



## Transcervical quinacrine sterilization: clinical experience

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### Abstract

**Objective:** To review the use of quinacrine pellets for non-surgical female sterilization. Background: The transcervical insertion of quinacrine pellets has been under study for over 15 years. It could potentially expand access to sterilization services, because it is relatively simple to administer, with the use of a modified IUD inserter, and is inexpensive. **Methods:** Published and unpublished data are reviewed. **Results:** The short-term safety of transcervical quinacrine appears to be better than surgical sterilization, but it is less effective, especially among women under 35, and there are virtually no data on its reversibility. Thus, it is probably most appropriate for older women, aged 35 and over, but it could be an option for others where access to surgical sterilization is limited. **Conclusion:** The use of quinacrine pellets for female sterilization needs to be reviewed by appropriate regulatory authorities, especially with regard to long-term safety issues, and additional clinical studies are needed to better define a standardized regimen.

**Keywords:** Quinacrine; Tubal sterilization; Side effects; Clinical trials; Contraception; Review

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### 1. Introduction

The use of quinacrine for non-surgical female sterilization was first proposed by Zipper et al. [1]. The method now most commonly used involves two transcervical insertions of seven pellets of quinacrine, each containing 36 mg of quinacrine hydrochloride, for a total dose of 252 mg per insertion. The pellets are inserted into the uterus using a modified intrauterine device (IUD) inserter. The pellets dissolve within about half an hour. Insertions are given at monthly intervals during the proliferative phase of the menstrual cycle. Quinacrine is cytotoxic and produces necrosis of the endometrial lining of the uterus and inflammation of the intramural portions of the Fallopian tubes. Although the endometrium regenerates itself, the Fallopian tubes are perma-

nently scarred in a high percentage of women. Different investigators have used different numbers of insertions, different doses and various adjuvants.

In the older scientific literature, quinacrine is often referred to as mepacrine or atabrine (Winthrop Pharmaceuticals). It was synthesized in Germany in the 1920s and first used for anti-malarial therapy in the 1930s. It is an acridine derivative and at room temperature is a yellow powder. The presently approved indications of quinacrine in the United States (US) are for the treatment of giardiasis, tapeworm infections and malaria [2]. However, these indications may not reflect its major current uses since it is no longer the drug of first choice for these indications. Quinacrine has also been used as a non-steroidal

anti-inflammatory drug in the treatment of lupus erythematosus, and as a sclerosing agent for the pleural and peritoneal cavities. Reviews of quinacrine and of its use in rheumatic diseases have been published [3,4].

This report presents a brief historical perspective on the clinical use of quinacrine and reviews the data on safety and efficacy as they are relevant to the clinical use of quinacrine pellets for non-surgical female sterilization. Some tentative conclusions are drawn concerning the safety and efficacy of quinacrine pellet sterilization. This paper will not directly address issues related to the delivery of sterilization services, such as counseling and informed consent.

## 2. Safety

### 2.1. Background

There are data from over 50 years of use regarding systemic toxicity from both acute and chronic administration of large doses of quinacrine in humans. During World War II, with the restriction of supplies of quinine by the Japanese, and the high rate of malaria in the Pacific theater, an emergency research program was mounted to test various substitutes for quinine. Quinacrine was chosen for the prevention and treatment of malaria. There are data on acute toxicity for several routes of administration from studies associated with the World War II malaria effort and from other medical uses.

As Paracelsus, a German scientist, said in the 16th century, "All substances are poisons; there is none which is not a poison. The dose differentiates a poison and a remedy". There is no question that at high doses quinacrine can be toxic. When chloroquine became available shortly after World War II, quinacrine became obsolete as an anti-malarial, because chloroquine was more effective with less frequent administrations (weekly versus daily) and with fewer side effects.

The dosage of quinacrine most commonly used for non-surgical female sterilization (two transcervical insertions of 252 mg each, one month apart) is lower than the dosages used for other purposes. The adult dosage for treatment of giardiasis, for example, is 100 mg three times daily for 5-7 days.

There are data on chronic toxicity from the experience of roughly two million US soldiers serving in the Pacific who received quinacrine at much higher doses than those used in quinacrine pellet sterilization.

**Chronic toxicity.** In World War II, soldiers usually took 100 mg of quinacrine orally per day, 6 or 7 days per week, for malaria prevention, although sometimes a dose of 200 mg per day was used. This prophylactic dose was continued for months or years, as long as soldiers were in malarial areas. Treatment for malaria involved a loading dose of about 1000 mg on the first day, and then smaller doses for 6 days for a total dose of 2800 mg in a week [5].

Major toxicity due to long-term quinacrine use was well-documented among soldiers. Quinacrine is eliminated from the body very slowly and levels build up with long-term administration. In soldiers, toxicity was rarely reported with less than a month of exposure or ingestion of about 3000 mg.

Long-term oral administration of quinacrine causes yellow skin discoloration in about one-third of individuals [5]. Various types of skin rashes were the most common side effect of quinacrine therapy, occurring in 1 in 2000 soldiers taking 100 mg per day and in 1 in 500 soldiers taking 200 mg per day. The rashes were of two basic but sometimes overlapping types, **eczematoid** or **lichenoid**. Some of the rashes were quite severe and there was a small number of fatal cases of exfoliative dermatitis attributed to quinacrine use [6]. In a review of his experience, Bauer reported that men with eczematoid reactions did not have permanent sequelae, but a small number of the men with severe lichenoid or exfoliative dermatitis developed late sequelae [7]. Among 11 men that Bauer reported, he described some serious late complications of these skin lesions: (a) one death due to hyperthermia secondary to **anhidrotic** skin (inability to sweat), and (b) three men whose chronic lichen planus-like lesions degenerated into squamous cell carcinoma. The average cumulative dose of quinacrine before onset of a rash that left permanent sequelae was 24 800 mg. Bauer estimated that among the 120 000 Australians who took quinacrine, there were about 12 men who had late sequelae.

**Aplastic** anemia was also noted among military personnel and occurred at a rate of 2-3 per 100 000 soldiers [8]. Custer reported that, of the 47 cases attributed to atabrine among US soldiers, the men had been taking the drug from 1 to 34 months, with the majority having taken the drug for between 4 and 14 months. About half of the cases were preceded by a skin rash. There have also been rare reports of hepatitis associated with long-term oral quinacrine use.

Since World War II, rare cases of **aplastic** anemia have been reported following long-term use of quinacrine for lupus erythematosus, but neither we nor the manufacturer (Sanofi Winthrop) are aware of any reports of **aplastic** anemia following the short-term use of quinacrine. The serious effects associated with chronic use are very rare and appear to be related to the high cumulative doses used for malaria and lupus erythematosus.

**Acute toxicity.** Acute toxicity data from administration of quinacrine are available for the following routes: oral, intravenous, intramuscular and intraperitoneal. Local toxicity from oral administration was examined in 12 men by gastroscopy in a study by the US Army Malaria Research Unit [9]. They reported a small zone of hyperemia of the gastric mucosa around the quinacrine tablet. The central nervous system (CNS) effects of quinacrine were examined in a small, well-controlled study of oral administration in five men with doses of 200–1200 mg per day given over 7–10 days [10]. Quinacrine produced CNS stimulation resulting in sleeplessness, nightmares and transient electroencephalogram (EEG) changes. Before the **toxicity** became disagreeable, subjects reported that they had high energy levels and got more work done than usual. Low-dose oral administration often produces headache, dizziness or gastrointestinal symptoms, but these usually disappear with continued administration or lowering of the dose to 50 mg per day.

Toxic psychoses occurred in about one per 1000 soldiers during treatment for malaria. These reactions were associated with total dosages of 1400–6300 mg over the course of a few days [11].

A small study of intravenous administration was tried for malarial therapy, but was quickly

abandoned [12]. Among six men who received 500 mg intravenously, two developed transient but severe toxicity, including depressed respiration and a seizure.

Detailed studies were also done to look at the effects of intramuscular injections [12]. Twelve men received intramuscular injections of 400 mg followed by oral administration. No toxicity was reported, except for local pain following the injections. Subsequently, for men too ill to take oral quinacrine, it was recommended that treatment be started with two simultaneous injections of 200 mg each for a total of 400 mg [5].

One of the concerns that has been raised about sterilization with quinacrine pellets is the possible toxicity that might result if the inserter perforated the uterus and the pellets were deposited in the abdominal cavity instead of the uterus. There are some data relevant to this concern in the cancer literature. Quinacrine solutions have been injected into the abdomens of cancer patients for the treatment of recurrent malignant effusions. In one study [13], treatments were administered on successive days for 1-6 days. A dosage of 400 mg was given each day, dissolved in saline before administration, which would probably lead to more rapid absorption than in the case of quinacrine pellets. Patients who received one or two injections (800 mg or less) had relatively mild toxicity. Most patients who received three or more injections (1200 mg or more) had severe abdominal pain with ileus and fever, and some of them also experienced CNS toxicity. The fact that there were only relatively mild side effects after one or two injections suggests that the consequences of accidentally depositing quinacrine pellets in the abdomen would not be serious. However, no firm conclusions should be drawn from these data because of the different dosage forms and the diseased state of the peritoneum among the cancer patients.

## 2.2. *Intrauterine administration*

Acute toxicity data from intrauterine administration are available from nearly 20 years of clinical studies. Most of this work was pioneered by Dr. Jaime Zipper in Chile, who developed an animal model using the rat uterus and who has

done numerous animal studies dating back to the 1960s. In the 1970s, a number of studies were done in women with quinacrine suspensions or slurries, but the use of slurries was abandoned due to their toxicity. Family Health International (FHI) worked with Zipper to develop less toxic preparations. One other abandoned approach involved the application of quinacrine to the arms of an IUD [14], which was initially tested in a pre-hysterectomy study. The quinacrine pellet method appeared to be the most promising and, in 1981, FHI decided to seek approval from the US Food and Drug Administration (FDA) to market quinacrine pellets in the US for non-surgical female sterilization. The FDA granted FHI an Investigational Exemption for a New Drug (IND) and FHI subsequently began Phase I studies of quinacrine pellets. In what follows, we will briefly describe the experience with quinacrine slurries and then discuss the safety of quinacrine pellets in more detail, including concerns regarding both acute and chronic effects.

*Quinacrine slurries.* From 1970 to 1979, about 1109 cases treated with quinacrine slurries were reported in the literature. Doses ranged from 250 to 3000 mg per insertion, and various adjuvants were used. It was concluded that three instillations were needed for reasonable efficacy, i.e., about 90% or more. Most of the instillations were performed by Zipper, but at least five other investigators in four countries were also involved.

Serious CNS excitation requiring sedation was noted in 2% of patients in one well-controlled trial [15]. The acute CNS excitation observed with the quinacrine slurry was transient and easily treated, but may have been indicative of dangerously high blood levels. While a small degree of CNS stimulation is a common side effect even with low doses of oral quinacrine, the effects seen by Zipper with the slurry were characterized by “nervousness, vertigo, irritability, emotional change and transient psychoses” [15]. Zipper has not seen any women with similar CNS effects following the use of quinacrine pellets.

Although no deaths were reported in the literature, three deaths were reported to the FDA and the manufacturer following the use of quinacrine slurries, two in the US and one in Bangladesh. At

least two of the deaths also involved the use of lidocaine and they occurred within minutes after instillation of the slurries. It was not clear whether these two deaths might have been due to intravascular spill of the lidocaine or of the quinacrine, but they led to the suspension of all work with slurries.

*Quinacrine pellets: acute toxicity.* Work with quinacrine pellets began in the late 1970s and FHI conducted a Phase I, single-dose pre-hysterectomy study in 1983-84 in the US. Under an IND, an FHI-sponsored 24-h pre-hysterectomy study of quinacrine pellets gathered detailed safety and pharmacokinetic data from ten volunteers over a 24-h interval between a single transcervical administration of quinacrine pellets and hysterectomy [16].

Adverse effects following the insertions were cramping pain and headache. Plasma, saliva and urine concentrations were measured over the 48 h following insertion. Compared to the military pharmacokinetic studies, the plasma levels found after intrauterine administration were similar to those found after oral administration. Quinacrine has a long half-life in humans, as do other anti-malarial drugs, and two women still had detectable levels of quinacrine at 446 weeks after the insertion and surgery. An analysis of tampons collected 24 h after insertion showed that about 25% of the quinacrine leaks out of the cervix into the vagina.

FHI cancelled its IND, and did not proceed to Phase II clinical trials for various reasons, including concerns about the number of insertions needed and quinacrine's mutagenicity. However, other researchers pursued studies of quinacrine pellets and, between 1977 and 1992, approximately 50 000 insertions of quinacrine pellets were performed [17]. Doses ranging from about 180 to 324 mg were used, and from one to three insertions were usually given at 1-month intervals in the proliferative phase of the menstrual cycle. The most commonly used protocol in recent years has involved two insertions of 252 mg, with or without adjuvants. These studies have been conducted in numerous countries.

The uterine cramping associated with quinacrine pellet insertion is similar to that expe-

rienced with an IUD insertion or menstruation. About 9-25% of women complain of cramping pain or lower abdominal pain following the insertion. Other minor, transient complaints include backache, vaginal bleeding, fever, headache and dizziness. The leakage of quinacrine from the uterus into the vagina causes vaginal pruritus in some women. Amenorrhea and irregular menstruation of several months' duration have been reported in 1–20% of women and may be more frequent in women who have had multiple insertions.

Major complications from the use of quinacrine pellets are rare. In a series of over 30 000 cases in Viet Nam, Hieu et al. [18] reported eight women with major complications for a rate of 0.03%, or about one per 4000 women. There were two cases of severe bleeding, one immediately following quinacrine insertion and one a year later. One woman had an allergic reaction consisting of severe pruritus. Three women had hysterectomies, two women with synechia and one woman with chronic pain. One woman had pelvic inflammatory disease (PID) 18 days after insertion and one woman had premenstrual pain and dysmenorrhea.

Three cases of presumed uterine perforation have been reported. One reported by Zipper et al. [19] resulted in about 48 h of severe pelvic pain. The woman was treated with penicillin and the incident resolved without apparent sequelae. Two perforations reported by Mullick were described by El Kady et al. [20]: "The women experienced transient lower abdominal pain, and one woman had tinnitus for 3 days. Neither woman required hospitalization". No information was provided as to whether any treatment was given. In their large series, Hieu et al. reported no cases of uterine perforation. They ascribed their absence to the vast experience of Vietnamese clinicians with IUD insertions and abortions; however, it is possible that some occurred but went unnoticed.

Significantly, despite its use in an estimated 70 000 women by 1994, no deaths have been reported immediately following quinacrine pellet insertions. In 70 000 surgical sterilizations in the developing world, about two to seven fatalities would have been expected, based on large international experience [21]. In summary, acute toxicity

from the use of quinacrine pellets for sterilization appears minimal and this is consistent with experience from other routes of administration.

**Non-cancerous uterine disorders.** Following multiple (but not single) quinacrine pellet insertions, there may be abnormal endometrial lesions [22,23]. Occasional cases of uterine synechiae with hematometra have been reported. Synechiae or cervical stenosis and subsequent hematometra may also occur following abortions, cone biopsies for cervical abnormalities or other gynecological procedures. In the absence of symptomatic hematometra, most authors have not attributed any clinical importance to endometrial lesions caused by quinacrine, but this issue has not been carefully studied.

**Ectopic pregnancy.** Ectopic pregnancies occur rarely with the use of all forms of female contraception, including female sterilization. In a review of the rates of ectopic pregnancies associated with IUDs, Sivin [24] noted that in assessing the risk of ectopic pregnancies, non-contraceptors are the appropriate comparison group, however not all authors agree [25]. The occurrence of ectopic pregnancies can be expressed as a ratio per 100 or per 1000 pregnancies or as a rate per 1000 woman-years. While the ratio of ectopic pregnancies per 100 pregnancies is increased during IUD use or after surgical sterilization, the rate of ectopics per 1000 woman-years is decreased compared to non-contraceptors.

Published reports of 3–4-year follow-up data from small trials of transcervical quinacrine pellet sterilization in Chile (151 women) [26] and India (81 women) [27] did not find any ectopic pregnancies. Data from the larger trial in Viet Nam [18] suggest that in the short-term the risk of ectopics after quinacrine sterilization is similar to the risk in IUD users. Based on Sivin's estimates, IUD users have an ectopic pregnancy rate per 1000 woman-years that is less than half the rate in non-contraceptors. Long-term follow-up data from Chile show that ectopic pregnancies can occur up to 10 years after quinacrine sterilization; however, the rate of ectopics per 1000 woman-years is below the rate that would be expected among non-contraceptors (Sokal et al., manuscript in preparation).

Regarding the long-term risk of ectopics, there may be a surprisingly high rate of ectopic pregnancies after some forms of surgical sterilization. Preliminary data have been presented from a Centers for Disease Control and Prevention (CDC) long-term follow-up study of female sterilization in the US, the Collaborative Review of Sterilization (CREST) [28]. The preliminary results suggest that both intrauterine and ectopic pregnancies may be more frequent than previously realized. The CDC data for sterilization using bipolar electrocautery show a cumulative life-table pregnancy rate of 2.8 per 100 women followed up for 10 years (Wilcox LS, Jamison P, Peterson HB, Hughes J. Ten-year pregnancy rates after unipolar and bipolar sterilization. Presented: 47th Annual Meeting of The American Fertility Society, Orlando, FL, 1991; Abstract no. o-028). At least half of those pregnancies are likely to be ectopic [29]. Most surgical sterilizations in developing countries are done using the Pomeroy technique. Based on US data, ligation procedures such as the Pomeroy technique appear to have a lower risk of later ectopic pregnancy than laparoscopic electrocautery [25]

*Carcinogenicity: human data.* There are some human data on the possible risk of cancer from the intrauterine use of quinacrine, but not sufficient to draw any firm conclusions. It is beyond the scope of the present article to review the issues involved in deciding whether quinacrine is likely to be a human carcinogen. However, we will briefly discuss some data relevant to the use of intrauterine quinacrine.

In comparison with the total doses used for female non-surgical sterilization, enormous oral doses of quinacrine were taken by about two million US military personnel and about 120 000 Australians in the Pacific during World War II. However, a search of the literature has not shown any follow-up studies that have tried to assess the risk of cancer from quinacrine among these men and women.

A cluster of eight cancers was detected during long-term follow-up of 572 women who had undergone transcervical quinacrine sterilization in Chile. This led FHI to commission a review of the potential carcinogenicity of quinacrine (Tice RR,

Griffith J, Recio L. An evaluation of the mutagenicity and carcinogenicity of quinacrine, 1990. Unpublished report) and to conduct a larger retrospective cohort study of all women in Chile who could be identified as having received quinacrine pellets. Tice et al. concluded that quinacrine was unlikely to be a human carcinogen. However, since quinacrine was marketed before the use of modern screening methods, Tice recommended that quinacrine be evaluated with modern mutagenicity tests and that any other available human exposures be reviewed.

The initial cluster of eight cases of cancer in Chile included a single case of uterine leiomyosarcoma. No other cases of leiomyosarcoma were identified in the larger retrospective cohort study of 1492 women, and it was concluded that the cluster was probably a random event [30]. However, the size of the cohort is not large enough to permit one to reject the possibility of a small or moderate increase in cancer risk. The cohort is being followed up for at least an additional 5 years, through 1996.

Although epidemiological studies have shown no obvious risk factors for the occurrence of uterine leiomyosarcoma based on demographic characteristics or reproductive health histories [3 1,321, cases of leiomyosarcoma often have chromosomal abnormalities, and cases at other anatomic sites have been associated with exposure to drugs. A number of reported cases of bladder leiomyosarcoma have been attributed to cyclophosphamide therapy [33], and a single case of small bowel leiomyosarcoma has been reported following chronic use of anthraquinone [34], an over-the-counter laxative compound. Cyclophosphamide is an alkylating agent that bonds covalently with DNA. Anthraquinone is mutagenic and causes intestinal tumors in rats. Quinacrine does not make covalent bonds with DNA and did not cause intestinal tumors in rats in an FDA study discussed below [35].

*Carcinogenicity: non-human data.* Quinacrine is positive in the Ames test and is clearly a mutagen. It binds to DNA through intercalation, not through covalent bonding. Its mutagenic effects may be similar to the mutagenic effects of chloroquine, another antimalarial presently in

worldwide use, which is also an intercalator. Other acridines which bind more strongly to DNA than quinacrine (e.g., acridine orange and proflavine) have not been shown to be carcinogens in animals [36]. Agents which bind to DNA through covalent bonding are considered to be much more dangerous in terms of mutagenicity and potential carcinogenicity. Quinacrine is an anticarcinogen in some animal models [37,38], in one model apparently because it reduces the production of arachidonic acid through its inhibition of phospholipase A2 [37].

In the context of intrauterine administration, a theoretical concern is that quinacrine will be present at the time of tissue injury and to a lesser extent during tissue repair. Toxicological studies have suggested that the occurrence of tissue injury and continuous exposure to high concentrations of a chemical during the cell multiplication accompanying the repair process may be an important factor in determining whether a chemical causes cancer in animals. This concept has been the rationale for serious criticisms of animal carcinogenicity trials which use maximum tolerated doses of the drugs in question [39].

The relevance of this concern for the use of intrauterine quinacrine is unclear because the same argument could be applied to sterilization with electrocautery. Millions of surgical sterilizations have been done with the use of unipolar or bipolar electrocoagulation and have not led to cases of cancer, despite the simultaneous presence of tissue injury and animal carcinogens. The production of animal carcinogens during cooking is well-documented, and the burning of human tissue by electrocoagulation probably produces some of the same or similar compounds.

Recent bibliographic work has unearthed three articles from the old toxicological literature that were apparently overlooked by other reviewers, probably because those publications were too old to appear in computerized databases. The three articles suggest that acridine, acridine homologs and quinacrine are not carcinogenic [35,40,41]. Kennaway [40] reviewed studies that were performed to identify the carcinogenic constituents of coal tar, and concluded that acridine was not carcinogenic. In the introduction to a 1956 article,

Lacassagne et al. [41], citing their own data and data from Kennaway and others, concluded that acridine and its homologs are not carcinogens. A 1945 paper by Fitzhugh et al. [35] reported a chronic, lifetime toxicity study of oral quinacrine in rats done by the FDA. The study concluded that quinacrine was not carcinogenic in rats.

However, these studies cannot substitute for a modern re-evaluation of quinacrine in accordance with current toxicological and regulatory standards, and of course none of them used a **transcervical** route of administration. More recently, Nasim and Brychcy [36] noted that "Up until now, only those chemicals that interact covalently with DNA have been shown to be both mutagens and carcinogens. As acridines [including quinacrine] belong to a class of compounds which **intercalate** DNA and do not bind covalently, it is therefore of major importance that further investigations be carried out..."

Four studies of quinacrine's mutagenicity using modern assay systems were completed in February, 1995, by an independent US laboratory. Quinacrine was positive in the Ames test, the mouse lymphoma test and the in vitro mammalian cytogenetic test (Chinese Hamster ovary cells), and negative in the micronucleus **cytogenetic** assay in mice. Based on these results, FHI believes that additional pre-clinical studies are needed.

*Contraindications for transcervical use.* The general contraindications and precautions for the use of quinacrine are described in standard texts and include warnings against using quinacrine in pregnant women and in people with a history of psychosis or seizures. Relative to its transcervical use, an additional exclusionary criterion has been used in clinical trials [20]: evidence of any significant pelvic pathology, including pelvic inflammatory disease, adnexal masses or tumors, suspicion of malignancy of the reproductive organs, or the presence of uterine anomalies.

### 3. Efficacy of quinacrine pellets for female sterilization

A large number of clinical studies have been done by various investigators in several countries,

but it is difficult to draw conclusions from much of the data because of limitations in study design. Illustrative estimates of crude pregnancy rates from the use of quinacrine pellets without adjuvants are: about 5% at one year after one insertion [18]; 3.7% at 4 years after three insertions [27]; and 8% at 10 years after three insertions (Sokal and Zipper, Long-term pregnancy rates following quinacrine pellet sterilization, manuscript in preparation). A recent study using adjuvants and supplementary contraception for the first few months after quinacrine insertion has found a lower pregnancy rate, 0.7% at 18 months following a single insertion (Mullick et al., manuscript in preparation). The two major limitations of the reported studies are small sample sizes and the use of historical controls. In addition, the absence of a consensus on a standard regimen, i.e., number of doses, insertion technique and use of adjuvants, makes it difficult to give any single representative estimate of efficacy. This section will discuss the major factors which appear to affect the efficacy of quinacrine pellet sterilization.

### 3.1. Timing of insertions

Based on his work with quinacrine slurries, Zipper [42] concluded that quinacrine instillations were more effective when given during the proliferative phase of the menstrual cycle. This is biologically plausible, as the endometrial lining is lower and the tubal ostia are more easily accessible at that time. Prehysterectomy data from Merchant et al. [23] following quinacrine pellet insertions in 33 women, show that pellets produced more frequent occlusions when administered earlier in the menstrual cycle. Although Merchant did not perform any statistical testing of that data set, we reanalyzed her Tables 2 and 3. The data show that the average day of the cycle of insertions for 'successes' was day 12.1, while the average day of the cycle for 'failures' was day 16.1,  $P < 0.01$  using Student's test. The definition of 'success' was tubal occlusion as demonstrated by histopathology. Recent work by El Kady et al. [20] has shown that bleeding at the time of insertion seems to be associated with a lower rate of tubal closure, and this is also supportive of Zipper's conclusion, since bleeding is

probably more likely if an insertion is done in the secretory phase in the presence of a thicker endometrium (Table 1). Based on a multivariate analysis of her prehysterectomy data, Merchant suggested that quinacrine was likely to be less effective in women with dysfunctional uterine bleeding [43].

### 3.2. Number of insertions/supplementary contraception

Data from several studies suggest that giving more than one insertion, one month apart, improves the efficacy of quinacrine pellet sterilization. Data from Mullick et al. [44], El Kady et al. [20] and Hieu et al. [18] suggest that three insertions are more effective than one or two, and that two insertions are better than one. Data from prehysterectomy studies by Merchant et al. [43] of single insertions in 40 women suggest that the reason for the different efficacy rates by number of insertions may be more complex than originally thought. Merchant's data suggest that the inflammatory and fibrotic process takes at least 6 weeks to complete (Table 2). She recommended a study of a supplementary form of contraception for 6 weeks following the last quinacrine insertion. Zipper, however, does not feel that supplementary contraception is needed. In his clinic, he tells women to refrain from sex for one week after each insertion, and does not recommend the use of any supplementary form of contraception. He

Table 1

Closure of both tubes on hysterosalpingogram by bleeding at insertion, and all cases after two and after two or three insertions of quinacrine pellets among 159 Egyptian women

	Total cases	Closures after two insertions	Closures after two or three insertions
No bleeding	52	42 (80.8)	52 (100.0)
Bleeding at insertion	107	74 (69.2)	97 (90.7)
All cases	159	116 (73.0)	148 (93.7)

Source: El Kady AA, Nagib HS, Kessel E, editors. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril* 1993; 59: 301–304.

"Values in parentheses are percentages.

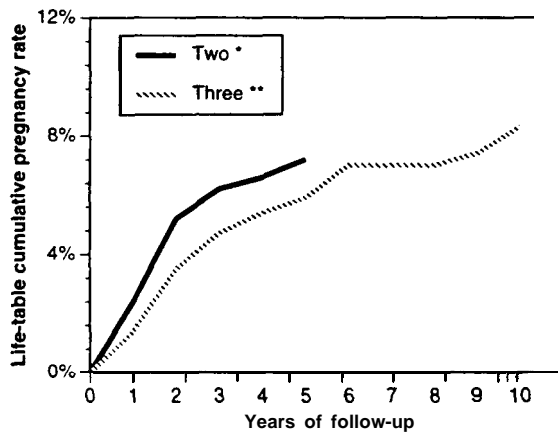
**Table 2**  
Effect of insertion-hysterectomy interval on success or failure of tubal closure after single pre-hysterectomy quinacrine insertion in 40 women

Outcome	Interval in weeks		Total
	0-6	7+	
Success	9	22	31
Failure	7	2	9
Total	16	24	40

Source: Merchant RN, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40: 47–54.

has only rarely seen pregnancies between quinacrine insertions.

Preliminary analysis of long-term follow-up data from the Chile cohort shows a relatively small difference in pregnancy rates following two versus three insertions (Fig. 1) (Sokal and Zipper,



\* n=487 at time=0, and n=118 at 5 years

\*\* n=959 at time=0, and n=195 at 10 years

\*\*\* The number of insertions in this graph is the number actually received, rather than the number intended.

**Fig. 1.** Cumulative pregnancy rates following quinacrine sterilizations. Preliminary results: two vs. three insertions\*\*\*. \*n= 487 at time = 0, and n=118 at 5 years. \*\*n = 959 at time = 0, and n = 195 at 10 years. \*\*\*The number of insertions in this graph is the number actually received, rather than the number intended.

**Table 3**  
Failure rates with single quinacrine insertions

Year	Number of women sterilized and adjuvants	Number of pregnancies <sup>a</sup>	
		N	%
1990	2100 without ibuprofen	85	4.0
1991	1583 oral ibuprofen	33	2.1
1992	1550 ibuprofen pellets	29	1.9

<sup>a</sup>Only one ectopic pregnancy has been reported. Source: Bashir A, Muhammad M, Muhammad AC, Muhammad YC. Non-surgical female sterilization: 3 years experience with quinacrine. Presented: Seminar on Quinacrine for Nonsurgical Female Sterilization. Karachi. 1994.

Long-term pregnancy rates following quinacrine pellet sterilization, manuscript in preparation). However, it should be noted that these data are from an exploratory analysis. The data represented here are from a number of trials using different regimens, and do not represent a randomized comparison of two versus three insertions.

Regarding the efficacy of single insertions, Bashir has been performing single insertions of quinacrine in Pakistan for several years with surprisingly low failure rates [45]. Recently, she reported a series of 5233 women receiving one insertion of 252 mg in 1990 through 1992, with and without ibuprofen (Table 3) (Bashir A, Muhammad M, Muhammad AC, Muhammad YC. Non-surgical female sterilization: 3 years experience with quinacrine. Presented: Seminar on Quinacrine for Non-surgical Female Sterilization. Karachi, 1994). However, these data have several serious limitations — they have not been analyzed by life-table methods, the degree of loss-to-follow-up is not known, and the different regimens were not compared in randomized controlled trials.

Based on preliminary data and an historical control group, Mullick and co-workers (manuscript in preparation) suggest that an intramuscular progestogen at the time of insertion markedly lowers the failure rates compared to providing 3 months of oral contraception. They used a regimen of 252 mg quinacrine plus 75 mg diclofenac.

### 3.3. Dose of quinacrine

A number of investigators have used different doses of quinacrine, but they have often made other protocol changes simultaneously, so that it is difficult to attribute differences in efficacy to the quinacrine dose alone. The most definitive demonstration of a dose-response relationship between quinacrine and tubal fibrosis is in a study by Merchant et al. [43]. In a pre hysterectomy study, after a single insertion, she compared three dose levels of quinacrine: 100, 252 and 324 mg. Merchant also did repeat hysterosalpingograms before surgery and on the surgical specimen. Table 4 shows the data regarding increased tubal closure by quinacrine dosage. Higher closure rates were seen from 324 than from 252 or 100 mg. However, the 324-mg dose also produced more inflammation in more distal portions of the tube. It is not possible to determine the optimum dose from these data alone, but one could conclude that 100 mg is too low a dose. Recent data from Bairagi et al. [46] show a 1% failure rate at 12 months with a dose of 216 mg of quinacrine using two insertions and the simultaneous administration of an antiprostaglandin, and three cycles of oral contraceptives beginning after the first insertion.

### 3.4. Insertion techniques

Two different insertion techniques have been proposed, one by Zipper et al. [47] and one by Hieu et al. [18]. Zipper proposed an insertion technique similar to that used with the copper-T

IUD. The inserter is inserted up to the fundus and the sleeve is withdrawn to release the pellets, then the plunger and sleeve are withdrawn. This procedure would be expected to leave a vertical line of quinacrine pellets in the uterus. Hieu's insertion technique calls for the inserter to be inserted to the fundus. Then, the inserter is withdrawn 0.5 cm, and the plunger is advanced so that the pellets are all expelled at the fundus of the uterus. There is evidence in Hieu's data showing that there were widely varying skill levels among the clinicians in the study [48], and Hieu attributed the differences in efficacy to the use of different insertion techniques. However these two techniques have not been compared in a controlled clinical trial.

### 3.5. Adjuvants

Zipper has conducted a series of animal experiments showing that intrauterine adjuvants may increase or decrease the efficacy of quinacrine insertion. He has shown in the rat uterus model that copper and antiprostaglandins increase the fibrotic reaction, while zinc decreases fibrosis. Zipper has recently reviewed his animal data [49]. Recent unpublished human data from Zipper show a low failure rate at 3 years (one pregnancy among 114 women) after two insertions with a combination of intrauterine quinacrine (288 mg), betamethasone (1.2 mg) and copper sulfate (0.5 mg). However, the small sample sizes of his studies and the use of historical controls make it hard to draw definite conclusions. From a drug regulatory point of view, the toxicological testing of formulations of quinacrine with other intrauterine adjuvants could be a major obstacle to approval.

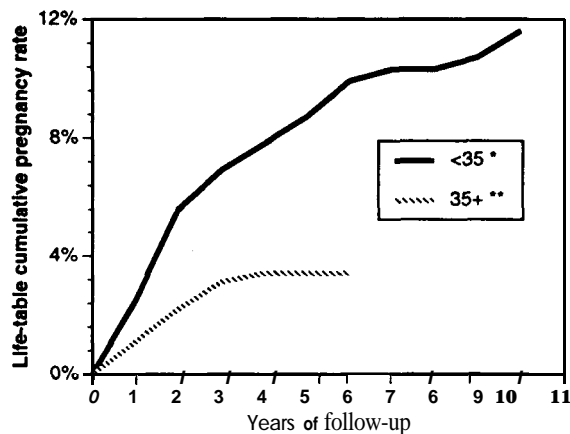
### 3.6. Age

Preliminary results of an analysis of the Chilean data suggest that age is a key factor in the pregnancy rate following quinacrine sterilization (Sokal and Zipper, Long-term pregnancy rates following quinacrine pellet sterilization, manuscript in preparation). The data show widely differing pregnancy rates between women sterilized before age 35, with 5-year cumulative life-table rates of about 9 per 100 women, versus 3.4 per 100 women after age 35. Cumulative rates for the younger women were only slightly higher at

Table 4  
Effect of dose of quinacrine pellets on success or failure of tubal closure after single pre hysterectomy quinacrine insertion in 40 women

Outcome	Doses of quinacrine (mg)			Total
	100	252	324	
Success	3	5	23	31
Failure	4	5	0	9
Total	7	10	23	40

Source: Merchant RN, Prabhu SR, Kessel E. Clinicopathologic study of fallopian tube closure after single transcervical insertion of quinacrine pellets. *Int J Fertil* 1995; 40: 47–54.



- n=866 at time=0, and n=183 at 10 years
- \*n=601 at time=0, and n=127 at 6 years

Fig. 2. Cumulative pregnancy rates following quinacrine sterilizations. Preliminary results by age at sterilization: < 35 vs. 35 + \*n = 866 at time 0, and n = 183 at 10 years. \*\*n = 601 at time = 0, and n = 127 at 6 years.

the end of 10 years, about 12 per 100 women (Fig. 2). Since women in the 35 + age group were removed from the analysis when they reached age 45, the number of women reaching 10 years of follow-up in that group was too low to justify reporting that data. However, there were no additional pregnancies. The efficacy of quinacrine sterilization in women in the 35 + age group appears similar to the efficacy of bipolar electrocautery among younger women in the US (Wilcox LS, Jamison P, Peterson HB, Hughes J. Ten-year pregnancy rates after unipolar and bipolar sterilization. Presented: 47th Annual Meeting of The American Fertility Society, Orlando, FL, 1991; Abstract no. O-028.).

### 3.7. Reversibility

No outcome data are available on the reversibility of quinacrine sterilization. Based on the location of the tubal obstruction, quinacrine sterilization is likely to be more difficult to reverse than surgical methods of tubal occlusion, especially those methods which use mechanical devices for tubal occlusion. However, newer methods for treatment of proximal tubal occlusion by transcervical cannulation of the tube might apply to

quinacrine-induced occlusions [50]. In two cases in which it was applied the occlusion was removed on one side of each case.

## 4. Conclusions

### 4.1. Safety

The data from clinical studies of quinacrine peilet sterilization, and data from other routes of quinacrine administration, are consistent and suggest that, in the short-term, sterilization with quinacrine pellets is safer than surgical sterilization. Additional data should be gathered concerning the risk of ectopic pregnancies and the prevalence and clinical significance of non-cancerous uterine abnormalities.

The potential carcinogenicity of quinacrine probably cannot be addressed in the near future by clinical studies, but can be addressed by animal and in vitro studies. As in the case of hormonal contraceptives, epidemiological studies of long-term human use by many women would be needed to definitively address this issue.

### 4.2. Efficacy

Quinacrine pellet sterilization is less effective than surgical sterilization, but the pregnancy rate of some regimens of quinacrine sterilization in women in the 35 + age group may not be much higher than the pregnancy rate after bipolar electrocautery among younger women in the US. While many of the studies described above have serious limitations, some tentative conclusions may be drawn.

- (1) Insertions should be done during the proliferative phase. While there are no controlled trials that demonstrate this, it is biologically plausible, and data from Merchant et al. [43] and El Kady et al. [20] support this conclusion.
- (2) The dose of quinacrine to be used in a single insertion should probably not be less than 216 or more than 324 mg. Merchant's prehisterec-tomy data suggest that a 100-mg dose of quinacrine is too low, and that more than 324 mg would be superfluous.

- (3) Two insertions are better than one. but three insertions may not be needed. No well-controlled trials have confirmed the need for three insertions. Data from Merchant et al. [43] and Bairagi et al.' [46] suggest that the use of an interim method of contraception for 6–12 weeks may improve efficacy. However, data from controlled clinical trials are lacking.
- (4) Intrauterine antiprostaglandins, intrauterine copper, and the Hieu insertion technique may improve efficacy, but data from randomized, well-controlled trials are lacking.
- (5) Quinacrine pellet sterilization has a significantly lower failure rate among women aged 35 and above at the time of sterilization.

In conclusion, the use of quinacrine pellets for non-surgical female sterilization is a promising method because of its lower immediate mortality and morbidity (no deaths reported to date), and because of its potentially easier accessibility compared to surgical sterilization. However, its use needs to be reviewed by appropriate regulatory authorities, especially with regard to long-term safety issues, and additional clinical studies are needed to better define a standardized regimen.

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### Addendum

Below are two recent references, and a correction. The paper by Mullick et al. on the use of an intramuscular progestogen at the time of quinacrine insertion, described in this article only as “in

preparation.” was recently published: Mullick DC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet non-surgical female sterilization. *Adv Contracept* 1995; 1 I: 239-244. Another more general review of quinacrine is in press: Zipper JA, Dabancens A, Guerrero A, Trujillo V. Quinacrine revised. *Human Repro Update* 1995 (in press). In the review, we stated that no outcome data are available on the reversability of quinacrine sterilization. We recently became aware of some relevant data – Chinese reports of about 100 pregnancies that occurred following successful reversal of chemically-induced tubal occlusion. The reversals were performed using a utero-tubal anastomosis technique.

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