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Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization: results in 180 women

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Abstract

Objectives: Document the effects on the tube and uterus of one, two and three doses of 252 mg of quinacrine. *Method*: The study included 180 fertile women seeking permanent contraception at the Shatby Family Planning Clinic in Alexandria, Egypt, in 1988. All cases received three applications of seven 36 mg quinacrine hydrochloride pellets during the proliferative phase of three consecutive menstrual cycles. The patients were randomly divided into groups A, B and C. Hysterosalpingography (HSG) was performed on the 6th day of menstruation and hysteroscopy on the 10th day of the same cycle after the first application in group A, the second, in group B and the third, in group C. The study was concluded in 1999. *Results*: HSG showed 52 cases of bilateral obstruction, four of bilateral patency, and four of unilateral patency in group A. All in groups B and C elicited bilateral tubal obstruction. Cornual obstruction was seen in 33%, 65% and 85% in group A, B and C, respectively. Intramural obstruction was found in 50%, 33% and 10% in the three groups. Isthmic tubal obstruction was detected in 8%, 2.5% and 5% in groups A, B and C, respectively. Four types of ostial appearances could be recognized hysteroscopically. Type 0 (patent tubes), Type I (distal tubal blockage), Type II (intramural obstruction) and Type III (cornual obstruction). In group A, Type 0 was evident in 10%, Type I in 8%, Type II in 50% and Type III in 33% of cases. The respective figures in group B were 0%, 2.5%, 33% and 65%, while in group C, they were 0%, 5%, 10% and 85%. Hysteroscopy showed no abnormal endometrial findings in group A, but 35% and 85% of cases in group B and C showed some changes. *Conclusions*: Two applications of quinacrine were 100% effective. The side effects of quinacrine pellet applications were minimal and well tolerated by all the users. The possibility of reversal of the procedure is outlined.

Keywords: quinacrine non-surgical sterilization, hysteroscopy, hysterosalpingography

1. Introduction

The need for female sterilization far exceeds the ability of most countries to provide services. A simple, non-surgical procedure is needed to fulfill the unmet contraceptive demand. Quinacrine was originally introduced in 1931 to prevent and cure malaria. Today it continues to be prescribed for giardiasis and lupus erythematosus. This drug has sclerosing properties for some tissues and has been used for the management of recurrent pleural effusion. Zipper and his colleagues performed blind transcervical instillation of quinacrine hydrochloride for effecting permanent sterilization [1]. Various doses, concentrations and solvents, as well as different instillation schedules were evaluated. Three instillations proved to be the most effective schedule of quinacrine delivery but there were still pregnancy rates of almost 10%. Zipper's research led to the development of quinacrine hydrochloride pellets and a delivery system designed to bring the chemical

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into prolonged contact with the tubal ostia. The results were encouraging. At one year after three insertions of 252 mg quinacrine pellets (7 pellets each containing 36 mg), the gross life-table pregnancy rate was 3.1 per 100 women [2]. It was suggested that high placement of pellets near the ostia resulted in more intense inflammation and presumably fibrosis [3]. Histopathological studies after transcervical insertion of quinacrine pellets in prehysterectomy volunteers indicated that tubal occlusion occurs by a process that starts with inflammation, leads to fibrosis, which is limited to the cornual area and the intramural portion of fallopian tubes [4,5].

The endometrial lining of the uterine cavity appears to recover from any inflammatory response. This was attributed to the protective action of zinc which is at high levels in the endometrium but is low in the fallopian tubes [6]. Toxicology studies for intrauterine use of quinacrine were completed at Johns Hopkins University in the early 1980s leading to approval of prehysterectomy trials by the United States Food and Drug Administration (USFDA) [7]. Recently, controversy concerning its use for sterilization has been reviewed by Benagiano [8].

The objective of this research was to evaluate the optimal number of quinacrine hydrochloride applications that allows the highest efficacy in tubal occlusion. Moreover, the intrauterine cavity and the condition of the endometrium were studied by both hysterosalpingography (HSG) and hysteroscopy after each of the three applications. The side effects of quinacrine instillation were also assessed.

2. Material and methods

A limited clinical trial of quinacrine sterilization was started in 1988. Initial promising data [9] led to a second longer trial involving 180 women who requested sterilization and volunteered for this method at the Shatby Family Planning Clinic of the University Hospital in Alexandria, Egypt. Before admission to the study the risks and benefits of the method and details of the procedure were carefully explained to them. Additional contraceptives were prescribed for 3 months after quinacrine insertion. Patients with pelvic inflammatory disease (PID), psychiatric problems, and severe liver infections were excluded. Those selected were randomly divided into three groups: A, B and C, each consisting of 60 cases.

Using a copper T-IUD applicator, seven quinacrine hydrochloride pellets 36 mg each, were deposited in the upper part of the uterine cavity [10]. Each woman received three applications on three consecutive cycles during the proliferative phase of the menstrual cycle.

HSG was performed on the sixth day and hysteroscopy on the tenth day of the menstrual cycle that followed the first application in group A, the second in group B and the third in group C. Hysteroscopy was performed under paracervical block using the 4 mm Storz panoramic instrument. The uterine cavity was distended with CO_2 gas. Systemic exploration of the anterior, posterior and lateral walls of the uterine cavity as well as exploration of the tubal ostia were done. The study was concluded in 1999.

3. Results

3.1. Demographic characteristic of the cohort (Table 1)

The women ranged in age from 32 to 45, with a mean age of 36.5 years in group A, 37.5 years in B and 36.4 years in C (Table 1). The parity ranged from 3 to 14 with mean parity 6.2 in group A, 7 in B and 7.5 in C. The number of living children ranged from 3 to 11 with a mean of 5.4 in group A, 6.5 in B, and 6.2 in C. There were no significant differences among the three groups.

Table 1
Age, parity, and number of living children in the three groups at Shatby Family Planning Clinic, Alexandria, 1988–1999

Group	Age (yr)		Parity (*N*)		Living children (*N*)	
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
A	32–45	36.5±3.3	3–12	6.2±2.3	3–10	5.4±1.7
B	32–45	37.5±4.1	4–12	7.0±2.0	4–9	6.5±1.6
C	32–42	36.4±3.2	3–14	7.6±2.9	3–11	6.2±2.5
Total	32–45	36.8±3.5	3–14	6.9±2.9	3–11	6.0±2.0

3.2. Hysterosalpingographic (HSG) findings (Table 2)

In group A, 52 cases of bilateral tubal occlusion were

Table 2
Distribution of cases according to the level of obstruction as seen by hysterosalpingography at Shatby Family Planning Clinic, Alexandria, 1988–1999

Condition of the fallopian tubes	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Patent	12	10	0	0	0	0
Obstruction						
Isthmic	9	8	3	2.5	6	5
Intramural	60	50	39	33	12	10
Cornual	39	33	78	65	102	85
Total	120	100	120	100	120	100

N, number of both fallopian tubes in 60 cases.
Significant ($p \leqslant 0.05$).

Table 3
Distribution of cases according to the type of obstruction as diagnosed by the hysteroscope at Shatby Family Planning Clinic, Alexandria, 1988–1999

Condition of the fallopian tubes	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Type 0[a]	12	10	0	0	0	0
Type I	9	8	3	2.5	6	5
Type II[a]	60	50	39	33	12	10
Type III[a]	39	33	78	65	102	85
Total	120	100	120	100	120	100

N, number of both fallopian tubes in 60 cases.
[a]Significant ($p \leqslant 0.05$).

seen, 4 showed bilateral tubal patency, and 4 unilateral tubal patency. While in group B and C bilateral tubal occlusion occurred in all the cases. Three types of tubal obstruction could be elicited on the HSG films (cornual, intramural and isthmic).

Cornual: The percentages of fallopian tubes with cornual obstruction were 33 for A, 65 for B, and 85 for C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

Intramural: Intramural obstruction was elicited in 50%, 33% and 10% of the fallopian tubes in groups A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

Isthmic: The proportions of isthmic obstruction in the fallopian tubes were 8%, 2.5% and 5% in groups A, B and C, respectively. The differences among the three groups were not significant.

3.3. Hysteroscopic findings (Table 3)

According to hysteroscopic appearances of the tubal ostia there were 4 patterns of changes: Type 0, 1, 2 and 3.

- *Type 0 (patent tubes):* No obstruction could be seen by the hysteroscope or noticed on the monitored CO_2 hysteroinsufflator system. In group A, 3 cases showed bilateral, and 6 unilateral tubal patency. Type 0 was not detected in groups B and C, which was significant ($p \leqslant 0.01$).
- *Type I (distal tubal blockage):* An obstruction could not be seen through the hysteroscope, but was noticed on the monitored CO_2 hysteroinsufflator. Type I obstruction was detected in 8%, 2.5% and 5% of the fallopian tubes in groups A, B and C, respectively. The differences among the three groups were not significant.
- *Type II (intramural obstruction):* An occlusion of the intramural portion was seen through the cornual orifices of the fallopian tube. Type II obstruction was detected in 50%, 33% and 10% in group A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).
- *Type III (cornual obstruction):* An obstruction was denoted by absence of the cornual orifices of the fallopian tube which is replaced by reactive fibrosis restricted to the expected site of the cornua. In some cases the reaction was extensive and seen in the form of a rough raised dome-shaped elevation in the tubal horn. We considered this intense cornual obstruction. The proportion of fallopian tubes that showed type III obstruction were 33%, 65% and 85% in groups A, B and C, respectively. The differences among the three groups were significant ($p \leqslant 0.05$).

3.4. Abnormal endometrial findings seen by the hysteroscope (Table 4)

In group A no abnormal findings were detected, while 21 cases (35%) in B and 51 (85%) in C showed abnormal endometrial changes. The differences among the three groups are statistically significant ($p \leqslant 0.05$). Various types of abnormal endometrial changes were noted by hysteroscopy. Atrophic/polypoid reactions were significantly higher in group C.

Table 4
Type of abnormal hysteroscopic endometrial findings (60 cases in each of the three groups) at Shatby Family Planning Clinic, Alexandria, 1988–1999

Type of abnormal endometrial changes	Group A		Group A		Group A	
	N	%	*N*	%	*N*	%
Bullous reaction	0	0	0	0	3	5
Ulcerative reaction	0	0	0	0	3	5
Atrophic reaction	0	0	12	20	18	30[a]
Hyperemic reaction	0	0	0	0	3	5
Polypoid reaction	0	0	6	10	15	25[a]
Fine adhesions	0	0	3	5	9	15

[a] χ^2 Significant.

Table 5
Side effects of the application of quinacrine pellets (60 cases in each of the three groups) at Shatby Family Planning Clinic, Alexandria, 1988–1999

Side effect	Group A		Group B		Group C	
	N	%	*N*	%	*N*	%
Transient yellow discharge	60	100	60	100	60	100
Menstrual changes	6	3.3	48	27	93	52
Colicky pain	6	3.3	24	8	30	17
Vaginal spotting	6	3.3	30	10	42	23

3.5. Side effects of quinacrine pellet application (Table 5)

- All patients had noticed a yellowish discharge that lasted for a few days after each application. The discharge was odorless and non pruritic.
- Some women complained of delay and diminished menstrual flow in the cycles that followed QS. These changes were observed in 3.3%, 27% and 52% of the patients after first, second and third applications, respectively.
- Colicky pain was observed immediately after pellets had been inserted and lasted for a few hours in 3.3%, 8% and 17% of the patients after first, second and third applications, respectively.
- Vaginal spotting was a temporary complaint that followed the procedures and lasted for few days. It was observed in 3.3%, 10% and 23% of the women after the first, second and third applications, respectively.

4. Discussion

In many parts of the world, sterilization has become the leading method of fertility control [11]. The need to make this procedure simple, safe, inexpensive and thereby more acceptable, even in countries with limited surgical facilities is well recognized. Use of quinacrine pellets has become the most widely adopted method of non-surgical female sterilization [12].

This present study supports previous research indicating that transcervical insertion of quinacrine pellets is free from serious side effects [13,14]. There were no deaths in the present series and no death has been reported for this method anywhere in the world [12]. Long-term follow-up of quinacrine sterilization acceptors in Chile found no increased risk of cancer [15]. All the side effects were transient and of short duration, as documented by others [10,16]. Those reported in the present study were temporary pain, vaginal discharge, hypomenorrhea and oligomenorrhea. Some patients complained of mild vaginal spotting which was easily tolerated in all cases. Randic and her colleagues [17] found that most women had an unpleasant yellowish vaginal discharge of which the duration varied, but only a few experienced mild pruritis of the vulval area. In the present study a yellow discharge was seen in all the patients but was transient, mild, non-pruritic and well tolerated by users.

Reports concerning the optimal number of transcervical insertions of quinacrine pellets are remarkably varied. A single intrauterine application of a low dose of quinacrine even when observed over a prolonged period of time is insufficient to cause tubal occlusion in a patient. All the tubes were patent with no histological changes in the tubal cavities [18]. Guzman-Serani and his colleagues recommended three insertions of quinacrine pellets, each one month apart and they reported 95% effectiveness after 3 years [19]. Other investigators have observed that 2 or 3 insertions have given similar results [20].

Merchant and her coworkers [5] considered the presumed need of three insertions at monthly intervals as an important drawback to the quinacrine pellet method of female non-surgical sterilization. The results

of their studies suggested that the second and third insertions do not contribute significantly to the efficacy of the method. They concluded that a single insertion of 324 mg quinacrine will be highly effective in bringing about occlusion of the tubes provided the insertion is carried out during the proliferative phase of the cycle in women with no endometrial abnormality.

This controversy indicates that there is a need for further clinical studies to determine the optimal number of transcervical insertions of quinacrine hydrochloride pellets for the occlusion of the fallopian tubes, as well as to detect any abnormal findings in the endometrium that may be related to quinacrine application.

Comparing the results of the two modalities used in this study, HSG and hysteroscopy showed that there was complete conformity of observations between the two methods. Hysteroscopic diagnosis of tubal patency, intramural and cornual obstruction was the same as the HSG diagnosis in the three groups. In distal obstructions, HSG has the advantage of precisely localizing the site of occlusion.

Tubal obstruction was elicited in only 90% of cases after one application, while it rose to 100% after both the second and third placements. This indicates that at least two insertions of quinacrine are required to achieve complete effectiveness of the method. Isthmic obstruction of the fallopian tube was insignificantly higher after one application compared to after two and three applications.

In general, the isthmus was the anatomical part to be least affected and least occluded by quinacrine, regardless of the frequency of insertions: 8%, 2.5% and 5% in groups A, B and C, respectively. Intramural occlusion was the most common after one application (50%), while cornual obstruction was significantly higher after the second and third insertions, 65% and 85%, respectively. This finding suggests that the proportion of cornual obstruction of the tubes is higher with more frequent quinacrine insertions. This has an important bearing when considering reversal of the method. The success rate of reversal in cases of intramural or isthmic obstruction is expected to be better than cases with cornual obstruction.In addition to its accuracy in the diagnosis of tubal obstruction, hysteroscopy has the advantage of determining the extent of the fibrosis at the cornual site and detecting any endometrial changes that might occur after quinacrine insertion. Abnormal endometrial findings in the form of bullous reaction, atrophic reaction, fine adhesions, hyperemic reaction and polypoid formations were hysteroscopically detected in women who received two or three applications, while they were not apparent after one application. Randic reported 2 cases of hematometra resulting from quinacrine sterilization when ibuprofen (3 pellets each containing 18.5 mg) was added in a second group. Hematometra were successfully treated with the introduction of a uterine sound through the cervical canal [17].

The differences among the three groups as regards the types of abnormal endometrial findings were significant among atrophic and polypoid reactions. Therefore, with more applications there may be a higher incidence of certain endometrial changes. These results need more prospective studies to detect whether these endometrial findings are temporary or permanent. Also the clinical implications of such changes have to be properly assessed, by subjecting these cases to a longer period of follow-up.

N.B.: Elsewhere in this issue: Soroodi questions the use of HSG as an endpoint rather than pregnancy. She has found that this procedure, even when performed with minimal pressure, opens closed tubes in a small proportion of women. The end result in her series was a pregnancy rate three times as high among women who received HSG as compared to others who did not.

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