

# Quinacrine sterilization: the imperative need for American clinical trials

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Quinacrine sterilization has been studied for over 20 years, ever since Dr. Jaime Zipper realized that it had the potential for sclerosing the mucosa of the human oviductal lumen (1). He took the technique from chest surgeons, who had safely and effectively used quinacrine to produce pleural adhesions to prevent the recurrence of pleural effusions. For his epochal contribution to the field of family planning, Dr. Zipper was honored by the American Fertility Society in 1970, when he delivered the Samuel L. Siegler Lecture, "Human Fertility Control by Transvaginal Application of Quinacrine on the Fallopian Tube" (2). The method he developed consists of using a modified inserter for a copper T intrauterine device (IUD) to insert 252 mg of quinacrine pellets into the uterine cavity on two occasions, spaced 1 month apart. Medical professionals who are qualified to insert an IUD can easily deliver quinacrine into the uterus.

In 1993, strong evidence for the safety of quinacrine-induced tubal sclerosis was provided when Dr. Do Trong Hieu reported on over 31,000 Vietnamese women who had undergone quinacrine sterilization (3). There were no deaths, and serious adverse events were estimated at 1/50th that of laparoscopic sterilization. Unfortunately, his clinical trial was cut short when the World Health Organization, Special Programme, Research Development and Research Training in Human Reproduction complained that toxicology data "was not adequate to justify large scale field studies" (Francis T.C. Webb, M.D., letter to Ms. Demers, 9 December 1993). In response to the study's termination, editors of the *Lancet* challenged WHO to explain its negative position on quinacrine sterilization, calling WHO's action "reprehensible" (4). WHO countered that "further clinical research is not justified until various toxicological issues have been resolved on intrauterine Quinacrine" (5).

In 1942, the Winthrop Corporation published a 40-page bibliography that listed 171 reference on the toxicology of quinacrine, also including some data from clinical trials (6). This document cannot be found in *Index Medicus*. Before there was an Internet or an *Index Medicus*, the United States Army kept its own medical index, where, after much searching, one could find the Winthrop list. Perhaps the difficulty in finding this document explains why WHO and some feminist groups have maintained that toxicology studies have not been done and thus clinical trials of quinacrine sterilization should not start. The fundamental purpose for doing a toxicologic study is to predict what a particular drug will do when it is taken by humans. However, when you are in possession of both preclinical toxicologic animal studies and human studies, human data are more valuable and hold priority. The Winthrop list contained studies on animals-including rabbits, guinea pigs, dogs, cats, monkeys, canaries, sparrows, turkeys, and chickens-as well as on humans. These toxicology studies predicted the safety of quinacrine. Indeed, quinacrine has been in use for over 70 years. It has been prescribed to cure and prevent malaria for more than 100 million people, including the 3 million American soldiers who took it daily while serving in the South Pacific during World War II. After treating these veterans for over 50 years, no Veterans Administration Hospital has reported any long-term serious side effects or any increase in cancer among the personnel

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who served in the South Pacific and took quinacrine daily as compared with those who served in Europe and did not take quinacrine.

Currently, quinacrine is used to treat rheumatoid arthritis, lupus, tapeworm, amebiasis, and *Giardia* infection. Until 1985, one could pick up a textbook of pediatric infectious disease and find that quinacrine was preferred over metronidazole (Flagyl), as the more effective, less costly treatment for *Giardia* infection in children (7). For unknown reasons, the American manufacturer withdrew quinacrine from the market; today metronidazole is used in spite of its higher price and carcinogenic potential.

Both animal and human observations overwhelmingly affirm the safety of quinacrine. Little doubt remains about systemic toxicity and quinacrine. What question is left? When it is inserted into the uterine cavity on two occasions, can quinacrine produce a new toxicologic problem, perhaps a cancer of the uterus? This issue has three unambiguous answers.

1. Many of the 100 million people who took quinacrine daily for many years were women living in areas where malaria was (and perhaps still is) endemic. With chronic exposure to quinacrine, the drug is absorbed and carried in the bloodstream to the uterus every day it is ingested. It is known from animal studies that repeated doses of quinacrine greatly increase the tissue levels of quinacrine (8). Such levels apparently rise for up to 30 days. Considering that this intense exposure continued for many years, surely the uterine exposure to quinacrine was of an order of magnitude greater than that experienced by the patient who receives two insertions of quinacrine, a month apart. Did this constant, chronic, cumulative level of exposure to quinacrine produce an increase of cancers of the uterus? No such report exists.
2. The uterus is known only to produce three cancers. Cancer of the cervix we now consider a sexually transmitted disease (STD) related to the papilloma virus. Cancer of the endometrium usually occurs after or around the time of menopause; in women of reproductive age it is found in conjunction with a functioning ovarian tumor where estrogen is produced unopposed by progesterone. Uterine sarcoma, a very rare malignancy representing 1% to 3% of uterine cancers, occurs at a mean age of 55 years and is associated with obesity, hypertension, and diabetes. None of the factors associated with uterine cancers can be related to quinacrine.
3. Data are already available on women who have undergone quinacrine sterilization. For over 20 years, Dr. Zipper has followed more than 1500 women who had quinacrine sterilization. No excess risk of cervical cancer was found when these women were compared with a control group who were not exposed to quinacrine (9). Nor was any increase in endometrial cancer found over those same 20 years (10). In general, quinacrine sterilization patients showed no excess risk of cancer compared with a control group who were not exposed to quinacrine (9-11). Further evidence will require decades of postmarketing surveillance of many thousands of quinacrine sterilization acceptors, as was done for oral contraceptives.

Because laparoscopic sterilization is the most popular method of limiting family size today, it is important and revealing to compare the safety of quinacrine sterilization with laparoscopic sterilization. With laparoscopic sterilization, serious complications from inadvertent trauma are associated with the use of the trocar, including perforations of bowel and bladder. Perforation of major blood vessels has led to hemorrhage and death. When cautery is used, the bowel and bladder have been accidentally burned. The dangers of a gas embolus from the pneumoperitoneum required for laparoscopy or the dangers of general anesthesia are well known. None of these complications are associated with quinacrine. In a survey of American laparoscopists, Phillips (12) found 3 deaths per 100,000 laparoscopic sterilizations. Chamberlain (13), surveying laparoscopists in England, reported 10 deaths per 100,000 laparoscopic sterilizations. Because medical malpractice lawsuits are far more common in the United States than in the United Kingdom, the 10 deaths per 100,000 report from England may be closer to reality. In a review of 100,000 documented cases of quinacrine sterilization, Kessel (14) reported no deaths and no events attributable to quinacrine that required surgery. One patient in the Vietnamese trial of 3 1,781 women (3) underwent a hysterectomy for heavy bleeding diagnosed as "hemorrhagic endometritis" 1 year after a third insertion of quinacrine (DT Hieu, personal communication, September 2001). Two other patients needed to have the cervical canal sounded to relieve hematometra. There also were rare reports of allergic reactions to quinacrine. What a remarkable safety record!

Women with some medical conditions may find that surgery and/or general anesthesia is dangerous and even contraindicated. Heart disease, chronic obstructive pulmonary disease, obesity, smoking, and diabetes come to mind. Quinacrine sterilization offers sick patients a safe option and offers all women another choice. With the evidence enumerated above, it was not surprising that the U.S. Food and Drug Administration granted approval for a Phase 1 clinical trial to be carried out at the Children's Hospital of Buffalo in Buffalo, New York. Furthermore, the investigation review board of the Children's Hospital of Buffalo unanimously approved of this clinical trial twice, once in 2000 and again in 2001.

What we do not know is what the effectiveness would be in an American environment. Gynecologists must keep in mind that transcervical chemical sterilization is still in its infancy. Improvements will come once physicians begin to use this technology. The situation is the same as when laparoscopic sterilization was introduced. As the years went by, clinical researchers found various ways to interrupt the fallopian tubes with rings and clips. They discerned differences in effectiveness between unipolar and bipolar cauterization and improvements in reducing pregnancy rates when more points of the oviduct were cauterized (15). Likewise,

we can expect clinicians to discover new ways to reduce failures and improve the quality of quinacrine sterilization. One example already comes to mind. Dr. Hieu recognized that the placement of quinacrine at the very top of the uterine fundus was essential in keeping the pregnancy rate low; variations in practice accounted for some of the differences between the lower and higher pregnancy rates in various provinces in Vietnam (3). More recent evidence by Bairagi et al. (16), Sarin (17), and Soroodi-Maghaddam (18) using the Hieu insertion technique has reported pregnancy rates of 0 to 1.7% at the 2-year mark. At this time there is a trade-off between safety and effectiveness. However, the choice should at all times be left to the well-informed woman. Although the failure rate with quinacrine sterilization at this early stage of development is still higher than with surgical sterilization, many women may choose it because it is a safer method.

Some physicians compare quinacrine sterilization to the copper T IUD (ParaGard T 380A, Ortho-McNeil, Raritan, NJ). From the combined data collected by the Population Council and WHO, we recognize that the continuation rate of the T 380A is only 23% at 3 years and only 5% at 10 years (19). Sterilization is the only method of limiting family size where the continuation rate approaches 100%.

The difference in cost for quinacrine is enormous, and it behooves physicians, health insurance companies, HMOs, and the government to take interest. When quinacrine was manufactured by SIPHARM, the cost in Asia for the inserter and quinacrine pellets was less than US\$1.00 per sterilization. In the United States, because we are not allowed to import this product, each quinacrine pellet must be individually prepared by a compound pharmacist. The cost in the United States for 14 pellets (i.e., two packs of seven pellets each with two inserters) is \$140.00; add the U.S. physician's charges, and the total might be \$500. Compare that to the expense of surgical sterilization (laparoscopic), which may run anywhere from \$3000.00 to \$5000.00, not counting treatment of complications from general anesthesia and surgery. With approximately 600,000 annual sterilizations in this country, the savings with quinacrine sterilization could reach \$2 billion per year.

Most critical of all is informed consent. No physician would dream of carrying out any procedure without the patient being completely informed, the patient must sign a detailed, but easily understandable, written and/or oral informed consent. Sterilization is not a procedure to be taken lightly. All precautions against coercion must be taken seriously and all healthcare providers must follow the respected conventions accepted worldwide, namely the Belmont Report, and the International Harmonic and Helsinki conventions. A patient considering quinacrine sterilization would be given an honest explanation of the advantages and the disadvantages of this method. Rigorously detailed information would be provided and all alternative methods would be

explained so that the patient's free choice is truly an informed choice. The patient would take the written informed consent home and read it at her leisure, discuss it with her relatives, friends, and advisers as she wishes. After a reasonable amount of time, say 2 weeks to 1 month (or more if she chooses), she can make a free choice without coercion or incentives.

Benagiano has denied the "polarization of opinions" (20) over quinacrine sterilization. I agree that concentration on extremes does not contribute constructively to a scientific debate on quinacrine sterilization, and I encourage letting scientific facts and scientific reasoning be the final arbiters. Why can't well-informed American women be given an option with quinacrine? Should the American Society for Reproductive Medicine take a position on this issue?

Many American women desiring a permanent method of limiting family size have difficulty obtaining surgical sterilization because of cost, fear of surgery, or a current illness that increases the risks of an operation and general anesthesia. Quinacrine is the leading candidate for nonsurgical female sterilization. Additional trials are needed in U.S. settings.

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