

## Association for Voluntary Surgical Contraception: A technical statement on quinacrine pellets for nonsurgical female sterilization

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### Abstract

For many years, researchers have been seeking nonsurgical methods for female sterilization because these methods may be safer, simpler, cheaper, and quicker than conventional techniques, and may require a lower level of skill to deliver. Various investigators have explored using intrauterine instillation of quinacrine for tubal occlusion. Until recently, reports of quinacrine use for nonsurgical sterilization have been scarce and limited to data sets involving small numbers with very short-term follow-up. The July 24, 1993 issue of the *Lancet* reports on 31 781 cases of nonsurgical sterilization with quinacrine in a field trial from Vietnam. The present paper is written as a background review to assist family planning providers in the dialogue regarding the introduction and use of quinacrine. It attempts to answer questions regarding what is currently known about the safety and efficacy of quinacrine, and what the recent article published in the *Lancet* adds to our knowledge. It also raises the question of how quinacrine sterilization affects free and informed choice and the other interests of family planning clients.

The July 24, 1993 issue of the *Lancet* includes an article about the use of quinacrine hydrochloride pellets as a nonsurgical method of female sterilization in Vietnam [1]. Until recently, reports of quinacrine use for nonsurgical sterilization have been scarce and limited to data sets involving small numbers with very short-term follow-up. the *Lancet* article reports on 31 781 cases of nonsurgical sterilization with quinacrine from a field trial in Vietnam. The report has revived interest in quinacrine.

The present paper is written as a background review to assist family planning providers in the dialogue regarding the introduction and use of quinacrine. It attempts to answer two questions and poses a third for consideration: What do we know about the safety and efficacy of quinacrine? What does the recent article published in the

Lancet add to our knowledge? How would quinacrine sterilization affect free and informed choice and the other interests of family planning clients?

## Background

For many years, researchers have been seeking nonsurgical methods for female sterilization because these methods may be safer, simpler, and less expensive than conventional techniques that require abdominal surgery. These advantages would help to increase the availability of female sterilization services.

Various investigators have explored using intrauterine instillation of quinacrine for tubal occlusion in women and have reported the results of several small clinical trials. Quinacrine is not approved by the US Food and Drug Administration (FDA) for this purpose. Quinacrine for intrauterine instillation was submitted to the Toxicology Panel of the World Health Organization (WHO) in 1991. Although quinacrine had been used for many years for other purposes, the panel classified it as a 'new drug' when used for female sterilization. As part of the review protocol, WHO requires that investigators submit the results of toxicology testing and studies to investigate teratogenicity, irritancy, and persistence of the compound in body cavities. The WHO did not find the investigative studies submitted for review to be adequate to ensure safety.

Large-scale clinical trials have not been reported previously, and therefore, health care professionals and the public have not had the opportunity to rigorously analyze and debate the safety and efficacy of this method. Equally important, they have not thoroughly discussed how to ensure that women undergoing quinacrine instillation are able to make free and informed choices from an array of reproductive options.

Quinacrine is remarkably inexpensive and easy to manufacture. It is as simple to administer as an intrauterine device. These features of the method make it especially appealing, and many programs may be inclined to consider quinacrine for widespread use despite the lack of complete information about it. These same features raise issues of free and informed choice because conceivably providers could instill quinacrine into women without informing them they have done so, or counseling them about the permanence of the method or other contraceptive choices available to them.

Because of hard work over the last 30 years, family planning providers are appropriately giving more attention to free and informed choice in existing surgical sterilization programs. This is a human right, and an absolute necessity to ensure the ongoing success of a program. The concern for assuring free and informed choice in settings where quinacrine is administered should at least equal the medical community's concern for safety and efficacy. Informed choice has not been adequately addressed in the literature thus far.

### What do we know about the safety and efficacy of quiaacrine?

There are several safety and efficacy issues regarding quinacrine; they include toxicity, teratogenicity, failure rates, and risk of ectopic pregnancy.

Quinacrine, a drug developed in the 1920s, was initially used to treat malaria during World War II. While it was replaced by chloroquine for malaria treatment, quinacrine has subsequently been used to treat tapeworm, *Giardia*, and lupus and to control malignant effusions of the pleural and peritoneal cavities. Its use as a sclerosing agent is what led investigators to look at its applicability as a tubal occlusion agent for nonsurgical female sterilization. In the 1970s, a 'slurry' of quinacrine was instilled into the uterus for this purpose. Because of high failure rates, believed to be related to the inability to contain the solution within the uterus, as well as concerns regarding the leakage of the solution into the peritoneal cavity, a pellet form of the drug was developed. The pellet form appears to create a higher concentration of the drug within the uterus for a prolonged period of time and is less likely to drain into the peritoneal cavity.

Toxicity, teratogenicity, and mutagenicity studies with quinacrine were performed in the late 1970s. Dubin et al. [2,3] performed intravascular, intrauterine, and intraperitoneal instillation of quinacrine solution in cynomolgus monkeys. The studies indicated that effects of the drug are dose-related. Circulating drug levels stimulate the central nervous system, and very high levels lead to death in the animal model.

Blake et al. [4] tested quinacrine in monkey and rat models for teratogenicity and mutagenicity. Although the studies were limited due to small sample size, intrauterine quinacrine appeared to have little potential for inducing malformations but was found to be embryolethal. Quinacrine is known to be a direct-acting frameshift mutagen in bacterial systems; however, its impact on mammalian cells is equivocal, based on lymphocyte studies in treated monkeys.

In the late 1970s and early 1980s, Zipper et al. [5], in Chile, with the help of Family Health International (FHI), began performing phase I clinical trials in women using, first, a 10-minute release formulation of quinacrine pellets requiring three separate insertions, and then a KM-minute release formulation requiring two insertions. The investigators reported a 12-month failure rate of 3.3 and 2.0 respectively, with follow-up of 80% of the study cases. In the three-insertion group, 24-month follow-up indicated a failure rate of 6.7, and no figure was reported for the two-insertion group. Studies were continued until 1989, when concern about an abnormal incidence of cancer among women in the study group prompted FHI to discontinue support for the study, pending a review of the data.

FHI investigators conducted a retrospective cluster analysis of the follow-up data from the Chilean studies (unpublished). In this paper, they reported that no association between quinacrine sterilization and future increased risk of cancer could be made. The follow-up of these Chilean women will continue for another five years.

Recent studies of quinacrine have also been reported from Egypt, Indonesia, and Chile [6-9]. However, each of these studies was small (ranging from 60-160 women) and used a different insertion protocol (one used an additional drug); furthermore, the results varied widely.

### **The *Lancet* article**

The July 24, 1993 issue of the *Lancet* included an article describing 31 781 cases of nonsurgical sterilization with quinacrine pellets performed in Vietnam. The authors report a total of 818 pregnancies; they calculate life-table pregnancy rates of 2.63 at one year and 4.31 at two years for 9461 women who received two insertions, and 5.15 at one year for 2225 women receiving only one insertion. These failure rates are based on only 11 686 cases because of the subsets chosen for analysis.

The paper reports eight major complications (two severe bleeding, one hysterectomy for severe pain and amenorrhea, one premenstrual pain and dysmenorrhea, one PID, one allergic reaction, and two synechiae of the cervical canal - one requiring hysterectomy). There were no deaths in the study group. All side-effects were reported to be minor and of short duration. The authors report **19** ectopic pregnancies and one birth defect in a fetus conceived 2.5 months after the quinacrine insertions.

The title of the report suggests that the findings are based on 31 781 cases. In fact, information on failure rates and side-effects is based on subsets of the study group, which the paper then extrapolates to the group as a whole. In addition, the study methodology suggests that there may be significant biases that occur as a result of the use of these subsets. These biases make extrapolation to the whole group difficult and cast significant doubt on the conclusions drawn from the analysis regarding safety and efficacy. Several examples are listed below.

### ***Inclusion criteria***

The paper defines the inclusion criteria for the study as follows: all women had to be at least 30 years old and have two living children, the youngest being at least three years old. However, women under the age of 30 were included in the study. The research was carried out in 24 provinces of Vietnam. In one of those provinces, Namha, 473 of 3502 women were <30. The authors report that 17 women, whose sterilizations failed and who became pregnant during the time of the study, were breast-feeding at the time of conception. The inclusion criteria state that the youngest child must be at least three years old. Is it likely that women would be breast-feeding a child older than three? If the youngest child was less than three years old, these women should have been excluded.

### ***Follow-up and failure rates***

Using pregnancy as the measure of success for quinacrine to cause tubal occlusion relies heavily on a presumption of baseline fertility and on the ability to follow women for a prolonged period of time. The authors give conflicting statements as to the completeness of follow-up. They state, "these studies have complete follow-up since they took place in communes where there is little mobility ...". Yet, to determine

efficacy, the authors state that only study sites with a minimum of 50 cases at one-year follow-up were included. Only four sites out of 24 met this criterion.

The life-table method that the authors chose to use for analysis is designed to permit inclusion of all durations of follow-up. Despite this fact, the investigators chose to exclude over 20,000 cases from their analysis; in doing so, they created a bias in calculation of the pregnancy rate. The life-table method of analysis, if used as it was designed to be used, might have eliminated this bias.

In the two-insertion studies used to determine efficacy, of 9461 women initially entered into the studies, 7048 (74%) were followed up at one year, and only 1146 (12%) at two years. Unknown numbers of women were admitted to the study as late as December 1992; these women were obviously not followed up for a year since the study was published in July 1993, yet the study includes them for the total number of cases.

The failure rate for single insertions is 5.15 at one year, with only 49% of the patients included at the one-year follow-up.

In the methods section, the authors state that the ectopic pregnancy rate was 'calculated' as 0.89 per 1000 woman-years of use, but they do not say how this was calculated, what the denominator was, or what the length of follow-up was in the women used for this calculation. In one province, two of nine pregnancies reported were ectopic, yet this troubling finding is not mentioned in the analysis of ectopic pregnancies.

Data from Hatinh province suggest possible problems with the accuracy of the follow-up information. In that province, 91 pregnancies are reported following 997 procedures, yet there presumably were fewer than 50 women followed up at one year (since this province is excluded from the life-table analysis). This would appear to be an exorbitant number of pregnancies for such a short time.

The authors attempt to analyze failure rates in terms of experience and skill of the providers. They report that there are providers with no failures and some providers with failure rates from 5.3% to as high as 17.2%. High failure rates do not correlate with a low number of insertions performed. When all providers are included, the authors conclude that experience is not important in determining failure. In their discussion, however, they state that skill is important, but they do not define what they mean by skill.

### ***Side-effects and safety***

Side-effects were determined based only on a group of 508 women from one province, Namha. The investigators extrapolate the findings of this small group to the entire study of 31781 women.

The safety of the quinacrine method is not adequately addressed by this study. The authors conclude that this method is safe in so far as no deaths occurred as a result of the quinacrine insertion. They claim this study supports the lack of mutagenicity found in monkeys (discussed above) as no birth defects were noted. The one anencephalic child born following quinacrine insertion was attributed to environmental factors since

the infant was conceived 2.5 months following the last quinacrine insertion. Because only 80 births were carried to term, it is difficult to make any judgements regarding the possible mutagenicity of the method from this study. No long-term data regarding possible risk of cancer are yet available from this study group.

### **Current work**

Family Health International has now obtained funding for a new prospective clinical trial in Vietnam, as well as further retrospective analysis of the data gathered in the Lancer study. Rather than using pregnancy rates to assess efficacy, the future studies will use hysterosalpingography. In addition, supplementary contraception for the immediate postinsertion period will be provided. The investigators plan to study the use of antiprostaglandins at the time of insertion to improve occlusion rates. This idea is based on the recent work by Trujillo et al. [9] in Chile that suggests amplification of effect by concurrent use of intrauterine diclofenac.

### **Conclusion**

Considering the findings from previously reported studies and those presented by Vietnamese investigators in the recent Lancer article, it is not possible to conclude that quinacrine pellets are a safe and effective nonsurgical method of female sterilization. If the questions regarding safety and efficacy can be satisfactorily answered, the low cost and ease of insertion would make quinacrine a promising method for areas of the world where maternal mortality is high, access and availability of family planning resources are low, and unmet demand for permanent methods is great. However, further, carefully designed studies that specifically address short- and long-term safety are needed. A standard protocol for insertion, with studies evaluating efficacy, must be established. Until the outstanding questions have been answered, the use of quinacrine pellets for female sterilization should continue to be considered an experimental procedure.

In addition, because of the low cost and ease of administration of quinacrine, issues regarding free and informed choice must be addressed with a loud voice. Past experience has shown that it is all too easy to assume that simply acknowledging the need to ensure free and informed choice assures that it is carried out with as much skill and attention as the procedure itself. In this case, the potential for coercion and abuse in the context of demographic goals may be of greater concern than the medical risk from side-effects and long-term health consequences of quinacrine itself. This risk must not be underestimated. Quality of care in family planning services must give equal weight to informed choice and safety.

## References

1. Hieu DT, Tan TT, Tan DN, Nguyet PT, Than P, Vinh DQ. 31,781 cases of nonsurgical female sterilisation with quinacrine pellets in Vietnam. *Lancet*. 1993;342:213-7.
2. Dubin NH, Parmley TH, DiBlasi MC, Ghodgaonkar RB, Jiffry MTM, Blake DA, King TM. Pharmacology of quinacrine hydrochloride with emphasis on its use as a tubal occluding agent. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra J, eds. *Female Transcervical Sterilization*. Philadelphia: Harper & Row. 1993:60-70.
3. Dubin NH, Blake DA, DiBlasi MC, Parmley TH, King TM. Pharmacokinetic studies on quinacrine following intrauterine administration to cynomolgus monkeys. *Fertil Steril*. 1982; 38:735-40.
4. Blake DA, Dubin NH, DiBlasi MC, Parmley TH, Stetten G, King TM. Teratologic and mutagenic studies with intrauterine quinacrine hydrochloride. In: Zatuchni GI, Shelton JD, Goldsmith A, Sciarra J, eds. *Female Transcervical Sterilization*. Philadelphia: Harper & Row. 1983:71-88.
5. Zipper J, Cole LP, Rivera M, Brown E, Wheeler RG. Efficacy of two insertions of 100-minute releasing quinacrine hydrochloride pellets for non-surgical female sterilization. *Adv Contracept*. 1987;3:255-61.
6. El Sahwi S, Kamel M, Haibi N, Osman M. Hysteroscopic and hysterosalpingographic study after intrauterine insertion of quinacrine pellets for non-surgical sterilization. *Adv Contracept Del Sys*. 1992;8:151-9.
7. El-Kady AA, Nagib HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. *Fertil Steril*. 1993;59:301-4.
8. Agoestina T, Kusuma I. Clinical evaluation of quinacrine pellets for chemical female sterilization. *Adv Contracept*. 1992;8:141-50.
9. Trujillo V, Zipper J, Viel B, Rivera M. Non-surgical female sterilization using quinacrine pellets. *Revue française de gynécologie et d'obstetricue*. 1993;88:147-50.

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## Resumé

Depuis de nombreuses années, les chercheurs s'efforcent de trouver des méthodes non chirurgicales de stérilisation féminine, car celles-ci présentent moins de danger, sont plus simples, moins onéreuses et plus rapides que les techniques classiques. En outre, leur exécution demande sans doute moins de compétences techniques. Plusieurs chercheurs ont exploré la méthode d'instillation intra-utérine de quinacrine pour provoquer l'occlusion des trompes. Jusqu'à récemment, peu de rapports ont décrit l'emploi de la quinacrine pour la stérilisation non chirurgicale et des observations limitées ne portaient que sur de petits nombres de patientes n'ayant bénéficié que d'une courte période de suivi. Dans son numéro du 24 juillet 1993, *The Lancet* publie un rapport sur la stérilisation non chirurgicale avec la quinacrine pratiquée sur 31.781 femmes dans le cadre d'un essai sur le terrain au Viet Nam. Le présent exposé décrit un tableau général destiné à aider les pourvoyeurs des services de planning familial dans le dialogue sur l'introduction et l'emploi de la quinacrine. Il cherche à répondre aux questions que l'on peut se poser sur ce qui l'on sait de la sécurité et de l'efficacité de la quinacrine et sur ce que l'article du *Lancet* ajoute à nos connaissances. Il soulève aussi la question de savoir comment la stérilisation à la quinacrine se répercute sur le choix fait librement et en connaissance de cause et sur les autres intérêts des clientes du planning familial.

## Resumen

Hace muchos años que los investigadores intentan encontrar métodos no quirúrgicos de esterilización femenina porque podrían ser más seguros, sencillos, económicos y rápidos que las técnicas convencionales y podrían requerir un menor nivel de competencia técnica. Varios investigadores han estudiado el uso de la instilación intrauterina de quinacrina para provocar la oclusión de las trompas. Hasta hace poco, eran escasos los informes sobre el uso de la quinacrina para la esterilización no quirúrgica y se limitaban a series de datos relativos a un pequeño número de pacientes con un período breve de seguimiento. En el número del 24 de julio de 1993, *The Lancet* publicó un informe sobre 31.781 casos de esterilización

femenina no quirúrgica con quinacrina en un ensayo de campo en Vietnam. Este artículo describe un cuadro general destinado a ayudar a los proveedores de servicios de planificación familiar en el diálogo relativo a la introducción y el uso de la quinacrina. Intenta responder a las preguntas que pueden surgir acerca de lo que se sabe sobre la seguridad y eficacia de la quinacrina y lo que el artículo en *The Lancet* aporta a nuestros conocimientos. También presenta la pregunta de cómo la esterilización con quinacrina afecta la elección libre e informada y los otros intereses de los clientes de los servicios de planificación familiar.