



Female sterilization with quinacrine using hysterosalpingography (HSG) as an endpoint after a single-insertion protocol in Caracas, Venezuela

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Abstract

Objective: To evaluate the intrauterine insertion of quinacrine as an alternative nonsurgical female sterilization method by confirming bilateral occlusion of the fallopian tubes using HSG in a group of women who desire permanent sterilization. **Methods:** After doing hysterosalpingography to confirm patency of both fallopian tubes, 324 mg of quinacrine were introduced with a modified IUD inserter in 30 patients who came to Concepción Palacios Maternity Hospital seeking permanent sterilization, between June 2000 and September 2001. Follow-up with HSG was done 3 months later to verify occlusion of the fallopian tubes. **Results:** 26 of 30 patients (86%) had bilateral tubal occlusion as determined by HSG. There were minor side effects such as: pain (66.7%), yellow discharge (100%) and menstrual abnormalities (13.3%). One woman became pregnant after HSG showed bilateral occlusion. HSG may interfere with the action of the quinacrine. **Conclusion:** QS is a simple and safe alternative to surgical sterilization with few side effects.

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1. Introduction

The world population in the year 2000 was 6,000 million inhabitants. The increase in population mainly affects less developed countries, where the average annual growth is 2%, equivalent to a doubling of the population in 35 years. In contrast, the population of industrialized nations will double in 115 years, representing an annual growth rate of 0.6% [1]. Obviously, there is a worldwide need to find better birth control methods.

Female surgical sterilization is currently the most prevalent permanent contraceptive method worldwide, and is in ever growing demand in developing coun-

tries [1]. In the United States, surgical sterilization has become the contraceptive method of choice for married couples, with an increase of 16% to 36% between 1973 and 1988 [1,2]. Yet several studies have reported failure rates of 3 to 4 per 1,000 surgical procedures within the first 2 years of surgery [2,3]. Surgical sterilization also involves large expenses for infrastructure and implementation, creating a heavy burden on the community, especially in countries with limited resources. In view of the burgeoning need for birth control in less developed regions, new methods for nonsurgical sterilization, applicable to large populations, are being investigated. In addition, a nonsurgical method could help to eliminate the concerns of women who fear surgery, or who cannot get transportation or child care during surgery and recovery, especially in rural settings [1].

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Among the new nonsurgical sterilization methods, several drugs, such as quinacrine, elemental iodine and other substances that cause sclerosis of the fallopian tubes have become available [2,4]. Quinacrine, a 9-aminoacridine[6-chloro-9(L-methyl-4-diethylamino)butyl-2-methoxy-acridine], is an anti-malarial drug which, until the introduction of chloroquine in 1945, was the main synthetic agent for anti-malarial prophylaxis, since it can effectively suppress the four types of human malaria. Although it is no longer used for this indication, it is prescribed as a therapeutic alternative for giardiasis and recurrent malignant pleural effusions [5,6]. Quinacrine's few side effects occur with the systemic administration of high doses for prolonged periods. Adverse events, such as dizziness, headaches, vomiting and diarrhea are infrequent. Stimulation of the central nervous system manifested as restlessness, confusion, anxiety, euphoria or changes in behavior, and its deposit in skin, characterized by yellow pigmentation, are even less frequent. Another effect attributed to quinacrine is its mutagenic potential [5,7], but it is recognized that administration by mouth is not carcinogenic [5,7,8]. Sokal et al. [9] in a follow-up involving 13,444 person-years concluded that the rate of cancer among women exposed to intrauterine quinacrine was not significantly different from the expected rates in the general population. Its use is contraindicated in people with psoriasis, exfoliative dermatitis and glucose-6-phosphate dehydrogenase deficiency (G6PD) [6].

In the quinacrine sterilization (QS) method, pellets are placed in the fundus of the uterus through the cervix, with a modified intrauterine device (IUD) inserter [7] during the proliferative phase of the menstrual cycle. Its effect is topical at low doses and for short periods of time. This precipitates a selective inflammatory process in the interstitial portion of the fallopian tubes, with eventual fibrosis and occlusion in a period of approximately 6 weeks [5,7,10]. Merchant and Prabhu [11] state that the tubal occlusion is directly related to the dose of quinacrine applied. The concentration of quinacrine in the uterus after the transcervical insertion is higher than that achieved after the administration by mouth, but only for a few hours [5,7,8]. Two basic insertion regimens have been described: in one of them, 252 mg of quinacrine are applied once a month for 2 or 3 months, and in the other, a single dose of 324 mg is used [8,11]. These

treatment plans may or may not be combined with the transcervical, parenteral or oral administration of non-steroidal drugs, such as ibuprofen or diclofenac, which decrease the local inflammatory response and the side effects [5,12,13].

Very few side effects associated with the transcervical insertion of quinacrine have been reported [12,14,15]. These adverse events (AE) are minor and transient compared with those caused by surgical sterilization; among them are: mild hyperthermia, mild vaginal discharge and menstrual abnormalities. Trujillo and his coworkers [16] report that the complications and side effects are similar to those that occur during the insertion of an IUD. In 1996 Laufe and Sokal [17] reported minor transient side effects such as: colicky abdominal and pelvic pain, headache and dizziness, in the 24 hours after insertion. No deaths have been reported with the use of QS [8,9]. The risk of birth defects from QS has been reported to be the same as one would expect from surgical sterilization [7].

From the decade of the 1970s to the present time, several studies have been completed [10,15,18] to evaluate the efficacy and safety of quinacrine as an alternative method for female sterilization. Currently, efficacy is estimated as 3 pregnancies per 100 women in one year [8]. Many authors agree that the failure rate is caused by an incorrect insertion technique [7,8,10,13].

The transcervical intrauterine insertion of quinacrine tablets has been shown to be a safe, acceptable and effective nonsurgical method of female sterilization [9,10]. The main advantage of the method is its capacity to increase contraceptive prevalence, and QS will thereby avoid maternal morbidity and mortality. This is especially true in rural and urban areas of the Third World [8].

We decided to undertake a study of the efficacy of QS in our hospital in Caracas, Venezuela. We would attempt to confirm the occlusion of the fallopian tubes by HSG three months after the procedure.

2. Materials and methods

A prospective, descriptive and experimental clinical study of QS was carried out in a population of patients who came to the Gynecology, Family Planning and Delivery Room Services of the Concepción Palacios Maternity Hospital in Caracas, Venezuela, and expressed

their desire to have permanent sterilization. The sample was a group of 30 women who fulfilled the following inclusion criteria: older than 25 years, having satisfied their personal reproductive expectations and who, after an explanation of the method to be used, and its risks and benefits, gave their consent in writing for inclusion in the study. We excluded those with a history of allergy to iodine, extensive ablative surgical procedures of the cervix, cervical pathology, tubal surgery, prior unilateral or bilateral occlusion of the fallopian tubes, fibroids and patients with associated medical problems, such as psoriasis and exfoliative dermatitis.

To inform the couples about the risks and benefits of the technique, they were invited to view a video explaining the technique. Then the staff discussed the QS procedure with them and answered all questions raised. To qualify for admission, the women were given a gynecological examination. Their medical history was entered on a clinical record and they were enrolled in the study.

HSG was done between days 7 and 10 of the menstrual cycle before the insertion of quinacrine, to evaluate for tubal patency. During the proliferative phase of the menstrual cycle after doing the HSG, 324 mg of quinacrine was introduced into the fundus of the uterus, through the cervix, with a modified IUD inserter; 400 mg of ibuprofen by mouth every 8 hours was prescribed for pain, for 3 days. It was recommended that patients use contraceptive barrier methods in the first three months after the insertion.

Follow-up was carried out to verify how well the patient tolerated the QS, the patency of the fallopian tubes, and the presence of side effects. Tolerability was evaluated by interviewing each patient 48 hours after the quinacrine insertion. The first interview was scheduled to discover the absence or presence of pain. We did not use a scale for it. We also asked about the use of ibuprofen, finding that some patients did not need to take the medication. The women were interviewed again before the second HSG, 3 months after the insertion. At that time, we asked about events affecting the menstrual cycle, bleeding and yellow spotting. The patency of the fallopian tubes was examined by HSG 3 months after the insertion. The time of follow-up was approximately 8 months after the second HSG. We telephoned all the patients to be sure they were satisfied with the method and had no pregnancies.

The data obtained were collected in a clinical record.

They were presented in tabular form and analyzed by a statistician, using descriptive and inferential statistical methods.

The project was carried out with the collaboration of the medical and paramedical staff of the Gynecology, Family Planning and Delivery Room Services of the Concepción Palacios Maternity Hospital, and with the technical and medical staff of the radiology service of that institution. The medication and the inserters, the video explaining the technique, as well as some financial support were donated by The Center for Research on Population and Security. The cannulae for performing the HSG were provided by the research group. The costs for the implementation of the project were covered by several sources that included supplies from the Concepción Palacios Maternity Hospital, and contributions from the research staff.

3. Results

The average age of the sample of women was 33.8 ± 4.05 years; 19 (63.3%) were between 28 and 35 years of age, as shown in Table 1.

After undergoing the QS procedure, 20 patients (66.7%) were in pain, and 11 of these (55%) needed an oral analgesic; 7 patients (23.3%) experienced bleeding; and the yellow discharge lasted less than 11 days in 23 patients (76.7%). In the following months, 4 patients (13.3%) had menstrual problems, 2 (6.7%) had oligomenorrhea, and 2 (6.7%) had polymenorrhea (Table 2). Twenty-six patients (86.7%) had bilateral tubal occlusion. Three women (10%) had unilateral tubal occlusion, and one (3.3%) bilateral tubal patency (Table 3); these 4 women were prescribed another contraceptive method.

Table 1
Distribution of patients according to age, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Age (years)	Frequency	Percentage
28–31	10	33.3
32–35	9	30
36–39	8	26.7
≥40	3	10
Total	30	100

33.8 ± 4.05 years.

Table 2
Distribution of patients according to complaints and treatment after QS, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Complaint	Frequency	Percentage
Pain		
without	10	33.3
with	20	66.7
Analgesic for pain (<i>N</i> = 20)		
used	9	45.0
not used	11	55.0
Menstrual abnormalities		
none	26	86.7
oligomenorrhea	2	6.7
polymenorrhea	2	6.7
Yellow discharge spotting (days)		
1–10	23	76.7
11–20	4	13.3
21–30	3	10.0
Bleeding		
without	23	76.7
with	7	23.3

Table 3
Distribution of 30 patients according to results of follow-up hysterosalpingography (HSG) after QS, Concepción Palacios Maternity Hospital, Caracas, June 2000 to September 2001

Results of HSG	Frequency	Percentage
Tubal exclusion		
bilateral	26	86.7
unilateral	3	10.0
Tubal patency	1	3.3

4. Discussion

The average age of our patients was 33.8 years, similar to the 35 years reported by Sokal and his colleagues [19]. This is explained by the fact that, at this age, most women have fulfilled their fertility expectations. It has also been demonstrated that the effectiveness of the method is greater in patients older than 35 because they are less fertile [19,20].

The percentage of patients with bilateral tubal occlusion demonstrated by HSG after the transcervical insertion of quinacrine in this series was 86.7%

(26 of 30 women). While there is research [21] that used HSG as a method to evaluate tubal occlusion, those studies are not comparable to the present one, since the doses and insertion protocols were different. El Kady and his coworkers [22] reported bilateral tubal occlusion in 73% of subjects after two doses of 252 mg. Generally, the efficacy of the method is determined by calculating the cumulative rate of pregnancy [7,8,14,19] and by anatomic/pathologic studies of sections of hysterectomy in patients with a history of QS [11]. We performed an HSG because we believed it to be an objective way to evaluate short-term tubal occlusion, since calculating the rate of pregnancy requires follow-up of patients for periods longer than 1 year, time which was not available to us. Failure of the QS was determined in a total of 5 patients: 4 women had either unilateral tubal occlusion or bilateral tubal patency, and a fifth woman became pregnant after HSG indicated bilateral tubal closure.

It is difficult to explain what occurred during and following HSG. There may be false interpretations of occlusion of the tubes due to: tubal spasm during the procedure; insufficient injection of contrast medium; or interruption of the procedure before tubal opacification [22–24]. On the other hand, the pressure of the HSG medium could have opened a tube in the woman who became pregnant following the HSG that had indicated bilateral closure. If this is true, then the HSG could just as easily have opened closed tubes during the performance of the test. The HSG may not be good following QS and needs further evaluation. Two patients, one with bilateral and the other with unilateral tubal occlusion, had a pregnancy after two months. Failure of the method occurred in a total of 5 patients which, according to the literature, is attributable to errors in the insertion technique [10].

After QS, 20 patients (66.6%) had pelvic pain, which differs from the reports by Mumford et al. [25] and Hieu et al. [10], who found pain in between 9% and 25% of patients. The rationale is that the dose generally used is 252 mg per application, different from the 324 mg applied in this study; higher doses may cause more tissue destruction and, consequently, more pain. Of the patients who had pain, 11 (55%) said they had taken an analgesic; data in the literature indicates that the administration of non-steroidal anti-inflammatory drugs does not modify the efficacy of the method [12,13].

The main menstrual abnormalities due to QS reported in the literature are oligomenorrhea or amenorrhea, with a frequency of 1% to 20%. These are caused by inflammation and desquamation of the endometrium as an effect of the medication. These abnormalities last several months while the endometrium regenerates [25]. In this series, 2 patients presented with oligomenorrhea and 2 with polymenorrhea, for a total of 13.32% with menstrual irregularities.

The yellow discharge caused by spillage of quinacrine into the vagina was present in 100% of cases, which contrasts with the 23% noted elsewhere [25]. We attributed this to the higher dose of the medication used, which increases the likelihood of spillage. There were none of the complications found by other investigators, such as pelvic infections, uterine perforation or synechia and hematometra, and there have been no ectopic pregnancies [10,25,26].

We can conclude from the results of this study that female sterilization with quinacrine is a simple and safe method that has few side effects, and that it is an alternative to surgical sterilization. We recommend consideration of the possibility of widespread application of QS so that populations with limited resources have access to the method.

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