedure*

Immediately before the start of the procedure, 1.5 g quinacrine powder (Winthrop Laboratories, New York) was suspended in 5 ml 2% Xylocaine and agitated for one minute. Before the quinacrine instillation, none of the patients were premedicated with tranquilizers, analgesics, or narcotics. After a bimanual examination, a vaginal speculum was inserted, the anterior lip of the cervix grasped with a tenaculum, and the uterine cavity sounded for direction and length. The quinacrine suspension was drawn into a syringe attached to a 4 mm diameter Randall endometrial biopsy cannula. The cannula was inserted transcervically to the uterine fundus, the suspension was slowly injected in about 30 to 45 seconds, and the cannula was removed about one minute later to avoid reflux of the suspension into the vagina. The patient was observed for about 2 hours before she was discharged from the clinic. No special instructions were given to the patient, except to wash her external genitalia with tap

water. Contraceptives were not prescribed for the patients.

All scheduled instillations of quinacrine have been performed, and to date 114 (81.4%) of the patients who have completed three instillations have been followed up.

### *Subjects*

Only those women who requested sterilization for family planning reasons and who did not have a history of psychiatric disorders or epilepsy were selected as subjects. All were fully informed about the experimental nature of the sterilization procedure and the need to return for several clinic visits to complete the procedure. If the patient appeared to be unduly nervous or had any pelvic pathology (except cervicitis) or cervical synechia, or had a total external os to fundus measurement of over 8.4 cm, she was excluded from the study. These patients were either scheduled for a surgical sterilization procedure or another method of contraception was prescribed.

Most subjects were 30 to 39 years of age (53 median age=31.3 years) and were of parity from 0 to 6 (57.9%; median parity=3.8). All subjects had at least one living child, and 33.5% were grandmultiparous (Table I). The mean number of pregnancies for the subjects was 5.9.

## III. RESULTS

### *Instillation complications*

Complications at the time of quinacrine instillation were infrequent and occurred for only 2% of the patients (4 had cortical excitation) during the first instillation. No complications occurred during the second or third instillations. Cortical excitation was characterized by nervousness, vertigo, irritability, emotional change, and transient psychosis. If not treated, the patient could convulse. After treatment with central ner-

Table II. Reasons for not performing the second quinacrine instillation

Reason	No.	%
Cortical excitation at first instillation	4	2
Ovarian cyst and subsequent salpingectomy	1	0
Pregnancy	18	9
Amenorrhoea	3	1
Acute adnexitis	1	0
Severe headaches	1	0
Patient failed to return for second instillation	4	2
Total	32	16

Table III. Reasons for not performing the third quinacrine instillation among 168 patients completing two quinacrine instillations

Reason	No.	%
Pregnancy	23	13.7
Amenorrhea	1	0.6
Metrorrhagia	1	0.6
Patient refused third instillation	2	1.2
Patient failed to return for third instillation	1	0.6
Total	28	16.7

system depressants, e.g. diazepam, the symptoms usually disappeared within 4 hours. None of the 4 patients with cortical excitation convulsed. In previous studies, there were no neurological abnormalities 24 hours after quinacrine-induced cortical excitation (11). Probably the syndrome is due to the rapid intravascular absorption of quinacrine when it is instilled into a highly vascular area (1).

*Incomplete procedures*

Thirty-two (16.0%) patients did not have a second instillation performed (Table II). For all but 4 (2.0%) of these patients who did not return for follow-up, the second instillation was not performed for medical reasons. One patient developed an ovarian cyst before the time of the second instillation and tubal ligation was performed at the time of the cystectomy. One patient developed acute adnexitis 7 days after the first instillation and she was hospitalized for 3 days for medical treatment. A second instillation was not performed in another patient because she complained of severe headaches at about one month after the first instillation.

Of the 168 patients for whom a second instillation was performed, 28 (16.7%) did not undergo a third instillation (Table III). For all but 3 (1.8%) of these patients the third instillation was not performed for medical reasons; one patient did not return for a third instillation, one patient refused a third instillation but did not give specific reasons for her refusal, and one patient who complained of slight headaches and dizziness one month after the second instillation also refused to have a third instillation. The 4 patients listed in Tables II and III as amenorrheic were not pregnant. Patients who did not have a second or third instillation were offered alternative

*Long-term complications*

Among the 114 patients who were followed up after the third instillation, the only reported complications were pregnancy and small changes in menstrual cycle function.

*Pregnancy*

To date, 25.5% of the patients have become pregnant (Table IV). Most of these pregnancies (80.4%) have occurred before completion of the three instillations of quinacrine. Among the 114 patients who were followed up after completion of the third instillation, the pregnancy rate was 7.1%. None of the pregnancies was ectopic.

IV. COMMENT

Based on the results of this study, it does not appear that the intrauterine instillation of quinacrine is sufficiently effective for widespread use as a non-surgical sterilization procedure.

The results from preliminary studies in which different dosages of quinacrine solutions for the suspension of quinacrine, and instillation schedules were evaluated (11) indicated that the three instillation procedure used in this study resulted in lower rates of complications and tubal patency. In the present study, the endpoint was pregnancy rather than tubal patency as demonstrated by hysterosalpingograms. For this reason the results of this study are not comparable to the results of other studies.

For 53 (26.5%) of the patients, a second or third quinacrine instillations were not performed for medical reasons. Pregnancy was the reason for 41 (77.4%) of these patients. Whether medical reasons, other than pregnancy, such as amenorrhea and headaches, are contraindica-

Table IV. Pregnancy rates

Time pregnancy occurred	No.	%
Before second instillation	18	9.0
After second instillation and before third instillation	23	13.7
After third instillation		
6-12 months	7	6.1 <sup>a</sup>
13-24 months	3	4.3 <sup>a</sup>
Total	10	7.1
Grand total	51	25.5

<sup>a</sup> Based on the number of women followed up and not on the number of women completing the third instilla-

tions for quinacrine instillation is not known. In order not to jeopardize the patient, however, no patient who developed a medical problem was given a subsequent instillation. Although no deaths have occurred in more than 1000 quinacrine sterilization procedures performed at our institution, two deaths have been reported following the intra-uterine instillation of quinacrine (1, 3). The cause of these deaths is not known, but may be related to the rapid absorption of quinacrine. It has been reported that the rapid absorption may result in arrhythmias, heart block, impaired cardiac output, hypotension, peripheral vasodilation, and depression of the vasomotor and respiratory centers of the brain (1). Since fatalities and complications have also occurred with surgical sterilization procedures (7), it has not been determined whether the intrauterine instillation of quinacrine compared to surgical sterilization procedures places the patient at an increased risk of complications.

The quinacrine instillation schedule used in this study is unsatisfactory since it results in an unacceptably high pregnancy rate. To improve the effectiveness, different instillation schedules are being evaluated. In one study the third instillation will be performed one month after the second instillation, the quinacrine will be delivered in a suspension of sterile water rather than Xylocaine, and patients will use another method of contraception until completion of the third instillation. It is anticipated that this instillation schedule will significantly reduce the proportion of patients who eventually become pregnant, by reducing the number of patients who become pregnant between the first and third instillations. In this study 80.4% of the pregnancies occurred before the third quinacrine instillation.

Further studies will be required to evaluate potentially safer and more effective methods of instilling quinacrine for sterilization. With improved methods of delivering quinacrine that prevent rapid absorption, and with more effective instillation schedules and the use of adjunctive contraceptives, a non-surgical sterilization procedure may be developed that would be available for widespread use.

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