

# 100 000 quinacrine sterilizations

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## Abstract

100 000 quinacrine nonsurgical female sterilizations have been completed over the past decade involving transcervical insertion of quinacrine (252 mg) as pellets by one, two or three monthly insertions. No deaths have been reported and serious complications are far fewer than for surgical sterilization. Side-effects are mild and transient. Efficacy has improved from 3 pregnancy failures per 100 women at one year to approximately 1 by improved insertion technique and use of adjuvants. Long-term follow-up of early cases in Chile shows no increased risk of cancer for this method.

The main advantage of quinacrine sterilization is its ability to raise contraceptive prevalence and thereby reduce maternal mortality and morbidity, especially in rural and urban slum areas of developing countries. It should be made available as an option to well informed women everywhere as an economical and safe permanent family planning method.

## Introduction

Having achieved the first 100 000 quinacrine nonsurgical female sterilizations, it is time to review what we have learned and what remains to be done regarding its safety, efficacy and acceptability. The unmet need for sterilization remains high and cannot be safely met in rural, developing country areas by surgical methods [1]. Quinacrine sterilization (QS) is the only method developed to the point where it could satisfy this need in the near future.

## Quinacrine pellet sterilization

This method, developed by Zipper [2], involves transcervical application of pellets of quinacrine in the proliferative phase of the menstrual cycle using a modified Copper T IUD inserter. The pellets are cylindrical in shape to accommodate the inner

diameter of the inserter. The application technique generally used is similar to that of an IUD insertion, leaving the quinacrine pellets deposited at the uterine fundus. Most experience is with pellets of 36 mg quinacrine with a rapid dissolution time, using seven pellets (252 mg). This procedure is repeated once or twice at monthly intervals. Recently, Zipper has added 50 mg of diclofenac pellets to the quinacrine insertions to both reduce mild side-effects and improve efficacy [3].

The quinacrine pellet method requires technical skills similar to those for IUD insertions. A large and increasing number of nurses are quite competent to carry this out, especially in developing countries. The potential access to the quinacrine pellet method is, therefore, very large.

### *Safety*

Using the definitions of the Centers for Disease Control and Prevention (CDC) for serious complications, QS compares favorably with laparoscopic sterilization, with rates of 0.03% vs. 1.7%, respectively [4,5]. Two rare complications have been noted with QS: hematometria, occurring in about one in 5000 cases, and generalized allergic reaction, occurring in about one in 30 000 cases. Even accidental perforation of the uterus and deposit of quinacrine in the peritoneal cavity has not been life-threatening, but with increased severity of side-effects, especially lower abdominal pain [6]. Side-effects are mainly headaches, lower abdominal pain, oligomenorrhea and amenorrhea, fever and pruritis of the vulvar area. All are transient and readily treated.

The main concerns have been expressed by the World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction (WHO/HRP) as failure to complete standard toxicity studies [7] inasmuch as quinacrine has been shown to be a mutagen in some in vitro tests. The required in vitro and in vivo tests, including rodent carcinogenicity tests, have been successfully completed for oral administration of quinacrine [8]. To repeat this and other toxicology tests for intrauterine administration is estimated to cost 8 million dollars and take 8 years to complete [9]. In the meantime, there is growing human evidence that QS does not increase the risk of cancer [10,11] and that it may even be anticarcinogenic for some cancers in rats [12]. The opinion of reputable toxicologists is that if QS increases the risk of cancer, such an increase must be low [13].

In contemplating the introduction of any medical procedure, its risk and benefits must be considered. Because benefits of a new contraceptive that can raise prevalence will be greater where prevalence is low and maternal morbidity is high, it follows that any risk/benefit assessment must be made for circumstances in each local area. In rural India, with low contraceptive prevalence and a high maternal mortality of 5 per 1000 live births, it is estimated that each sterilization on average prevents two births. For every 1000 additional QS procedures, 10 lives of women of reproductive age are saved by reduced maternal deaths. No one is suggesting that QS could kill that many women. Most regulatory agencies consider a risk/benefit assessment in approving a clinical trial. The United States Food and Drug Administration does this – for Americans. As Americans have high contraceptive prevalence and very low maternal

mortality, QS will have only modest improvement of health for American women. It would be of value economically, as QS is far less expensive than surgery, and socially, as an additional option for women. WHO/HRP is not permitted by its regulations to conduct a risk/benefit assessment for any clinical trial. They must have prior approval of their toxicology panel before recommending a trial. It is interesting to note that the WHO Special Programme for Research and Training in Tropical Disease (WHO/TDR) does conduct risk/benefit assessments and frequently approves clinical trials concurrently with toxicology studies [14]. These differences have been summarized recently [15].

Based on risk/benefit assessments, clinical trials and service programs have been approved by governments, private and government research centers and nongovernmental organizations (NGOs), providing the present experience of 100 000 cases of QS. To date, only the government in Chile has approved QS for use in government facilities with an evaluation component.

### *Efficacy*

Zipper and his co-workers [2] have reported a pregnancy failure rate of 3.1 per 100 women at one year, using three insertions of 252 mg of quinacrine as pellets. Other reports of two or three insertions have given similar results [4,16-21]. Hieu and his co-workers [4] noted great variation in efficacy among inserting clinicians and hypothesized that this was due to different insertion techniques. The Copper T IUD technique involves insertion to the fundus and, while holding the inserter plunger steady, withdrawing the sheath. This results in a vertical column of pellets, starting at the fundus, but ending at the lower uterine segment. The other technique used in this large field trial involved insertion to the fundus, but withdrawing the inserter  $\frac{1}{2}$  cm. Then, holding the sheath steady, the plunger is slowly advanced. This technique deposits all pellets at the fundus. A study by Bairagi and his co-workers provides evidence of the superiority of the latter technique [22].

A pre hysterectomy study of Merchant and her co-workers [23] demonstrated that longer periods between quinacrine insertion and hysterectomy resulted in a higher incidence of tubal closure, and she recommended an additional contraceptive for at least six weeks post-insertion. Her study also documented a positive correlation between dose of quinacrine and efficacy, but higher doses extend tubal damage beyond the intramural segment. A randomized trial to confirm the effect of an additional contraceptive remains to be reported.

Trials of both Hieu et al. [4] and Mullick and co-workers [24] show improved efficacy by number of insertions. Sokal and his co-workers have documented improved efficacy for women 35 years of age and over [25], as is expected for all contraceptive methods.

A recent report by Mullick and his co-workers provides evidence for acceptable efficacy with a single insertion and medroxyprogesterone (150 mg im) given at the time of insertion of pellets [26]. This improved efficacy may be due to the ability of medroxyprogesterone to relax uterine musculature, including the tubal ostia, with

more consistent delivery of quinacrine to the tubes. It might be also due to its antiestrogenic effect. Zipper and his co-workers have demonstrated that estrogen promotes recovery of the quinacrine-induced tubal inflammation in the rat [27].

### *Acceptability*

It is a commonsense notion that a nonsurgical method is more acceptable to women than a surgical one. Women in developing countries especially fear surgical procedures involving entry to the peritoneal cavity. In Vietnam [4], acceptance of QS was 11 to 1 over surgical sterilization in Nam Ha Province. In rural West Bengal, India, over 10 000 QS procedures have been performed. Families paid for these procedures while foregoing government financial incentives available for surgical sterilization.

There is little doubt that the availability of QS would raise contraceptive prevalence, particularly in areas of unmet need for terminal methods. Numerous demographic and health surveys, especially in countries with low female sterilization prevalence [27,19] show the unmet need as about 50%.

### *Efficacy vs. safety*

We have seen that the benefits of a new contraceptive method that can raise contraceptive prevalence are greater for developing countries than for industrialized societies. However the health costs of contraceptive failures are greater for developing countries because of their high maternal mortality [28,29]. This can be seen in Table 1, showing two levels of efficacy for QS: 3 and 1.5 failures per 100 women at one year. For QS in developing countries the proportion of these failures that are ectopic is assumed to be 3% [4] with 5% case fatality and general maternal mortality of 5 per 1000 live births. For surgical sterilization in industrialized countries, failures are assumed to be 0.25 per 100 women at one year, and 50% are ectopic [30] with 0.08% case fatality [31] and general maternal mortality of 0.08 per 1000 live births [32]. The proportion of these surgical sterilization failures that are ectopic in developing countries is assumed to be half of that of industrialized nations. Procedure case fatality is assumed to be 10 per 100 000 in developing countries and 4 in the industrialized world for surgical sterilization and nil for QS.

With these assumptions, attributable mortality is higher for the nonsurgical method, assuming a 3% failure rate, but lower than surgical sterilization at a 1.5% failure rate. Recent reports indicate that efficacy of the nonsurgical method may be approaching 1.5% [22,33,34] and this may be true for a single insertion of quinacrine if accompanied by medroxyprogesterone im [26]. But the major potential benefit of QS is its ability to raise contraceptive prevalence in areas with high maternal mortality. For industrialized countries, it could reduce their high cost of surgical sterilization and be a welcome additional option for women [35], while preventing a small number of maternal deaths [36].

**Table 1 Estimated deaths attributable to surgical and nonsurgical female sterilization in developing and industrialized countries per 100000 procedures**

Mortality	Surgical		Nonsurgical	
	Developing	Industrialized	Developing 3% failure *	Industrialized 3% failure
Procedure	10.0	<b>4.00</b>	<b>0.00</b>	<b>0.00</b>
Ectopic pregnancy	<b>22.5</b>	<b>9.80</b>	<b>37.50</b>	<b>18.75</b>
Delivery/abortion	1.25	0.20	15.00	7.50
Attributable	33.25	14.00	52.50	26.25

\*Based on first **100 000** procedures

## The work ahead

Additional clinical trials are needed with adequate numbers and randomization of cases to know accurately the effects of an additional contraceptive and for how long, as well as the effect of present leads for adjuvants and different insertion techniques. Because of the convenience and safety of a single insertion protocol, studies of the effect of medroxyprogesterone are a high priority. Both prospective and retrospective studies comparing QS with surgical sterilization are needed. Expansion of field trials and evaluated service programs can give assurance there are no additional rare but serious complications. Probably the most important need is to encourage expansion of QS in the private sector as an 'off label' drug [37] as it is approved almost anywhere for the treatment of malaria. Official government approvals for this use of quinacrine are desirable but not necessary. Finally, additional epidemiological studies to confirm the lack of increased risk of cancer for QS should continue.

Physicians and program administrators, as well as feminist groups, need to become aware of the positive risk/benefit ratio of QS for some women in some areas. Well informed women should have the right to QS if it best suits their needs.

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**MS received 1 June 96.**

**Accepted for publication 17 June 96.**

## Resumé

Au cours de la **décennie écoulée**, 100.000 femmes **ont été stérilisées** par intervention non chirurgicale, **sous forme** de pellets de 252 **mg** de quinacrine **à** raison d'une, de deux ou de trois insertions mensuelles par voie transcervicale. Aucun **décès** n'a **été** enregistré et les complications graves ont **été** moins fréquentes que lors de stérilisations chirurgicales. Les effets secondaires sont **bénins** et passagers. **L'utilité** de la méthode s'est **améliorée**, passant de 3 échecs par grossesses **à** 1 pour 100 femmes au terme d'un an, **grâce** au perfectionnement de la technique d'insertion et de l'emploi d'adjuvants. **Le** suivi **à** long terme des premiers cas au Chili n'a pas **révélé** l'accroissement d'un risque de cancer pour cette **méthode**.

Le principal avantage de la **stérilisation à la quinacrine** vient de ce **qu'elle permet** de rehausser la prevalence contraceptive et, par consequent, de **réduire la mortalité** et la morbiditi maternelles, surtout dans les zones **rurales** et **les quartiers** pauvres des villes de pays en **développement**. Cette **méthode** devrait **être présentée** comme option ouverte aux femmes bien **informées**, dans quelque pays que ce **soit**, et comme une **méthode** de planning familial économique, sans danger et permanente.

### Resumen

En **los últimos diez años** se realizaron 100.000 esterilizaciones femeninas no **quirúrgicas** con la **inserción** transcervical de 252 mg de quinacrina en forma de bolitas mediante inserciones **cada** mes o **cada** dos o **tres** meses. No se **notificó** ninguna muerte y las complicaciones graves son **mucho** menos frecuentes que en el **caso** de la **esterilización quirúrgica**. Los efectos secundarios son leves y pasajeros. La eficacia **mejoró** de 3 fracasos con embarazos por **cada** 100 mujeres al **año** a aproximadamente 1 mediante una mejor técnica de **inserción** y el uso de adyuvantes. El seguimiento a largo plazo de **los primeros casos** en Chile no **señala** un riesgo **más** alto de cancer al utilizarse este método.

La ventaja principal de la **esterilización** con quinacrina es su capacidad de aumentar la prevalencia anticonceptiva y **reducir así** la mortalidad y morbilidad maternas, especialmente en zonas rurales y en barriadas **urbanas** de países en desarrollo. Debe facilitarse **como opción** a mujeres bien informadas de todas partes, **como método económico** y seguro de planificación familiar permanente.