Clinico-pathological study of Fallopian tubes after transcervical insertion of quinacrine hydrochloride pellets

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Abstract

This study lends support to others indicating the apparent safety and effectiveness of multiple transcervical insertions of quinacrine hydrochloride as pellets in 240 mg dosage to achieve permanent sterilization. In order to study the effects of the number of quinacrine pellet insertions and the site of placement of the pellets in the uterus of prehysterectomy volunteers, a scoring system of histological changes in the Fallopian tube was designed. Quinacrine pellets were deposited at the fundus using a straight inserter in 16 women, and at the cornua using a curved inserter in 17 women. Each group had at least five women receiving one, two or three insertions at one-week intervals. Results indicate that neither the number of insertions nor the place of deposition of the pellets affects the degree of tubal inflammation and fibrosis.

Introduction

There is an urgent need for a safe, effective and inexpensive non-surgical method of Fallopian tube occlusion to meet the rising demand for female sterilization, especially in rural areas of developing countries [1]. The method developed by Zipper and colleagues involving three transcervical insertions of 250 mg of quinacrine hydrochloride a month apart using a modified copper-T IUD inserter has potential for meeting this need because of its simplicity, low cost and apparent

safety in limited clinical trials. The life-table failure rate is reported as 3.1% at one year after the third insertion in 128 women [2]. A confirming study showed failure rates of 3.8% and 4.3% at the end of the second and third year respectively after the third insertion in 149 women [3].

Previous histopathologic studies of transcervical insertion of quinacrine pellets in prehysterectomy volunteers indicate that tubal occlusion is by inflammation and fibrosis is limited to the cornual area and intramural portion of the tube [4]. The endometrium appears to recover from any inflammatory response. Zipper provides evidence that the limited area of fibrosis is due to the protective action of zinc which is found to be at high levels in the endometrium but low in the Fallopian tube [5]. Wheeler has hypothesized that repeated insertions of quinacrine pellets are needed as it was thought that approximately half the open tubes were closed by each insertion [6].

Early studies of transcervical instillation of a slurry of quinacrine did indicate that repeated instillations improved efficacy [7]. Limited animal studies suggest that close placement of pellets near the ostia results in more intense inflammation and presumably fibrosis [8]. There is a need, however, for further clinical studies to determine the optimal number of transcervical insertions and placement of quinacrine pellets for tubal occlusion.

The purpose of this study was to observe hystopathologic effects on the uteri and Fallopian tubes of women receiving one, two or three transcervical insertions at one-week intervals of 240 mg of quinacrine as pellets, when the pellets were deposited at the fundus or at the cornual areas.

Materials and methods

Thirty-three women of reproductive age who were awaiting a hysterectomy for prolapse, non-malignant lesions of the cervix or dysfunctional uterine bleeding and who gave consent to participate in the study were selected. Four pellets of quinacrine hydrochloride, each of 60 mg, were inserted into the upper segment of the uterine cavity by means of a plastic cannula and a rod in a manner similar to
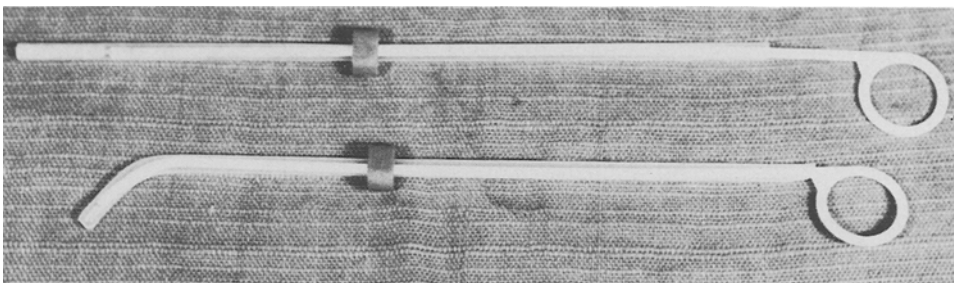

Figure 1   Straight and curved inserters for transcervical administration of quinacrine pellets at the fundus and at the cornua

the insertion of an IUD. As shown in Figure 1, two types of inserter were used: with the curved inserter, two quinacrine pellets were deposited in each cornu of

the uterus and with the straight inserter, four quinacrine pellets were deposited

Table 1 Histopathological changes in intramural segment of Fallopian tubes by insertion technique and number of transcervical insertions of quinacrine pellets

Type and no. of insertions	No. of cases	Total no. of intramural tubes	Type of histopathological change		
			A	B	C
Straight Group I					
1	5	10	0	1	9
2	6	12	3	2	7
3	5	10	4	1	5
Total	16	32	7	4	21
			21.8%	12.5%	65.6%
Curved Group II					
1	7	14	4	4	6
2	5	10	2	1	7
3	5	10	3	0	7
Total	17	34	9	5	20
			26.5%	14.7%	58.8%

at the fundus. The study therefore included two groups of women (Table 1) who were alternately assigned to Group I (16 women) in whom straight inserters were used, and Group II (17 women) in whom curved inserters were used.

The number of insertions in each group was based on operating room schedules and the patient's need for surgery. In Group I, five women had one insertion of quinacrine, six had two insertions and five had three insertions. In Group II, seven women had one insertion, five had two insertions and five had three insertions. The second and third insertions were carried out at weekly intervals after the first. The first insertion was intended to be in the proliferative phase of the cycle (soon after cessation of the menstrual flow). This was so in the majority of women.

A total hysterectomy with bilateral salpingectomy (partial in most cases) was carried out at various intervals, usually between two and 12 weeks after the last quinacrine insertion. However, three women in Group I failed to keep their scheduled surgery dates and hysterectomy was carried out at eight months in two women and at nine months in one woman following the last quinacrine insertion. Similarly in Group II, hysterectomy was performed six months after the last quinacrine insertion in one woman and 11 months after in a second woman.

Each of the 33 uteri with varying segments of their Fallopian tubes were used for histopathological studies, with sections obtained from the cervix, endometrium, myometrium and different areas of each tube. Blocks of tissue 3 mm thick were obtained serially from both cornua so as to obtain full lengths of intramural and isthmic tubes as described earlier by Merchant and colleagues [9]. The number of tubal sections averaged 16 per case. Routine haematoxylin and eosin sections were then prepared.

The pathologist was kept blind to clinical history and study assignment of subjects, and the histological changes identified in the Fallopian tubes were divided into the following three types:

Type A: A patent lumen, an intact epithelial lining and absence of significant inflammatory response or hyalinization marked this group. Cases showing minimal submucosal inflammation were, however, included in this group. Figure 2 is an example of this type.
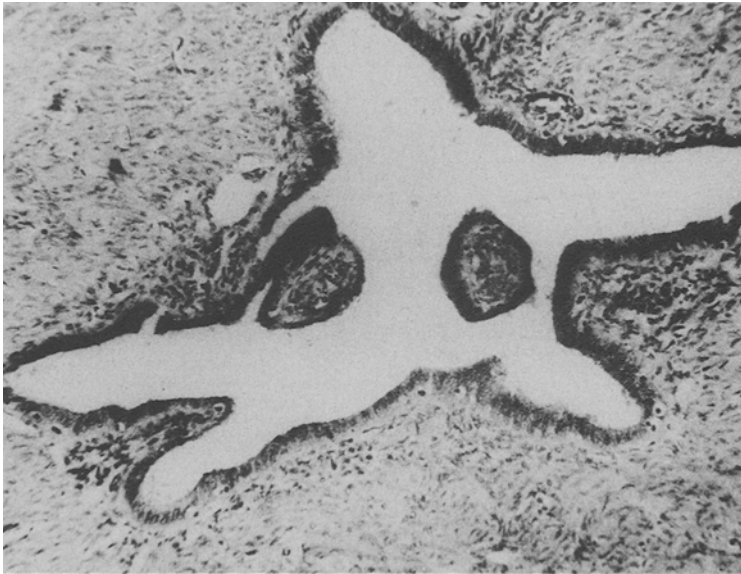

Figure 2 Type A change. The star-shaped patent lumen is lined by an intact mucosa. A sparse chronic inflammation is noted in the submucosa (× 100)

Type B: A spectrum of reactions ranging in intensity as in an inflammatory process was evident. The lumen was patent or slit-like, with an intact epithelial lining. The lamina propria or the muscularis revealed collections of inflammatory cells consisting of lymphocytes, histiocytes, eosinophils and frequently foreign body giant cells forming a granuloma, which at times was encroaching upon the tubal musculature or was associated with marked subepithelial hyalinization and fibrosis. Figure 3 is an example of this type.

Type C: The striking feature of this type was complete occlusion or only a slit-like lumen. The epithelial lining was completely lost. The surrounding lamina propria and muscularis showed a quiescent hyalinization to a variable depth. Figures 4 and 5 are examples of this type.

Histologically we would consider the 'B' and 'C' changes as having affected the tube with potentially occlusive changes, and 'A' changes as not having significantly affected the tubes, with likelihood of complete recovery.

Figure 3 Type B change. Around the intact mucosa surrounding a patent lumen is seen variable fibrosis of the muscular layer. A sparse inflammation is present (× 100)
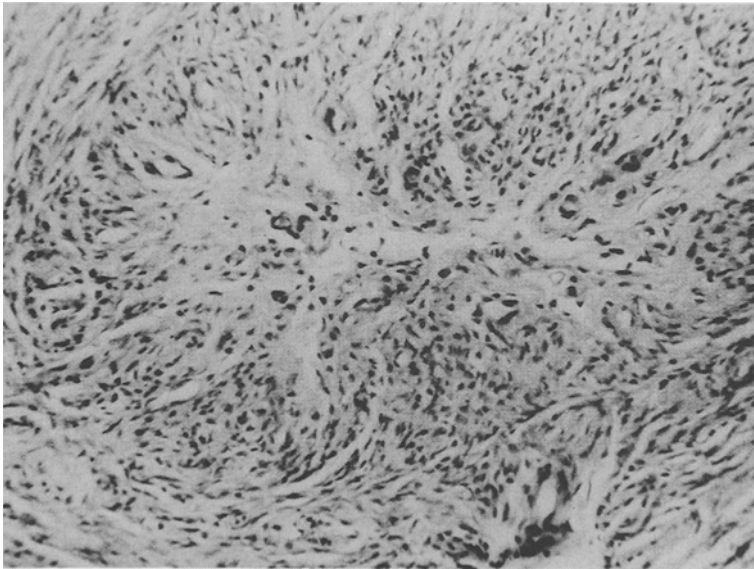

Figure 4 Type C change. There is complete loss of mucosa around a slit-like lumen. The muscular layer is fairly well preserved (× 100)
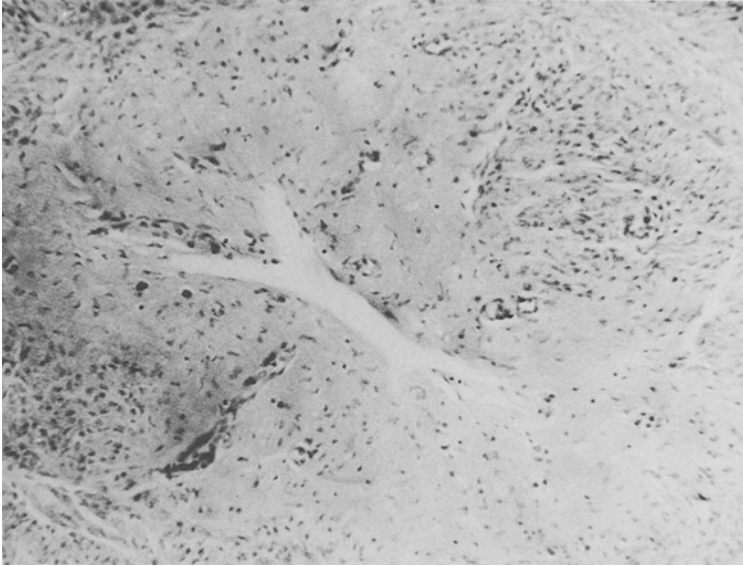
Figure 5 Type C change. A slit-like lumen is seen with complete denudation of the epithelium. There is extensive fibrosis of the muscular layer (× 100)

Results

Table 1 shows the type of histological changes produced in both groups of cases and the number of weekly quinacrine insertions. Neither fundal or cornual placement of the pellets, i.e. curved or straight insertion technique, nor the number of quinacrine pellet insertions had any significant effect on the outcome of histopathological changes in the intramural tube.

Table 2 shows bilateral type B or type C changes by insertion technique, number of insertions, age, parity, clinical diagnosis, recent history of menorrhagia, time of quinacrine insertion in the menstrual cycle, insertion/hysterectomy interval and height of the endometrium in the hysterectomy specimen. Table 3 shows the same information for women with a type A change in either Fallopian tube. Bilateral occlusive-type changes (i.e. B or C type changes) were more likely to occur when quinacrine pellet insertions were in the proliferative phase of the menstrual cycle. Only one of the 21 women (4.7%) with the occlusive-type changes (Table 2) did not have at least one insertion by day 14 of the menstrual cycle and this woman had a recent history of menorrhagia. All of the 15 women with bilateral type C changes had at least one insertion as early as day 14 of the menstrual cycle. Of the 12 women with a type A change, two (16.7%) did not have an insertion of quinacrine pellets by day 14 of the menstrual cycle (Table 3). Of the four women with bilateral type A changes, all tended to have insertions late in the menstrual cycle and three out of four had a recent history of menorrhagia. One-third of the women with occlusive-type changes had a recent history of menorrhagia whereas half of the women with a type A change had such a history.

Table 2   Type B and Type C histological changes

Type and no. of insertions	Age (years)	Parity	Clinical diagnosis	Menorrhagia (recent)	Insertion day(s) of menstrual cycle (next cycle)	Insertion/ hysterectomy interval (weeks)	Type of histological changes in tubes Right	Left	Height (mm) and menstrual phase or condition of endometrium in hysterectomy specimen	
Straight inserter *Group I*										
1	46	2	Myoma	–	10	3	C	C	3	Early secretory
3	34	5	Myoma	–	12 (4 12)	4	C	C	1	Proliferative
2	45	3	Myoma	+	8 14	8	C	C	2	Secretory
1	41	3	DUB	–	10	32	C	C	3	Proliferative
1	35	4	CIN	–	8	12	C	C	1	Proliferative
1	48	5	Prolapse	–	14	36	C	C	2	Proliferative
2	41	3	CIN	–	10 17	6	C	C	2	—
2	35	4	CIN	–	13 18	32	C	C	3	Proliferative
3	40	6	DUB	+	8 13 22	2	B	C	2	Necrotic endometrium
1	32	7	DUB	+	16	6	B	C	1	Proliferative
2	35	3	CIN	–	12 19	6	B	B	1	Proliferative
Curved inserter *Group II*										
3	55	5	Myoma and DUB	–	7 13 18	11	C	C	7	Mild cystic hyperplasia
1	30	8	DUB	–	10 15	2	C	C	1	Proliferative
2	43	3	CIN	–	8	3	C	C	2	Proliferative
3	40	7	CIN	–	10 (6 13)	4	C	C	1.5	Secretory
2	45	6	DUB	–	10 15	4	C	C	3	Proliferative
1	43	4	Myoma	+	11	6	C	C	4	Cystic glandular hyperplasia
3	42	5	CIN	+	25 (6 13)	24	C	C	1	Proliferative
2	40	4	DUB	+	6 13	8	C	B	1	Secretory
1	47	2	Prolapse	–	9	12	C	B	2	Proliferative
1	40	4	DUB	+	11	6	B	B	2	Proliferative

DUB = dysfunctional uterine bleeding
CIN = cervical intraepithelial neoplasia

Table 3 Type A histological changes

Type and no. of insertions	Age (years)	Parity	Clinical diagnosis	Menorrhagia (recent)	Insertion day(s) of menstrual cycle (next cycle)	Insertion/ hysterectomy interval (weeks)	Type of histological changes in tubes Right	Type of histological changes in tubes Left	Height (mm) and menstrual phase or condition of endometrium in hysterectomy specimen	
Straight inserter Group I										
2	31	4	DUB and prolapse	+	14 20	6	A	A	4	Early secretory
3	35	1	DUB	+	13 17 24	8	A	A	4	Secretory
2	40	3	Prolapse	+	11 18	7	C	A	8	Proliferative
3	38	4	DUB and prolapse	+	11 20 27	11	A	C	1	Proliferative
3	35	0	DUB	+	5 11 20	12	C	A	1	Secretory
Curved inserter Group II										
1	45	3	Chronic PID	–	6	44	A	C	3	Proliferative
1	35	2	DUB	+	17	8	A	A	5	Secretory
3	35	3	CIN	–	25 (18) (21)	10	A	A	3	Secretory
2	35	3	Prolapse	–	10 17	6	C	A	3	Proliferative
2	45	5	CIN	+	12 20	7	C	A	1	Proliferative
3	45	6	Prolapse	–	12 19 23	12	C	A	8	Secretory
1	40	3	DUB	–	8	8	A	B	1	Proliferative

DUB = dysfunctional uterine bleeding
CIN = cervical intraepithelial neoplasia
PID = pelvic inflammatory disease

Neither the clinical diagnosis nor the insertion/hysterectomy interval appears to be related to histological changes in the Fallopian tubes.

The average age and parity of women with occlusive-type changes was 40.8 and 4.4 compared to 38.3 and 3.1 for women with a type A change. However, it is likely that this difference is due to the age distribution of women with and without a recent history of menorrhagia. The average age and parity of women without a recent history of menorrhagia was 40.8 and 4.1 compared to 33.6 and 3.5 for women with a recent history of menorrhagia.

The average height of both proliferative and secretory endometrium in specimens with occlusive-type intramural tube changes was 1.9 mm. For specimens with a type A change the average height of the proliferative endometrium was 2.8 mm and of the secretory endometrium 4.2 mm.

Table 4 Type of histological change by segment* of Fallopian tube and type of inserter among 33 women receiving one, two or three transcervical insertions of quinacrine pellets

Type of inserter and segment of Fallopian tube	Total tubes examined No.(%)	Type of histological changes		
		A No. (%)	B No. (%)	C No. (%)
Straight inserter				
Group I				
Intramural	32 (100.0)	7 (21.9)	4 (12.5)	21 (65.6)
Isthmic	28 (87.5)	12 (37.5)	8 (25.0)	8 (25.0)
Ampullary	16 (50.0)	14 (43.8)	2 (6.2)	0 (0.0)
Fimbrial	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Curved inserter				
Group II				
Intramural	34 (100.0)	9 (26.5)	5 (14.7)	20 (58.8)
Isthmic	30 (88.2)	10 (29.4)	4 (11.8)	16 (47.0)
Ampullary	15 (44.1)	11 (32.4)	3 (8.8)	1 (2.9)
Fimbrial	4 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)

* Available segments in surgical specimen

Table 4 shows that the type of insertion technique (straight or curved inserter) did not influence the extent of the tube affected. However, with either delivery system the tube is progressively less affected on moving away from the uterine cavity. The fimbrial end was never affected, and no peritoneal involvement was noted at surgery.

There were no changes in the endometrium on examination of the uteri, and no changes were noted in the cervix. The presence of quinacrine was noted in the uterine cavity of four uteri where hysterectomy was performed within four weeks of the last quinacrine insertion, but no quinacrine was found in uteri examined four or more weeks after insertion.

In two cases which revealed a myoma (5–6 mm in size) at hysterectomy, only one tube out of four showed type C changes, while the other three showed type B changes.

No untoward side-effects of quinacrine pellet insertion were reported by any of the women. Six women complained of mild pain in the lower abdomen for a few hours to four days, but did not require any specific treatment. Ten women complained of a yellow vaginal discharge (quinacrine) for a few days following insertion.

Discussion

The present study supports other studies indicating that transcervical insertion of quinacrine pellets in a dosage of 240 mg is free from serious side-effects. In this form and dosage the chemical remains in the uterine cavity for about three weeks, during which time it is absorbed or discharged into the vagina. Over this period it is believed to bring about inflammatory and fibrotic changes in the Fallopian tubes by physical contact.

An important drawback to the quinacrine pellet method of female non-surgical sterilization is the presumed need for three insertions, recommended generally at monthly intervals. The results of this study suggest that the second and third insertions may not contribute significantly to the efficacy of the method. Although our insertions were done at weekly rather than monthly intervals, the inflammatory process is likely to be well advanced in this time period.

Placement of these 10-minute dissolution pellets at the cornua did not affect the inflammatory process when compared to placement at the fundus. It is likely that as the pellets disintegrate a slurry is formed which is equally distributed throughout the uterine cavity.

The early work of Zipper and colleagues [7] with a quinacrine slurry indicated that the secretory endometrium would interfere with the action of quinacrine and Zipper has therefore recommended application in the proliferative phase of the menstrual cycle. Our data support this recommendation for the quinacrine pellet method and also suggest that greater height of the endometrium plays a protective role against the action of quinacrine.

The results of this study suggest that even a single insertion of quinacrine will be highly effective in bringing about occlusion of the tube provided the insertion is carried out during the proliferative phase of the cycle in a woman with no endometrial abnormality. Zipper's recommendation of repeated applications of quinacrine was based on his observations of the liquid quinacrine slurry [2,7]. Clinical trials of the quinacrine pellet method of non-surgical female sterilization do not provide evidence that repeated insertions improve efficiency. In Zipper's quinacrine pellet study [2] there was only one pregnancy between the first and third insertion of quinacrine pellets, which would only marginally raise the pregnancy rate of the method; there were no pregnancies between insertions in a confirming study [3]. Only a prospective trial of one insertion of quinacrine pellets can determine whether or not the second and third insertions increase efficacy of the method, and if so by how much.

A marked decline in side-effects of the quinacrine method of female sterilization was noted with the change from slurry to pellet [2]. Additional experience with

the quinacrine pellet method is needed to be confident that there are no rare or serious complications. If the safety can be documented and the single application of pellets does not appreciably increase the failure rate compared with the present recommended three insertions, as is suggested in our data, a most useful new method of fertility control will be available to meet the growing demand for female sterilization in the world today. The benefits of the method could accrue to women in both developed and developing countries [10].

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Resumé

Cette étude vient appuyer d'autres recherches qui ont indiqué la sécurité et l'efficacité apparentes d'insertions transcervicales multiples de doses de 240 mg d'hydrochlorure de quinacrine en pillules pour obtenir une stérilisation. Pour étudier les effets d'un certain nombre d'insertions de pillules de quinacrine et d'insertions de pillules dans l'utérus de volontaires en pré-hystérectomie, un système de comptage des points a été conçu pour noter les changements hystologiques dans la trompe de Fallope. Des pillules de quinacrine ont été placées au fond de l'utérus de 16 femmes à l'aide d'un tube d'insertion droit et dans le col de 17 femmes à l'aide d'un tube d'insertion recourbé. Dans chaque groupe, au moins 5 femmes ont reçu une, deux ou trois insertions à une semaine d'intervalle. Les résultats indiquent que le nombre d'insertions et le point d'insertion de ces pillules n'ont aucun effet sur le taux d'incidence des inflammations des trompes et de fibroses.

Resumen

Este estudio corrobora las conclusiones de otros autores indicando la aparente inocuidad y efectividad de múltiples inserciones transcervicales de 'pellets' de hidroclorato de quinacrina de 240 mg, a efecto de establecer una esterilización permanente. A fin de estudiar los efectos del número de inserciones de 'pellets' de quinacrina y el lugar de su emplazamiento en el útero, se estableció un sistema de puntaje para evaluar los cambios histológicos en la trompa de Fallopio en mujeres que iban a ser histerectomizadas. Los 'pellets' de quinacrina fueron depositados en el fondo del útero utilizando un insertor recto en 16 mujeres; y a nivel de los cuernos uterinos utilizando un insertador curvo en 17 mujeres. Cada grupo tuvo no menos de 5 mujeres con una, dos o tres inserciones semanales. Los resultados indican que ni el número de inserciones ni el lugar de emplazamiento de los 'pellets' afecta el grado de inflamación y fibrosis tubaria.