

Clinicopathologic Study of Fallopian Tube Closure After Single Transcervical Insertion of Quinacrine Pellets

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ABSTRACT Objective-To determine the effect on tubal closure of intrauterine quinacrine by dose and time from administration. **Design and Participants-**Subjects included 33 women of reproductive age who were awaiting hysterectomy for nonmalignant conditions at a Bombay, India medical college. Ten women received 252 mg quinacrine as pellets using a modified Copper-T IUD inserter followed by hysterectomy within 6 weeks, and 23 women received 324 mg quinacrine followed by hysterectomy 6 to 20 weeks post-insertion. Hysterosalpingograms were done before insertion, prior to surgery and on the fresh surgical specimen. The uteri and tubes were subjected to histology studies, including grading of tubal damage. For study of dose, an additional 7 women receiving 100 mg quinacrine (and previously reported) were included. **Main Outcome Measure-Tubal** closure rates by hysterosalpingogram and tubal histology. **Results and Conclusion-Tubal closures were directly related to quinacrine dose and** length of insertion-hysterectomy interval. For the 252 mg quinacrine dose, 55.0% of intramural tubal segments and 5.9% of isthmic segments showed histologic evidence of closure. For the 324 mg dose, all intramural tubal segments and 58.8% of isthmic segments showed histologic evidence of closure. Clinical conditions, such as dysfunctional uterine bleeding, were associated with lower tubal closure rates. Multivariate discriminant analysis showed quinacrine dose to be more important than quinacrine-hysterectomy interval. Int J Fertil 40(1):47-54, 1995

KEY WORDS: quinacrine (pellets), tubal closure, fibrosis, hysterectomy, sterilization (female)

INTRODUCTION

A METHOD OF NONSURGICAL female sterilization that could be delivered safely by health personnel who are not surgeons would meet an important

need in developing countries [1]. Zipper's quinacrine pellet method is the leading candidate method today [2]. His group's report of the action of antiprosta-glandins as potentiating agents to improve efficacy makes it important to study this method thoroughly [3]. We have expanded our pre-

vious pre hysterectomy study [4] to evaluate the effects of quinacrine insertion-hysterectomy intervals and quinacrine dose on rates of tubal closure.

While there are several reports [5-10] on the safety and efficacy of 252 mg of quinacrine hydrochloride pellets at monthly intervals for three insertions, there is only one report of a single insertion of 324 mg [10]. Recently, Zipper and co-workers [11] reported improvement in efficacy with 100-minute dissolution pellets with just two insertions a month apart as compared to lo-minute dissolution pellets with three insertions, each a month apart, the dosage being 252 mg in both instances. The pattern of failure seen in quinacrine pellet studies is that a preponderance of pregnancies occurs in the first 3 months following the first insertion. In Mullick and Kessel's study of 1,342 cases of two insertions of 252 mg of quinacrine, 45 of 55 failures (82%) occurred within 3 months (B. Mullick, E. Kessel, personal communication, 1992). This suggests that use of an additional contraceptive in this period may improve efficacy of the method. However, this may only delay pregnancy failures.

PATIENTS AND METHODS

The study was conducted at the Obstetrics and Gynecology Department of B.L.Y. Nair Hospital of T.N. Medical College in Bombay. Thirty-three women of reproductive age who were awaiting hysterectomy for prolapse or nonmalignant lesions of the cervix, who did not have menorrhagia or gross abnormality of the uterus or endometrium, and were willing to participate in the study were selected. Informed consent was obtained from each subject prior to entry into the study. Group I comprised 10 women and Group II 23 women. Thirty-minute dissolution pellets, each containing 36 mg quinacrine, were deposited transcervically in the upper uterine cavity in the proliferative phase of the menstrual cycle, using a modified Copper-T IUD inserter. In women with clinical diagnosis of dysfunctional uterine bleeding (DUB), curettage was performed, and women with gross endometrial pathology were excluded. Quinacrine was then introduced in these cases only after bleeding stopped. Seven pellets (252 mg) were inserted in each of the Group I women; nine pellets (324 mg) were inserted in Group II women. In each group,

the women had a hysterosalpingogram (HSG) prior to quinacrine insertion (HSG I) and just prior to hysterectomy (HSG II), except for two Group I women whose hysterectomy was delayed as noted below.

Total hysterectomy was performed with removal of as much of the tubes as possible before the end of the sixth week post-insertion in Group I, and between the sixth and the twentieth week post-insertion in Group II. X-rays of the removed uterus and tubes were also obtained after injecting radiopaque dye through the cervical canal of the fresh specimen (HSG III). This last HSG was done to exclude functional or nonpathologic causes (e.g., tubal spasm, tubal plugs, errors in HSG technique) of tubal closure seen on HSG II. Each specimen of uterus and tubes was fixed in 10% formalin and subjected to histologic studies with sections obtained from cervix, endometrium, myometrium and serial sectioning of fallopian tubes as described earlier [12]. The intramural, isthmic, and ampullary portions of the fallopian tubes were sectioned into blocks of tissues taken at 3-mm intervals. Three serial sections were taken from each block. All serial sections were stained with hematoxylin and eosin. Masson's trichrome stain to study muscle tissue and hyalinization was used whenever required.

Detailed evaluation of the light microscopic histologic changes in the tubes was performed, including presence or absence of inflammation, degree and nature of inflammation, degree of necrosis, depth of



FIG. 1. Stage 0 (unaffected tube). Scanner view, x14. The lumen is patent and is lined with intact mucosa and a focal papillary fold. There is no damage to the muscle coat.

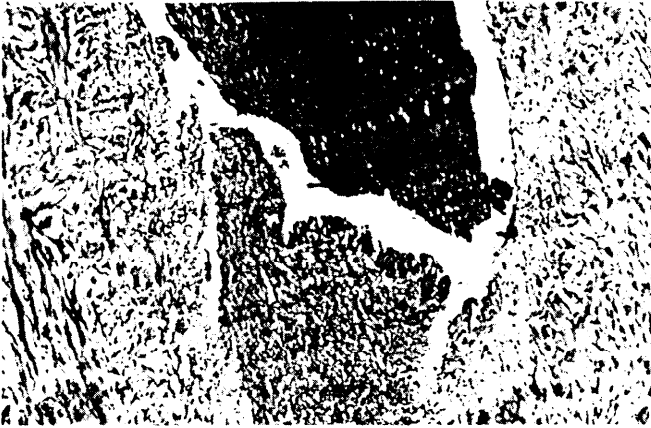


FIG. 2. Stage I (acute inflammation). Low-power view, x150. There is an acute inflammatory reaction with hemorrhage and marked mucosal damage with destruction of inner muscle coat. The lumen is not reduced.

penetration, presence and degree of fibrosis, and status of the tubal lumen. The pathologist was kept blind to the clinical history and the study assignments of the subjects. The histologic appearance of the sections of the tubes was classified into the following four sequential histologic changes:

Stage 0 (Figure 1): Patent tube with normal lumen, intact normal epithelium, minimal or no inflammation in lamina propria, intact normal muscle. We consider this to be a tube unaffected by the chemical.

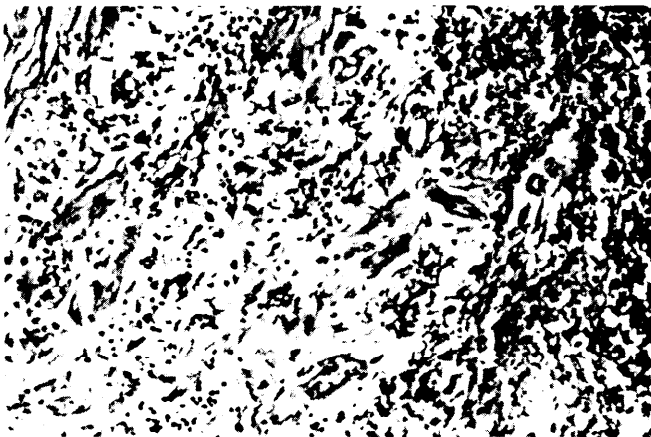


FIG. 3. Stage II (chronic inflammation) Low-power view, x150. The lumen is small with a flat lining. A few scattered inflammatory cells are seen. Distortion of inner one-third of the muscle coat is visible.

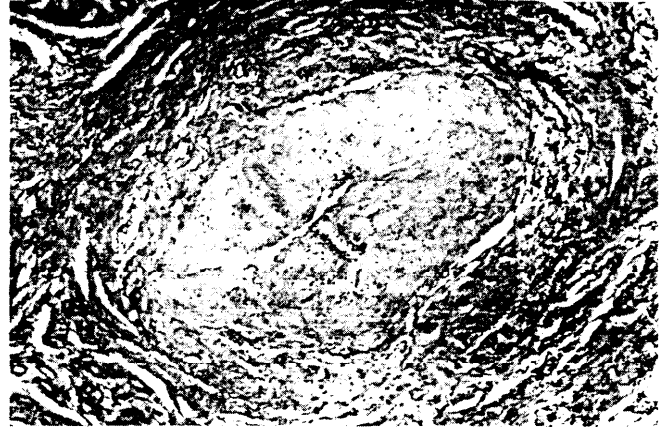


FIG. 4. Stage III (fibrosis and tubal occlusion). Low-power view, x60. There is total reduction in lumen and complete hyalinization of inner two-thirds of muscle coat. Inflammatory cells not seen.

Stage I (Figure 2): Stage of acute inflammation. Damage to epithelium, with slight or no decrease in lumen. Acute inflammatory change in lamina propria, often with hemorrhage. Minimal to moderate damage to inner muscle coat. Areas of necrosis as a result of tissue damage. Heavy infiltration of submucosa and muscle by neutrophils, lymphocytes, and plasma cells with vascular congestion and vasodilatation.

Stage II (Figure 3): Stage of chronic inflammation. Loss of epithelium or flattening of mucosal lining



FIG. 5. Patchy recanalization. Low-power view, x200. A new lumen has formed with a lining of low, cuboidal epithelium. Destruction of inner muscle coat is seen in center of the field beneath the epithelium (arrow).

TABLE I
Clinical features in Group I women, patency status of fallopian tubes on HSC prior to insertion of 252 mg quinacrine, prior to surgery and on the hysterectomy specimen, the quinacrine-hysterectomy interval, and histologic changes in intramural tubes.

Serial no.	Age (years)	Parity	Clinical Diagnosis	Patency Status of Tubes on HSG						Q-H Interval (weeks)	Histologic Staging of Intramural Tubes	
				I		II		III			Rt	Lt
				Rt	Lt	Rt	Lt	Rt	Lt		Rt	Lt
1	40		Dysmenorrhea	P	P	P	P	P	P	2	I	I
2	38	5	CIN	P	P	P	P	P	P	3	I	I
3	35	3	DUB	P	P	Bl	Bl	Bl	Bl	3.5	III	III
4	35	4	CIN	P	P	Bl	Bl	Bl	Bl	4	III	III
5	40	4	Prolapse	P	P	Bl	P	Bl	P	5	I	I
6	50	5	DUB with CIN	P	P	P	P	P	P	5	I	I
7	35	6	?DUB	P	P	P	Bl	P	Bl	5	I	III
8	35	4	Prolapse	P	P	Bl	Bl	Bl	Bl	5.5	III	III
9	36	5	CIN	●	P	P	P	Bl	Bl	6	III	III
10	37	3	Prolapse	†P	P	P	P	Bl	Bl	7	III	III

CIN = Cervical intraepithelial neoplasia
 DUB = Dysfunctional uterine bleeding

HSG I = Prior to quinacrine insertion
 HSG II = Prior to surgery
 HSG III = On the surgical specimen

HSG = Hysterosalpingogram
 Rt = Right
 Lt = Left

Q-H = Quinacrine insertion to hysterectomy
 P = Patent
 Bl = Blocked

†HSG II 2 weeks post-quinacrine. HSG III 7 weeks post-quinacrine.

with marked reduction in lumen. Hyalinization in submucosa and inner muscle coat. Chronic inflammatory cellular infiltrate in lamina propria, submucosa, and the inner muscle coat consisting of lymphocytes and plasma cells.

Stage III (Figure 4): Stage of fibrosis and tubal occlusion. Complete loss of mucosal lining with absence of lumen or severe reduction with a fish mouth slit. Organization of exudate, marked fibrosis of inner muscle coat.

Some Stage III tubes showed a process suggestive of recanalization, characterized by reepithelialization, subepithelial and inner muscle coat hyalinization with formation of a small circulating lumen. However, the lumen is neither lined with normal epithelium, nor continuous with the lumen of the rest of the tube in this series (Figure 5).

RESULTS

Group I

Table I shows patency status of fallopian tubes in women prior to quinacrine insertion (HSG I), prior to surgery (HSG II) and on hysterectomy specimens (HSG III). It also shows the salient clinical features of the women, the quinacrine-hysterectomy interval and the histologic changes in the intramural tubes. In three of the ten women in Group I, both tubes were found to be patent on HSG I, II as well as III. The histologic appearance of intramural tubes in these three cases was of Stage I, and the quinacrine-hysterectomy interval was from 2 to 5 weeks (cases 1, 2, 6). In another three women, both tubes were patent at HSG I, but a bilateral cornual

TABLE II

Clinical features in Group II women, quinacrine-hysterectomy (Q-H) interval, and histologic changes in intramural tube after insertion of 324-mg quinacrine hydrochloride pellets.

Serial NO.	Age (years)	Parity	Clinical Diagnosis	Q-H Interval (weeks)	Histologic Staging of Intramural Tubes	
					Rt	Lt
	37	3	DUB	6	II	III .
2	34	7	CIN	6	III	III
3	43	4	DUB	7	III	III
4	35	3	Prolapse	8	III	III
5	35	4	Prolapse	8	III	III
6	35	5	CIN	8	III	III
7	35	3	Prolapse	8	III	II
8	35	4	CIN	8	III	III
9	30	4	DUB	8	III	III
10	32	3	Prolapse	9	III	III
11	35	3	Prolapse	9	III	III
12	35	2	CIN	9	III	III
13	40	4	Dysmenorrhea	9	III	III
14	30	3	Prolapse	10	III	III
15	40	3	DUB	11	III	II
16	37	6	CIN	11	III	III
17	45	4	CIN	11	III	III
18	36	4	CIN	12	III .	III
19	37	6	DUB	15	III	III
20	40	4	CIN	18	III	III
21	37	3	DUB	18	III	III
22	35	2	PID	20	III	III .
23	35	4	Prolapse	25	III	III

*(III) = Tubes with patchy recanalization. DUB = dysfunctional uterine bleeding, CIN = cervical intraepithelial neoplasia.

block was detected on HSGs II and III. The histologic changes in intramural tubes in these three cases were of Stage III, and quinacrine-hysterectomy interval was between 3.5 and 5.5 weeks (cases 3, 4, 8). In subject 5, HSGs II and III showed right tube blocked and the left tube patent, but the histologic appearance of both tubes was Stage I. In subject 7, HSG II and III showed the right tube patent and the left tube blocked, and the histologic appearance was Stage I for the right tube and Stage III for the left tube. In the remaining two women, HSG II was done at 4 and 2 weeks post-quinacrine inser-

tion and showed both tubes patent; but HSG III was performed at 6 and 7 weeks post-quinacrine insertion (cases 9 and 10), respectively, and showed both tubes blocked.

Group II

In Group II, all 23 subjects had patent tubes on HSG I and all were blocked on HSGs II and III. Table II shows the salient clinical features of women in Group II, the quinacrine-hysterectomy interval, and

TABLE III
Histologic staging by segment of fallopian tube.

<i>Tubal Segment</i>	<i>Total Tubes Examined No. (%)</i>	<i>Histologic Stage</i>			
		<i>0 No. (%)</i>	<i>I No. (%)</i>	<i>II No. (%)</i>	<i>III No. (%)</i>
Group I (252 mg quinacrine)					
intramural	20 (100.0)	0 (0.0)	9 (45.0)	0 (0.0)	11 (55.0)
isthmie	17 (85.0)	6 (35.3)	10 (58.8)	0 (0.0)	1 (5.9)
Ampullary	13 (65.0)	12 (92.3)	1 (7.7)	0 (0.0)	0 (0.0)
Fimbrial	11 (55.0)	11 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Group II (324 mg quinacrine)					
Intramural	46 (100.0)	0 (0.0)	0 (0.0)	1 (6.5)	43 (93.5)
Isthmic	34 (73.9)	6 (17.7)	8 (23.5)	0 (0.0)	20 (58.8)
Ampullary	30 (65.2)	24 (80.0)	6 (20.0)	0 (0.0)	0 (0.0)
Fimbrial	20 (43.4)	17 (85.0)	3 (15.0)	0 (0.0)	0 (0.0)

the histologic changes in intramural tubes. Hysterectomies were performed sometime after the sixth and before the twentieth week except for one patient, who underwent the surgery 6 months after quinacrine insertion. The histologic appearance of the intramural tubes showed Stage III changes in all except three tubes of separate specimens, where it was Stage II change (cases 1, 7, 15).

The sections through the regenerated endometrium, cervix, and myometrium of the uterus in all cases of Groups I and II did not reveal any abnormality, thereby indicating that the chemical has no lasting effect on these structures.

Histologic changes from intramural to the fimbrial end of the fallopian tube showed maximum changes in the intramural section. The effect was minimal on the outer parts of the tube. Table III shows a higher incidence of Stage III changes in the isthmie portion of the tube for Group II, with its higher dose of quinacrine and longer insertion-hysterectomy interval. The effect of the chemical starts from the lumen of the tube but stops short of the level of the outer muscle coat. At hysterectomy, no adhesions or other abnormal changes were detected following any quinacrine insertion.

Clinically, five women complained of some vague hypogastric pain following quinacrine insertion, one in Group I and four in Group II. The pain lasted from a few hours to three days. None required treatment.

DISCUSSION

There is a suggestion from Group I data that hysterosalpingograms taken before 5½ weeks from insertion of 252 mg of quinacrine are likely to show patency of at least one tube. This was the case in seven of the nine subjects. In all nine of these subjects, blocked tubes on HSG were associated with a Stage III histologic change, except one tube of case 5, which showed a Stage I change. This tube may have been blocked by necrotic tissue in the lumen of the tube. Cases 9 and 10, who had early pre-hysterectomy hysterosalpingograms showing patency, went on to show tubal occlusion on the hysterectomy specimens, when hysterectomy was delayed until the sixth and seventh week post-quinacrine insertion. This suggests the reasonable possibility that the progress of inflammation to scarring and

closure takes time, which may vary between individual women. A study by El-Kady and co-workers [13], who used similarly short quinacrine-hysterectomy intervals, also showed predominantly lower stages of inflammation.

To explore the relationship between tubal closure and quinacrine-hysterectomy interval, we pooled data of this and our previous report [4] providing a total of 40 pre-hysterectomy cases. If we consider Stages 0 or I histologic changes in either tube as failure of the procedure and Stage II or III of both tubes as success, the results of the pooled data can be seen for intervals before and after the seventh week quinacrine-hysterectomy interval:

Changes	Interval (weeks)		Total
	0-6	7+	
Success	9	22	31
Failure	7	2	9
Total	16	24	40

P = 0.01 (Fisher's Exact Test)

It does appear that this interval is one factor in success. The hypothesis that prolonging this interval will increase success could be tested by prescribing a contraceptive in clinical trials through the first 6 weeks after the last quinacrine insertion. An injectable progestogen would also promote a proliferative-stage-like endometrium. In fact, application in the proliferative stage appears to increase efficacy of the method [4].

In the same way, a strong dose-response effect is seen in pooling present data with our previous study:

Changes	Dose (mg)			Total
	100*	252	324	
Success	3	5	23	31
Failure	4	5	0	9
Total	7	10	23	40

P = 0.01 (Fisher's Exact Test, 252 mg vs. 324 mg)

*From previous study [4]

One would expect from Group II that a single insertion of 324 mg quinacrine would be highly effective if the women were protected with contraception

until fibrosis and closure occurred. But Table III provides evidence of Stage III tubal damage (58.8 %) extending beyond the intramural portion and likely irreversibility of the method with this dosage in a high proportion of cases. Zipper's group has shown that an adjuvant, an antiprostaglandin, may be a better approach to improving efficacy than a higher dose [3]. The potentiating action of an antiprostaglandin is unknown, but it may relax the muscles at the tubal ostia, permitting more consistent entry of quinacrine into the tube.

As for clinical conditions, in the pooled data, myoma, CIN and prolapse lead to greater success as opposed to other diagnoses, which are mainly DUB:

Changes	Clinical Condition			Total
	Myoma, CIN and prolapse	Others		
Success	21	10		31
Failure	2	7		9
Total	23	17		40

P = 0.02 (Fisher's Exact Test)

Mullick and co-workers [10] and El-Kady and co-workers [14] have shown that the presence of blood lowers efficacy, and this may be the basis for less success in pre-hysterectomy studies among DUB cases. However, dose is still a significant factor even in "other" cases. Neither age nor parity is statistically significant in determining success as we have defined it for pre-hysterectomy studies.

In order to determine the relative importance of the three factors-quinacrine-hysterectomy interval, dose, and clinical condition-that are significantly related to closure of both tubes, a multivariate discriminant analysis procedure was applied to the pooled data. The standard discriminant function coefficients were as follows:

Clinical condition	0.57
Dose	0.55
Quinacrine-hysterectomy interval	0.35

The coefficients for the nonsignificant variables of age and parity were 0.34 and 0.03, respectively. The clinical condition variable is influenced mainly by DUB and we recommend that DUB cases be excluded from future pre-hysterectomy studies

designed to predict efficacy of intrauterine administration of quinacrine. DUB cases are probably poor candidates for sterilization by the quinacrine pellet method—a suspicion that needs confirmation in large clinical trials. The remaining significant variables of dose of quinacrine and quinacrine-hysterectomy interval appear to be the main determinants that may predict tubal closure in women choosing this method of sterilization, with dose being the more important of the two.

CONCLUSION

Our analysis suggests that some early failures of the quinacrine pellet method of nonsurgical female sterilization may be due to the extended time needed for some women undergoing quinacrine-induced inflammation to achieve tubal closure. A prospective clinical trial with and without an additional contraceptive is needed to confirm this hypothesis. While increasing the dose of quinacrine appears to increase tubal closure rates in pre-hysterectomy studies, a better approach to improving efficacy may be the addition of adjuvants to the present doses (or lower doses) of quinacrine now in use for sterilization.

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