

## Studies of quinacrine and of tetracycline for non-surgical female sterilization

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### Abstract

The transcervical quinacrine pellet method developed by Zipper and co-workers is potentially a much needed safe, inexpensive, and effective non-surgical method of female sterilization. This method utilizes an intrauterine device inserter to deposit 250 mg of quinacrine hydrochloride as pellets in the uterine cavity. No complications or side effects, other than temporary pain and oligomenorrhea, have been reported.

Tetracycline has an established track record for safety. It also has been reported to have properties similar to quinacrine as a sclerosing agent, with potential as a non-surgical method using the quinacrine insertion technique.

To expand the experience with quinacrine and to study tetracycline as an alternative, studies were undertaken under the auspices of the Indian Rural Medical Association in Calcutta, India. During the period 14 August, 1979 to 28 June, 1984, 414 women received three insertions of 200 mg of quinacrine. There were 29 failures and a three-year life table failure rate of 8.5. During the period 25 April, 1984 to 28 December 1984, 55 women received three insertions of 200 mg of tetracycline. By 1 June, 1986 there were 32 failures among the 55 cases for a failure rate of 58%. A more recent study using a single dose of 1000 mg of tetracycline also produced unacceptably high failure rates.

Voluntary sterilization is the most prevalent method of fertility regulation, and its use is widespread in both developed and developing countries. The country reporting the highest prevalence of use is the United States, where 31.3% of married women of reproductive age are protected by surgical sterilization or by vasectomy of their husbands [1].

The potential benefits of sterilization are considerable. In the developing world, the risk of maternal and infant mortality is high [2], and such risks are greater for high-parity women, even in developed countries [3]. Maternity is the single greatest cause of death in women of reproductive age in developing countries and is mainly due to high-order pregnancies and births (>4). High-order births (>4) in the least developed countries account for a full one-half of all infant deaths [4]. In most developing countries there is no other feasible health service that could match the positive impact of sterilization on health [5].

Sterilization also offers important socioeconomic benefits. High-parity women tend to belong to the least privileged segments of society. Because higher fertility frequently leads to greater poverty and because sterilization is ultimately the most cost-effective of the available methods, it has the most to offer from a socioeconomic standpoint.

Not to be ignored is the most important role that sterilization must play in maintaining peace and security given the disastrous implications of world overpopulation [6].

### **Non-surgical versus surgical sterilization**

In the developing world, especially in the most populous countries, the demand for sterilization is steadily rising, the preference being for female sterilization. At the beginning of this decade it was estimated that there would be a demand for 180,000,000 sterilizations worldwide during the decade of the 1980s (excluding China), about 80% of the demand appearing in the developing world [5]. This would be a 5-fold increase in demand there and a 20-fold increase in rural areas.

However, at mid-decade the demand continues to far exceed the supply of surgical sterilization services, which are virtually non-existent in the rural areas where approximately 80% of the women live. Because of the fragile condition of health care delivery systems in the developing world and the rural residence of the population, it is unrealistic to expect surgical sterilization to meet the projected need. A non-surgical method must be relied upon.

An acceptable non-surgical female sterilization method has been described as one that is safe, 95% effective, that can be performed by non-physicians on an outpatient basis after a brief training period, and that requires only a single visit by the woman [7]. The transcervical quinacrine pellet method developed by Zipper and colleagues [8] over the last 15 years, which utilizes an intrauterine device inserter to deposit 250 mg of quinacrine hydrochloride as pellets in the uterine cavity, has potential for meeting this description.

### **The quinacrine pellet method**

Studies have shown that quinacrine produces inflammation and fibrosis that is confined primarily to the intramural portion of the Fallopian tube [9]. Quinacrine pellets (250 mg) [8] (Figure 1) are inserted through an IUD inserter (Figure 2) at monthly intervals in the proliferative phase of the menstrual cycle for three insertions.

This method can be performed by non-physicians on an outpatient basis after a brief training period or by any personnel capable of performing an intrauterine device insertion. Most important, the cost of materials for this procedure is very low; approximately US \$1.00. All but the very poorest women in the world can afford this procedure.

In the studies of the quinacrine pellet method reported to date [10-12], which included over 1000 insertions, the method appears to be quite safe. No complications or side-effects, other than temporary pain and oligomenorrhea, have been reported.

Toxicology studies were previously performed and approved by the United States Food and Drug Administration for premarketing requirements of quinacrine used orally as a malaria suppressant drug during World War II by millions of soldiers in the dose of 100 mg daily. In this extensive experience, there were a few cases of dermatitis and rare cases of convulsions or transient toxic psychosis reported; the only common side-effect was discoloration of the skin after chronic use [13]. More recently, toxicology studies of the quinacrine sterilization method in cynomolgus monkeys were encouraging with twice the comparative human dose in the form of a solution for both intravascular and intrauterine administration [14,15].

The major concern with this method has been the potential of toxic psychosis, and with good reason. Earlier studies with a liquid slurry of 1500 mg of quinacrine, 6 times the current dose, did produce a 2% rate of transient toxic psychosis shortly after quinacrine instillation, but this has not appeared with the 250 mg quinacrine pellet method [8].

Neither the optimal dose nor the optimal number of insertions of quinacrine has been firmly established [16]. Recently, Zaneveld and Goldsmith concluded that the animal models used for the study of quinacrine are not adequate for these purposes and that there are no animal models which are known to be appropriate [17]. As with other methods of fertility control, these answers are only going to come from clinical field trials.

Merchant and colleagues [18] recently found in a pre hysterectomy study that greater height of the endometrium may play a protective role against the action of quinacrine. This finding suggests that vacuum aspiration of the uterus just prior to quinacrine insertion would enhance the effectiveness of the procedure. Merchant also found that a recent history of menorrhagia markedly reduced the effects of the quinacrine on the tube with respect to histological changes.

### **Tetracycline as an alternative sclerosing agent**

The potential toxic effects of quinacrine have prompted a search for other drugs that are equally effective in producing inflammation and fibrosis of

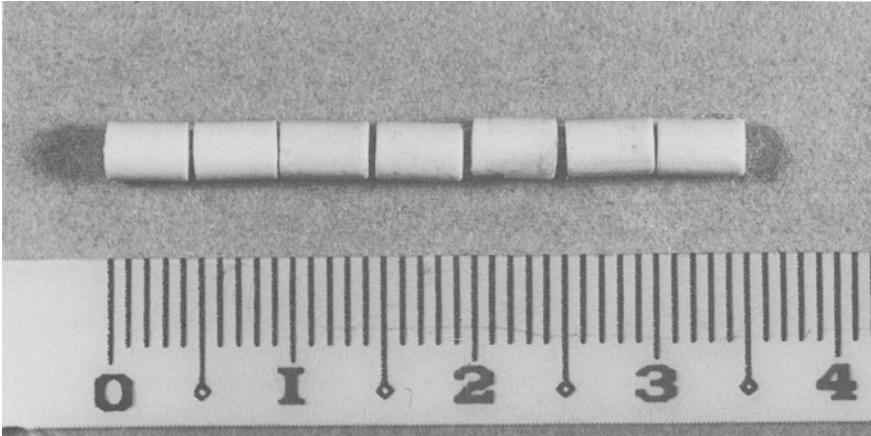


Figure 1 One insertion of quinacrine pellets (250 mg); length in centimetres

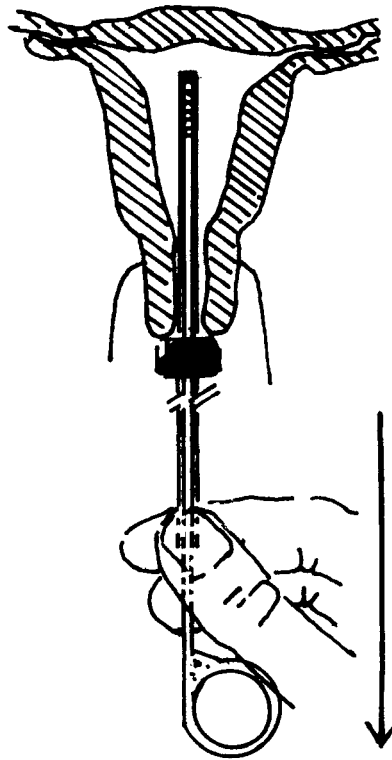


Figure 2 Quinacrine pellet insertion technique using an IUD inserter

the tube but having no known risks of side-effects. Recent studies [17,19,20] indicate that tetracycline hydrochloride may be as effective as quinacrine in producing tubal closures when administered directly to the uterotubal junction. One study [19] has demonstrated that tetracycline when directly applied to the uterine lumen in rats resulted in morphologic changes similar quantitatively and qualitatively to that of quinacrine.

A study of cynomolgus monkeys indicates that the intrauterine administration of tetracycline is capable of inducing lesions in the reproductive tract. These lesions are morphologically comparable to those caused by administering intrauterine quinacrine pellets in this species [20]. Blood chemistry, hematology tests, and liver and kidney biopsies indicate that the dosage used for tetracycline is non-toxic. Blood levels achieved in monkeys following intrauterine pellets or solutions of 100 mg tetracycline are comparable to those levels achieved when 2 g of tetracycline were administered via the intraperitoneal route in women [21,23]. Thus, it is expected that intrauterine instillation of tetracycline in a dose of 1 g in humans would result in blood levels well within the safe range, even in the event of accidental intraperitoneal spillage [20].

Furthermore, studies have demonstrated the sclerotic action of tetracycline in treating neoplastic pleural effusions [23,24]. One randomized study demonstrated greater efficacy in the treatment of pleural effusions with tetracycline compared to quinacrine [24] and the patients treated with tetracycline had less fever and pain. Tetracycline apparently has not been studied as a potentiating agent for the Zipper quinacrine method.

Tetracycline is indeed an attractive alternative to quinacrine because its safety is very well established. Some investigators were being told that tetracycline looked sufficiently promising to cause them to hold up on undertaking quinacrine studies. One large research agency in India delayed the decision to undertake a field trial with the Zipper method when informed that tetracycline would almost surely replace quinacrine. This agency awaited the determination of whether tetracycline produced comparable results before proceeding with planned studies using quinacrine.

## Materials and methods

All cases reported here were performed by the first author at an Indian Rural Medical Association clinic in Calcutta, India. All follow-up was done by the first author and the follow-up reported is until 16 October 1986. At the time of recruitment of these women, they were informed of the risks of failure and that they would be given an MR (menstrual regulation procedure) in the event of failure at no charge. The women were not charged for the non-surgical sterilization procedure, nor were they paid to participate in the research. The costs of these studies were entirely borne by the first author.

The first of the nine studies reported here was undertaken on 14 August 1979 in order to expand on the work of Zipper and others, though a slightly more conservative dose of 200 mg was used. As tetracycline emerged as a possible alternative to quinacrine a 200 mg x 3 insertion series was initiated to examine effectiveness since the safety of

tetracycline was well established. It soon became apparent that at this dose level tetracycline would not be adequate. Since it appeared that tetracycline was having some effect, it was thought that it might enhance the effectiveness of quinacrine and a series using 200 mg of quinacrine and 200 mg of tetracycline was initiated to see if it would serve as a potentiating agent for the quinacrine method.

With the finding of Merchant that increasing height of the endometrium reduced the effects of the quinacrine, a series was initiated in which the uterus was vacuum-aspirated before insertion of the pellets. This procedure was done in order to minimize the height of the endometrium in the hope of increasing the effectiveness of the procedure. This modified procedure was first attempted with the combined 200 mg quinacrine + 200 mg tetracycline procedure. Failures continued. It was decided that the tetracycline may be interfering with the action of the quinacrine and its use as an adjunct was terminated.

It was reported that there were no clinical trials which showed that three insertions of quinacrine were more effective than one. A series using a single insertion of quinacrine after vacuum aspiration of the uterus was initiated. After failures continued, the dose was increased to 300 mg. As follow-up of all uterine vacuum aspiration cases continued, it became apparent that aspiration of the endometrium was reducing the effectiveness of the procedure.

Terminating the use of vacuum aspiration of the uterus, a series using only a single insertion of 300 mg of quinacrine was initiated. The effectiveness was much improved. However, at this point it was decided that the ineffectiveness of the tetracycline method may be due to the low dose used. A series was undertaken using the maximum dose previously determined to be safe in women, 1000 mg. Subsequently, a second series using only a single insertion of quinacrine at a dose of 324 mg was initiated.

The periods of the insertions for all nine studies are given in Tables 1, 2 and 3. The nine studies were done consecutively, the recruitment for one study being completed before the next study was initiated.

## Results

The results of the four studies of quinacrine without aspiration of the uterus are shown in Table 1. Most important, the 414 women who received three insertions of 200 mg each had a 3-year life table failure rate of 8.5. The 41 women who had received a single insertion of 300 mg had a failure rate of 15% after 9-11 months of follow-up. Admission to the study of a single insertion of 364 mg of quinacrine continues with 62 women admitted as of 16 October 1986. There have been no failures with this very limited follow-up (4 months or less). When 200 mg tetracycline was inserted at the time of a single insertion of 200 mg quinacrine, the failure rate was an unacceptable 24% after 20-22 months of follow-up.

The two tetracycline studies, the results of which are shown in Table 2, were both most disappointing. The 200 mg x 3 insertion technique had a failure rate of 58% after 21-29 months of follow-up. The study of a single insertion of 1000 mg of tetracycline showed a failure rate of 34% after only 4-9 months of follow-up.

**Table 1 Quinacrine non-surgical female sterilization: failure rates by dose and number of insertions. Follow-up to 16 October 1986**

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	3	414	14 Aug. 79-28 June 84	29	7*
300	1	41	27 Oct. 85-1 Jan. 86	6	15
200+200 tetracycline	1	50	30 Nov. 84-28 Feb. 85	12	24
324	1	62	9 June 86-24 Sept. 86	0	0

\* 3-year life table failure rate = 8.5

**Table 2 Tetracycline non-surgical female sterilization: failure rates by dose and number of insertions. Follow-up to 16 October 1986**

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	3	55	25 Apr. 84-28 Dec. 84	32	58
1000	1	102	4 Jan. 86-10 June 86	35	34

**Table 3 Quinacrine non-surgical female sterilization following vacuum aspiration of the uterus: failure rates by dose and number of insertions. Follow-up to 16 October 1986**

Quantity (mg)	No. of insertions	Total clients	Period of insertions	No. of failures	% failures
200	1	17	12 June 85-8 July 85	4	24
300	1	50	14 July 85-26 Oct. 85	15	30
200+200 tetracycline	1	50	28 Feb. 85-11 June 85	12	24

The results of the studies, which included the vacuum aspiration of the endometrium, are shown in Table 3. Failure rate for these studies ranged from 24% to 30% with 12-19 months of follow-up.

In none of these nine studies was there a single serious complication or side-effect.

## Discussion

While the 414 women accepting the three insertion-200 mg method had a 3-year life table failure rate of 8.5, this method has much to offer the tens of millions of women who have no hope of ever having a surgical sterilization operation. The study of a single insertion of 300 mg of quinacrine suggests that this method has promise, but the failure rate of this method cannot be established with these small numbers and with this short follow-up period. The study of a single insertion of 324 mg of quinacrine also shows promise but suffers from the same shortcomings.

The two studies of tetracycline all but rule out the use of this chemical for this purpose. Though sclerosing may occur in some cases, the

failure rate is unacceptably high. When used with quinacrine, it might even interfere with the action of the quinacrine on the tubes in ways that are not clear.

Vacuum aspiration of the uterus for the purpose of diminishing the heights of the endometrium for the purposes of enhancing the effectiveness of quinacrine is counterproductive. The reason for this may be related to Merchant's finding that there was a markedly reduced effect of the quinacrine on the tubes in women who had a recent history of menorrhagia. It may be that the presence of blood at the time of insertion of the quinacrine in some way reduces the effect of the quinacrine.

These studies suggest that a three-insertion technique of quinacrine for chemical female sterilization does show promise, though the best dose level has not yet been established. They also show that a single insertion technique may possibly be as effective or nearly as effective as a three-insertion technique.

An important lesson learned from these studies is that research of the quinacrine pellet three-insertion method should continue with all deliberate speed. We should not be distracted by possible alternatives, such as tetracycline, until the alternatives have been well proven.

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### Resumé

La méthode d'implantation transcervicale de pellets de quinacrine mise au point par Zipper et ses collaborateurs est potentiellement une méthode non chirurgicale beaucoup plus sûre, meilleur marché et efficace de stérilisation féminine. Cette méthode utilise un dispositif d'insertion intra-utérine pour déposer, dans la cavité utérine, 250 mg de chlorhydrate de quinacrine sous forme de pellets. Aucune complication ou réaction secondaire n'a été signalée, si ce n'est des douleurs et une oligoménorrhée passagère.

Par ailleurs, la tétracycline présente une sécurité largement établie. On a également signalé qu'elle avait des propriétés similaires à celles de la quinacrine en tant qu'agent sclérosant et qu'elle pourrait être utilisée comme méthode non chirurgicale en appliquant la technique d'insertion de la quinacrine.

Des études ont été entreprises sous l'égide de l'Association indienne de médecine rurale à Calcutta (Inde), dans le but d'élargir l'expérience acquise avec la quinacrine et d'étudier la tétracycline en tant que méthode de remplacement. Au cours de la période du 14 août au 28 juin 1984, 3 insertions de 200 mg de quinacrine ont été pratiquées sur 414 femmes. On a constaté 29 échecs et, d'après une table de survie portant sur 3 ans, un taux d'échec de 8.5%. Au cours de la période du 25 avril 1984 au 28 décembre 1984, 55 femmes ont reçu 3 insertions de 200 mg de tétracycline. Au 1 juillet 1986, il y avait eu 32 échecs parmi les 55 cas, soit un taux de 58%. Une étude plus récente basée sur une seule insertion de 1000 mg de tétracycline a également produit une proportion d'échecs d'une importance inacceptable.

### Resumen

El método transcervical de comprimidos de quinacrina desarrollado por Zipper y colaboradores, es potencialmente un método no quirúrgico que hacía mucha falta, seguro, económico y efectivo para la esterilización femenina. Este método utiliza un insertador de dispositivos intrauterinos para depositar 250 mg de comprimidos de hidrocloreto de quinacrina en la cavidad uterina. No se han denunciado otros efectos colaterales mas que dolor pasajero y oligomenorrea.

La tetraciclina tiene una trayectoria establecida con antecedentes de seguridad. También se sabe que posee propiedades similares a la quinacrina como agente esclerosante, con potencial para método no quirúrgico usando la técnica de inserción para la quinacrina.

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Para aumentar la experiencia con quinacrina y estudiar la tetraciclina como alternativa, se hicieron estudios auspiciados por la "Indian Rural Medical Association" en Calcutta, India. Durante el período des de agosto 14, 1979, hasta junio 28, 1984, 414 mujeres recibieron 3 inserciones de 200 mg de quinacrina. Ocurrieron 29 fracasos y la tabla de vida a tres años dió una tasa de fracasos de 8.5. Durante el periodo de abril 25, 1984, a diciembre 28, 1984, 55 mujeres recibieron 3 inserciones de 200 mg de tetraciclina. Hasta julio 1, 1986, ocurrieron 32 fracasos entre los 55 casos, con una tasa de fracasos de 58%. Un estudio más reciente, usando una dosis única de 1000 mg de tetraciclina, también produjo tasas altas no aceptables de fracasos.