



Quinacrine female nonsurgical sterilization (QS): endometrial assessment by vaginal ultrasonography in 128 women

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Abstract

Objective: Investigate effectiveness, safety and endometrial pattern after QS. **Method:** This study began in March 1999 and ended March 18, 2003; 128 women received transcervical insertions of quinacrine. Follow-up visits with ultrasound were scheduled at 1, 3, 6, 12-month intervals. **Results:** Two pregnancies occurred, one at 25 months, the other at 37. Adverse events (AE) were: yellow vaginal discharge, headache, mild abdominal pain, vaginal pruritus, nausea and transient decrease in endometrial thickness. One patient had allergic reaction. A third insertion was done in case of vaginal bleeding (16.4%). One year after QS 10% still had amenorrhea, which may be the result of the fact that 73% of our patients had received DMPH. Once inside the uterus, the dissolved quinacrine could be seen within seconds, via ultrasound as a "Lake of Quinacrine" which stays for up to two hours. Frequently, a transverse vaginal ultrasonographic view of the uterine cavity showed plug-like echogenic points at the cornua. **Conclusion:** Quinacrine sterilization is safe and effective. The echogenic points need to be more thoroughly studied in order to affirm whether ultrasonography may identify the blockage of the tubes. Since early pregnancy is due to imperfect tubal closure, the use of ultrasound may prevent failure. However, pregnancy due to later recanalization cannot be avoided.

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Keywords: quinacrine; nonsurgical female sterilization; endometrial assessment after QS

1. Introduction

It has been estimated that in Brazil in the year 2003 the female population of a reproductive age (15 to 49 years) will reach 49 million. Less than 20% of this total has access to family planning information and procedures [1]. The official statistical maternal mortality in Brazil during 1999 was 55.7 deaths per 100,000 live registered births. In some regions, the actual incidence might amount to as many as 150 deaths per 100,000 live births. About 50% of the deliveries, between 1990 and 1995, were from

unplanned pregnancies [2]. Unplanned and unwanted pregnancies often end in voluntary abortion (illegal in Brazil), and are an important cause of the increased ratio of maternal mortality.

Women with medical conditions like cancer, stroke, hypertension, obesity, diabetes, heart disease, thromboembolic events, varicose veins, smoking addiction etc, needed a definitive and secure contraceptive.

In Brazil, the need for family planning of an elderly multipara is different from that of an older affluent primigravida [3]. Women entering the perimenopausal years have many menstrual irregularities due to anovulatory cycles. This often confuses patients about the fertile phase of the menstrual cycle. Effective and safe family planning methods are needed in this age group as well as in the young. Pregnancy for the elderly

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woman carries health risks which include an increased incidence of genetic defects, miscarriages, medical disorders, fetal growth retardation and a greater need for operative deliveries.

Surgical female sterilization accounts for 27% of contraception in Brazil [2]. It requires sophisticated equipment and trained personnel. Serious complications are associated with general anesthesia, pneumoperitoneum, cautery and trocar caused trauma in laparoscopic sterilization.

Quinacrine nonsurgical sterilization (QS), developed by Zipper and his colleagues, is safe and inexpensive. It can be done quickly and without the risks of the surgery [4]. Experience has shown that it offers a low risk of serious, immediate side effects [5]. QS is a reasonable option, especially for women who have medical contraindications to a surgical procedure, or have had an earlier surgical sterilization failure. Also, there are numerous women who desire no more children but fear surgery, despite their obvious need for sterilization [6].

While there are several reports on the safety and efficacy of QS, there is no report of ultrasound evaluation in QS. It can be helpful in diagnosing congenital anomalies or tumors of the uterus and may help to avoid technical failure. Transvaginal ultrasound (TUS) is a powerful technique that reveals the endometrial pattern and gives considerable diagnostic information, helping to detect possible pathology of all organs in the pelvis. It can show unexpected adnexal masses, hydrosalpinx, tube-ovarian abscesses, tumors, endometriosis and ectopic pregnancies as well as early intrauterine pregnancies. Transvaginal pelvic ultrasonography can be used for screening of asymptomatic patients. It is an adjunct to the pelvic examination and is especially valuable in examining obese patients. When ultrasound detects an increased endometrial thickness or the presence of air with fluid collections in the intestines, diagnoses of a serious nature can be suspected and will require further detailed study to determine causes. The distension of the endometrial cavity can be due to an obstruction of the normal drainage of the uterus and may be seen with US. It is an invaluable tool for candidates undergoing QS.

Efficacy may be improved with protocol innovations, e.g. multiple insertions, higher doses, use of antibiotics, anti-inflammatory drugs and contraceptives for 3 months after QS [7–9]. The position as well as

duration of rest post-insertion might help tubal closures [10,6]. The most important advance in reducing failure rate of QS was the discovery, by Hieu, of the value of placing all pellets at the fundus of the uterus [11,12]. Drugs as an adjunct may help improve results with QS. The pregnancy rate appeared lower in a subgroup that received oral papaverine [13].

2. Materials and methods

A prospective non-randomized study using QS in 128 women requesting sterilization was developed at the Family Planning Clinic, School of Medicine, Federal University of Minas Gerais, in Belo Horizonte, Brazil. After approval of the protocol by the Ethics Committee of the University, this clinical trial was begun in March 1999 and ended March 18, 2003. Patient volunteers received education about QS from printed brochures and from oral communication by doctors. Both the wife and husband signed an informed consent.

Initially, patients requesting sterilization for family planning were selected. Inclusion criteria were as follows:

Age – older than 29 years.

Parity – 2 or more live children; the last child older than 3 months.

In younger women, i.e., less than 30 and/or with fewer than 2 children, medical indications for QS were accepted but only after careful evaluation.

Exclusion criteria were: pregnancy, pathologic pelvic conditions, liver disease, mental health problems, uterine fibroids depending on the size, as well as patients unable to return for a second insertion or for follow-up visits. Choices of other methods of contraception were offered to these women.

The quinacrine used was packaged as 7 pellets in a modified Copper-T IUD inserter (Sipharm, Sisseln, Switzerland). After making a voluntary informed choice of the method, each woman in the reproductive age received the first transcervical insertion of 252 mg of quinacrine, during the proliferative phase of the menstrual cycle. One month later, a second insertion was made. At all times aseptic precautions were taken. Insertions were done making sure that each quinacrine pellet was placed at the very top of the uterine fundus as described by Hieu. To accomplish this with certainty, the inserter loaded with pellets, is advanced to 0.5 cm

from the top of the uterus and then the push rod is advanced until all pellets are in the upper uterine cavity. The patients were advised to lie in a supine position for at least 60 minutes after the procedure.

To study quinacrine pellet breakdown inside the uterus, we did ultrasound (US) scanning during the first 60 minutes after QS. Following that period, the patients were asked to stand up and walk around for 5 minutes. We repeated US scanning at 20, 25 and 30-minute intervals after standing up (80, 85 and 90 minutes elapsed since QS).

Next, standing up for the second time, walking around again for 5 minutes, US scanning was repeated at 10 and 30-minute intervals – i.e., at 100 and 120 minutes after QS.

The women who had had vaginal bleeding greater than 10 ml shortly after the QS, had a third insertion one month after the second.

Sony Video graphic Printer UP 890MD documented all the images; the Ultrasound Scanner was an SA-880 Medison, with the range of frequency of the vaginal probe between 5.5 and 7.5 MHz.

The temporal pattern of failure seen in QS studies shows a preponderance of pregnancies taking place in the first 3 months following the initial insertion. This suggests that use of an additional contraceptive in this period may improve the efficacy of the method [14]. Before the first insertion, 94 women (73.4% of the patients) received 150 mg of Depot medroxyprogesterone acetate (DMPA), for the purpose of controlling the effect on the endometrium thickness; 34 women (26.6%) used some other contraceptive method for 3 months after QS. Since some patients could not tolerate hormones, they utilized barrier methods. Others continued with the same contraceptive as had been used before.

Follow-up visits with transvaginal pelvic US were scheduled after the last dose, at 1, 3, 6 and 12-month intervals. In addition, patients were asked to return once a year, as well as at any time if complications or complaints occurred.

3. Results

The incidence of gross failure pregnancy rate was 3.1% with an efficacy of 96.9% [15]. The intended sample size of 147 patients was based *a priori* on a sample

size calculation. The precision was assumed to be 2% (CI 95%). The sample size was 65 patients when type 1 error was assumed to be 3% (CI 95%).

SPSS V.8 for Windows statistical software was used to make the statistical analysis.

The risks are low or non-existent for the main concerns of ectopic pregnancies, birth defects, and cancer [12], as well as inflammatory diseases. Gynecologic problems and ectopic pregnancy rate were similar in women who had received either one or two insertions [16]. In histological studies of sections obtained from cervix, endometrium, myometrium and fallopian tubes after transcervical insertion of quinacrine, no abnormalities were revealed [14]. Lippes, citing the Winthrop bibliography of 1942, observed that numerous toxicologic studies (animal and human observations) predicted the safety of quinacrine, which has been in use for many other indications for over 70 years [17].

Patients' median age was 34 years, ranging from 21 to 46 years.

Parity's median was 3.0, ranging from 1 to 10 live children.

The hysterometer measurements averaged 7.85 (SD 0.59), ranging from 6 to 9.5 cm.

The mean follow-up time was 23.3 months.

Before the first insertion, 94 women (73.4% of the patients) received DMPA (Depo-Provera®). During 3 months after QS, 34 women (26.6%) used some other contraceptive method (Table 1).

When quinacrine pellets are inserted at the uterine fundus, the dissolved pellets can be seen within seconds via ultrasound. This "Lake of Quinacrine" stays at the fundus for up to two hours. When the patient stands up and walks about, some quinacrine flows out through the vagina and the image of the puddle on the screen

Table 1
Contraceptive method used for 3 months after QS, Maternidade Santa Fé, Belo Horizonte (N = 128)

Method	Frequency	Percentage
Depo-Provera®	94	73.4
Oral contraceptives	28	21.9
Condom	5	3.9
Abstinence	1	0.8
Total	128	100.00

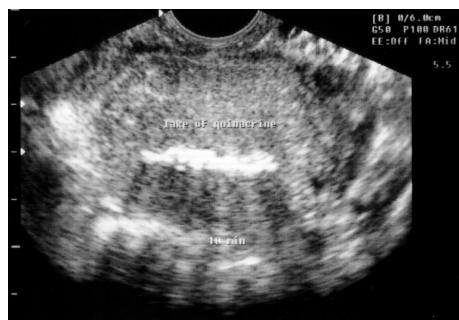


Fig. 1. Transvaginal ultrasound scanning. Coronal plane: “Lake of Quinacrine”. Transversal view of the uterus, 10 min after QS.

Table 2
Menstrual pattern one year after QS in Maternidade Santa Fé, Belo Horizonte ($N = 110$)

Menstrual pattern	Frequency	Percentage
Amenorrhea	11	10.0
Small increase	4	3.6
Reduction	14	12.7
No change	81	73.6
Total	110	100.00

becomes a little less opaque. These procedures were repeated with 10 patients, obtaining the same results in each case (Fig. 1).

A total of 129 women participated voluntarily in this QS trial. One of them exhibited such a narrow cervix canal that it was impossible to insinuate the inserter into the uterine cavity without causing bleeding. Since the presence of much blood lowers efficacy [18], we decided to exclude this patient.

The remaining 128 patients demonstrated the following transient side effects: yellow vaginal discharge for 7 to 10 days (all patients); headache (4 cases; 3.1%); mild abdominal pain (11 cases; 8.6%); vaginal pruritus (7 cases; 5.5%) and nausea (1 case, 0.8%). Twenty-one patients (16.4%) had vaginal bleeding after QS which was sufficient to require a third insertion. This was done one month later. No cases of pelvic inflammatory disease have been diagnosed so far. Neither infections nor pregnancy failures were observed before two years elapsed after QS. Two pregnancies were reported, one occurred at 25 months and the other at 37 months after QS. One terminated with a spontaneous abortion and the other is having a normal gestation.

One year after QS, menstrual patterns could be evaluated in 110 cases (Table 2). A reduction in menstrual flow was reported and was acceptable to 14 patients (12.7%). Only 4 women (3.6%) described a small increase in their vaginal bleeding while 81 patients (73.6%) observed no change in their menstrual pattern. Eleven women (10%) still had amenorrhea one year after QS.

3.1. Case report

S.M.A.⁴⁻⁰⁻⁰⁻⁴, 38, was admitted to the first US study in June 2001. After discovering her bicornuate uterus, we recognized that both IUD and QS might fail. Her last delivery was in February 2001; she suffered mastectomy of the left breast during pregnancy and was breast-feeding on the right.

In the previous year, she had not only had breast cancer, but also venous thromboses after delivery. Thus, a new pregnancy and the use of hormones were seriously contraindicated. Even though they were poor and already had 4 living children, her husband did not accept vasectomy. So, in December 2001 we decided to do two quinacrine sequential insertions guided by US scanner – one in each cavity of the uterus. The ultrasound screening showed two “Lakes of Quinacrine” completely separated. The process was repeated one month later. The patient did not complain of any side effects (Fig. 2).

One of the 128 patients had an allergic reaction with abdominal pain and hemorrhagic diarrhea, which started twenty days after the first insertion. Although she received oral analgesics, it was necessary to hospitalize her. She was examined at the Emergency Service in the Hospital of the Federal University of Minas Gerais, and was then submitted to all necessary appropriate exams (including laboratory tests, tomography and endoscopy). No associated pathologies were found. One month later, uncertain about the association between QS and her symptoms, we did the second insertion. Her reaction was the same, however, and after only 24 hours was once again admitted to the hospital. In the past, the patient had not taken either quinacrine nor suffered malaria before the QS. Neither the pain nor the hemorrhagic diarrhea returned, while her anemic state has been cured. Her follow-up by US scanning and pelvic exams were normal.

Only a transient decrease in endometrial thickness was observed during the first 6 months, which cor-



Fig. 2. Transvaginal ultrasound scanning. Transverse view of bicornuate uterus. Two “Lakes of Quinacrine”, 30 min after QS. Maternidade Santa Fé, Belo Horizonte (case report S.M.A.).



Fig. 3. Transvaginal ultrasound scanning. Endometrial line with high-level echogenicities. Intrauterine adhesions. Coronal plane. Maternidade Santa Fé, Belo Horizonte.

responds to the incidence of oligomenorrhea. Some patients, who had received DMPA, have had a variable period of amenorrhea followed by menstrual irregularities. Therefore US of the endometrium could only be analyzed 3 months after QS. The pregnancy failure rate (Pearl) was 0.805 per 100 women.

In most patients the endometrium could be observed as an echogenic interface in the center of the uterus. After QS, the endometrial line was frequently seen with irregular high-level echoes, or punctuated echogenicities. Those images might be produced by intrauterine adhesions and were much more visible when patients had amenorrhea (Fig. 3).

Frequently, vaginal ultrasonographic transverse views of the uterine cavity when seen as a triangle, showed two plug-like echogenic points, at the level of the cornua (Figs. 4–6). The plugs could be measured and the length of the scars were graded and dually classified by two different sonologists, using a standardized set of objective criteria (Table 3). The scars were easier to see 3 to 6 months after QS (Table 4 and Fig. 7).

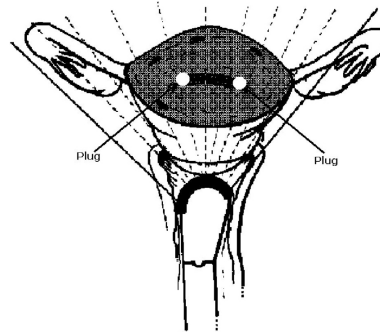


Fig. 4. Diagram of semicoronal plane. Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

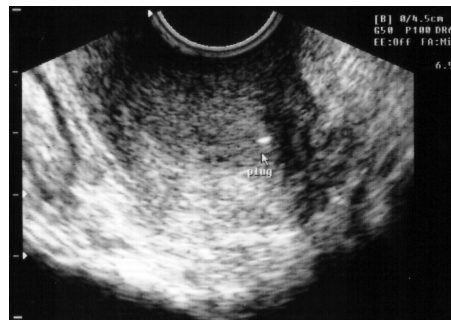


Fig. 5. One echogenic point (right-hand side). Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

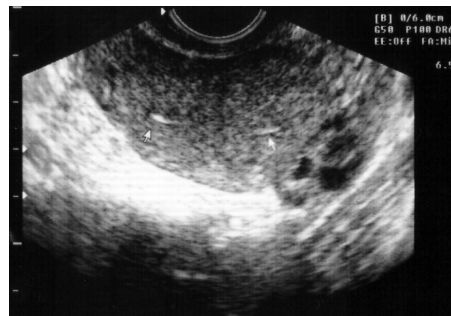


Fig. 6. Two echogenic points. Transverse view of the uterine cavity when seen as a triangle, Maternidade Santa Fé, Belo Horizonte.

Table 3

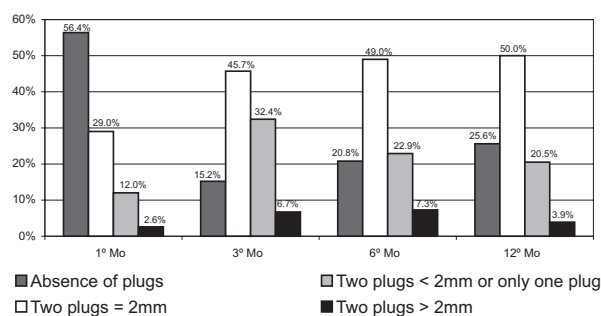
Classification of echogenic points, Maternidade Santa Fé, Belo Horizonte

0	Absence of plugs
+	Two plugs <2 mm or presence of plug at only one side
++	Two plugs = 2 mm
+++	Two plugs >2 mm

Table 4

Classification of echogenic points (frequency of plugs in each follow-up visit), Maternidade Santa Fé, Belo Horizonte

Classification of echogenic points	Follow-up visits (months)			
	1	3	6	12
Absence of plugs	56.4%	15.2%	20.8%	25.6%
Two <2 mm plugs or presence at only one side	29.0%	45.7%	49.0%	50.0%
Two 2 mm plugs	12.0%	32.4%	22.9%	20.5%
Two >2 mm plugs	2.6%	6.7%	7.3%	3.9%
Total	100.0%	100.0%	100.0%	100.0%

Fig. 7. Frequency of plugs according to elapsed time after QS, Maternidade Santa Fé, Belo Horizonte ($N = 128$).

4. Discussion

The most important factor limiting the sample size (128 patients) was our insistence that all procedures be done by the same physicians. Failure rate was strongly affected by each operator's skill [11]. In order to minimize errors, the first author (CRCF) assisted by Dr. Magalhães has done the sterilizations and examinations. The pregnancy failure rate of 0.805 per 100 women was low, compared to the literature on QS. We believe vaginal ultrasound had prevented some technical failures because it permitted a better approach for exclusion of patients with anatomic abnormalities.

When the quinacrine pellets are inserted at the uterine fundus, the dissolved pellets can be seen within seconds via ultrasound. This "Lake of Quinacrine" stays at the fundus for up to two hours. This observation introduced a protocol innovation. We increased the time patients lie in the supine position after a quinacrine insertion [7].

In a country like Brazil with a high incidence

of iron deficiency anemia, vaginal bleeding patterns should be evaluated. With heavy or prolonged bleeding, especially if anemia is noted clinically, Copper-T IUD and operative procedures are not recommended [19]. The levonorgestrel IUD (an expensive choice for Brazilian people) showed 11.2% of patients with reduced bleeding and 5.6% with increased bleeding [20]. As we have noted, QS showed a pleasantly surprising and positive effect by reducing menstrual flow in 12.7% of the patients evaluated one year after QS. Furthermore, 10% developed amenorrhea. A reduction in blood loss is a convenient and beneficial event for our women. These results coincided with the fact that 73.6% had no menstrual changes, which were largely considered desirable by our patients. An increase in blood flow was mentioned by only 3.6% of the women. It was not a real complaint and was always referred to as a "small difference".

After QS, the endometrial line was frequently seen with irregular high-level echoes, or punctuated echogenicities. Those images might be produced by intrauterine adhesions, or perhaps linked to inflammatory processes with scarring. They were much more visible when patients had amenorrhea. The transient decrease in endometrial thickness was observed during the first 6 months and corresponds to the greater incidence of oligomenorrhea in some QS patients. It was observed after QS, both in patients who used DMPA and those who adopted other contraceptive methods. In this period of time it is difficult to affirm whether this effect is due to the use of contraceptives or to the cicatrization process which accompanies QS.

Hysterosalpingography (HSG) and hysteroscopy revealed the same accuracy in the diagnosis of tubal obstruction [22]. However, HSG is not a good choice

to confirm the closure of fallopian tubes because the pressure it creates can dislodge tubal occlusions [23].

Ultrasonography scanning is a non-invasive real-time image method to scan the pelvis. According to the current study, this tool may be helpful to identify the blockage of the cornua of the uterus based on the echogenic points we observed and classified (Table 4). The potential difficulty with the utilization of this approach is the ability to obtain a proper image of the whole length of the “plugs” optimally visualized for measurement. Fig. 4 shows a diagram of a vaginal ultrasonographic transverse view of the uterine cavity seen as a triangle, with two plug-like echogenic points at the level of the cornua. The plugs could be visualized and measured.

The length of the scars were doubly graded and classified by two different sonologists (Ferreira and Magalhães). Each patient was scanned twice, and results compared. Because of the great simplicity of US, classifications were similar. This procedure was designed for greater accuracy, reproducibility and lower interobserver discrepancy of measurements. Our results should be confirmed by additional large randomized studies.

Prehysterectomy studies [16] showed that the inflammatory and fibrotic processes take six or more weeks to complete. This suggests a reasonable possibility that the progress of inflammation to scarring and closure may vary individually in time. The scars were easier to see 3 to 6 months after QS.

Once inside the uterus, quinacrine becomes fluid within seconds, seen as a “Lake of Quinacrine”. This lake stays at the fundus for up to two hours. The echogenic points need to be more thoroughly studied in order to affirm whether ultrasonographic scanning may be helpful in identifying the blockage of the uterine cornua. The echogenic points seem to be linked to the scars and inflammatory processes. They are more easily seen 3 to 6 months after QS. Because an early pregnancy failure is probably due to imperfect tubal closure, the use of ultrasound may prevent such a failure. However, pregnancy due to later recanalization cannot be avoided as we have seen this more than 2 years after QS.

QS is safe, effective and acceptable. It should be offered everywhere as an option to women requesting sterilization.

Acknowledgments

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