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Review article

Quinacrine sterilization (QS): time for reconsideration☆

Jack Lippes*

State University of New York at Buffalo, School of Medicine, 31 Hampton Hill Drive, Buffalo, NY 14221

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Abstract

Dr. Jaime Zipper, the Chilean inventor of the quinacrine method of nonsurgical permanent contraception, was aware that when chest surgeons injected quinacrine into the pleural cavity to treat and prevent reoccurrence of pleural effusion, it resulted in the formation of fibrous adhesions between the lung and costal pleura. Zipper thought that a similar scarring effect could occur in the fallopian tubes if quinacrine was instilled into the uterine cavity. A series of refinements of the methodology culminated in the use of a modified Copper T intrauterine device inserter tube as a delivery system to introduce seven quinacrine pellets into the uterus. This approach with quinacrine sterilization (QS) was introduced into clinical practice in several countries, and a national clinical trial of over 50,000 women was conducted in Vietnam. However, in 1993, the World Health Organization raised concerns that quinacrine might be carcinogenic. This resulted in abandonment of QS in Vietnam and other countries. Subsequent epidemiologic data from extensive human studies do not support an increase in cancer risk. This paper reviews the history, limitations and clinical potential of QS.

Keywords: Quinacrine; Nonsurgical; Permanent contraception; Epidemiology

1. Introduction

Quinacrine was discovered, synthesized and patented in 1928 in Germany [1]. The Winthrop Pharmaceutical Company acquired the patent. Winthrop published a bibliography of 121 references on quinacrine in 1942 [2]. Included were human data as well as data on the use of nine different animal species. Quinacrine is known to be safe and effective in the treatment of a variety of parasitic infections, including malaria, giardia and tapeworm. Quinacrine also was effective for collagenous tissue diseases, such as lupus erythematosus, and rheumatoid arthritis. It remains one of the most thoroughly studied drugs of all time [3].

Where did the idea of using quinacrine as a contraceptive originate? Quinacrine is known to be effective treating a collapsed lung, which may be a consequence of a pleural effusion. When the pleural fluid is drained and replaced by quinacrine, the instilled quinacrine stimulates production of fibrous tissue causing the visceral pleura and parietal pleura to adhere, a process known as pleurodesis [4]. Pleurodesis eliminates the cavity in the chest, which allows the lungs to expand, and the patient is made more comfortable. Dr. Jaime Zipper, who first used quinacrine as a method for permanent contraception, postulated that a similar reaction would occur, when quinacrine was placed in the uterine cavity, and cause sclerosis of the lumen of the human oviduct (fallopian tube). His hypothesis turned out to be true. Dr. Zipper's initial approach was to instill 1500 mg of quinacrine into the uterine cavity as a slurry [5]. The 1500-mg slurry was discovered to have significant toxicity, including at least one death. The slurry technique was abandoned. Subsequently a refinement of the quinacrine sterilization (QS) formulation was made. Quinacrine was administered as seven 36-mg pellets for a total dose of 252 mg. The pellets dissolve slowly, and quinacrine interacts with the fallopian tube epithelium, replacing the epithelium with fibrous tissue. This effectively occludes the oviductal lumen [6]. Hysterectomy/Salpingectomy specimens and pelvic sonography have identified scar tissue (2–4 mm) in the intramural portion of the fallopian tube following QS [6,7].

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* Tel.:+1-716-633-6663, +1-716-390-4482 (mobile).
E-mail address: jacklippes90@gmail.com.

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2. QS technique

Subsequently QS was extensively used in developing countries as a nonsurgical method of female sterilization. The method offers a particular advantage in settings where surgery is difficult to access or unsafe. Seven pellets of quinacrine are loaded into an inserter similar to the one used to insert the Copper T intrauterine device (IUD). The health worker, nurse, nurse practitioner or physician deposits the seven 36-mg pellets of quinacrine to the fundus of the uterine cavity. Insertion of quinacrine is done at the end of menses when quinacrine easily scleroses the lumen of the oviduct. The insertion is repeated 4 weeks later. It is necessary to protect the patient against pregnancy for 3 months to be certain that the oviductal lumen is occluded. Diaphragms, condoms and/or injected Depo-Provera are recommended for the 3-month period.

Dr. Do Trong Hieu described the importance of technique when inserting the pellets of quinacrine [8]. While using the Copper T inserter, there is the expectation that as the operator pulls back the barrel of the inserter, it leaves the pellets in a straight line. This is known as the "Copper T IUD technique" of insertion. Hieu found that failure or pregnancy rates were much lower if the operator held the barrel of the inserter steady and gently applied pressure to the push rod, thereby depositing all pellets at the very top of the uterine cavity and not in a straight line. This is known as the "Hieu technique" (see Fig. 1).

3. Efficacy

A pregnancy rate of 12.1% was reported by Sokal [9]. But in that article he wrote, "…various insertion techniques may have contributed to the relatively high failure rate." Feldblum reported that the cumulative 10-year pregnancy probability for two insertions was 9%, but commented that "The variety of pellet regimens combined in this analysis makes it difficult to compare pregnancy rates…." [10]. Moreover, these failure estimates reflect the use of the Copper T IUD technique, which was abandoned 21 years ago and replaced by the more effective Hieu technique.

Two treatments also reduce the risk of failure. In a study of QS sponsored by the Indonesian government to compare single insertion versus two insertions, the pregnancy rate within 8 years of treatment was 14.3% among 70 patients receiving a single insertion of quinacrine, and there were zero pregnancies among 30 women who received 2 insertions [11].

Efficacy results using the more advanced Hieu method for placing quinacrine at the top of the uterine fundus can be seen in Table 1. The Lu et al. paper described in Table 1 reports on a Chinese clinical trial of 589 patients that compared pregnancy rates of 289 QS patients versus 300 women who had a surgical tubal ligation. Patients were matched by age, parity and other variables. There were no serious adverse events (SAEs) attributed to QS. With QS, the cumulative life table revealed a 1.2% failure rate per 100 women at 24 months compared to 0.7% for tubal ligation patients [12]. Further study is needed to confirm the advantage of the Hieu technique.

4. Human safety data

Quinacrine has been used extensively to treat malaria. It was the only effective synthetic antimalarial available during the Second World War. Three million American soldiers took 100 mg of quinacrine daily while serving in the South Pacific during WWII. These millions of service men and women suffered few SAEs from quinacrine [22]. Side effects from the chronic daily use of quinacrine include gastrointestinal upset and yellowing of the sclera and skin in a small percentage of patients. Rare cases of aplastic anemia were reported after long-term use [23]. For the treatment of

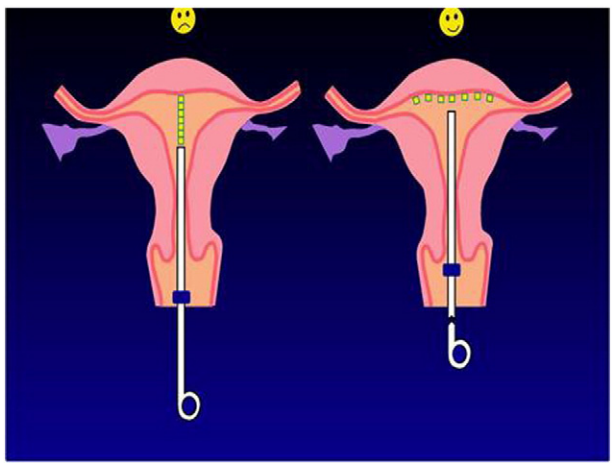

Fig. 1. Copper T IUD technique (left) vs. Hieu technique (right) of quinacrine intrauterine insertion for permanent contraception.

Table 1
QS failure rate using current protocol, i.e., employing the Hieu technique.

Investigators	No. cases	Follow-up years	Crude pregnancy rate (%)
Lu, et. al. [12]	265	2	1.2
Bashir, Bashir [13]	885	5	1.1
Sarin, Sarin [14]	134	7.2	0
Roy [15]	122	3.5	0.8
Soroodi-Moghaddam [16]	85	0.5–5	2.6
El Mahaishi [17]	66	3	0
	80	2	0
	54	1	0
Alfonso, Albano [18]	36	42.9 woman–years	0
Bilgrami [19]	1000	4	2
Agoestina [11]	30	8	0
Garabedian [20]	297	0.5–2	0.3 (ectopic)
Alpizar [21]	694	0.5–5	2.5
Ferreira [7]	128	0–4	1.6

malaria, quinacrine was replaced by chloroquine in 1946 because it was both more effective and less toxic [24]. Before chloroquine, in malarial endemic areas, people ingested 100 mg of quinacrine daily for many years, even as long as a decade or more. A daily dose of 100 mg a year equals 36,500 mg/year or 365,000 mg over 10 years. By comparison, to provide QS, the clinician installs quinacrine into the uterine cavity in two split doses of 252 mg each, 1 month apart, for a total lifetime dose of 504 mg. Long-term oral exposure during World War II was associated with the development of a cutaneous lichenoid eruption called *atabrine dermatitis*, and some patients with this condition subsequently developed squamous cell carcinoma of the skin [25]. No other evidence for human carcinogenicity exists.

In 1993, Hieu et al. reported results on 31,781 women who had chosen QS [26]. This article, published in The Lancet, provided evidence for the safety of quinacrine-induced tubal sclerosis. The authors estimated that because 31,781 women had received QS, 242 maternal deaths had been averted. Although this study provided reassuring human safety data, the World Health Organization (WHO)[1] issued a statement in 1993, declaring that quinacrine should not be used for permanent contraception. Presumably, the WHO decision was based on a positive Ames test for mutagenicity. However, Ames recognized that his test often gives false positives [27]. Nevertheless, the WHO statement caused the clinical trial of QS in Vietnam to be discontinued and inhibited other countries from pursuing QS trials. In 1994, the editors of The Lancet published an editorial entitled, *Death of a study, WHO, what and why*, calling these actions of WHO "reprehensible" [28].

Several epidemiology studies published between 1995 and 2012 evaluated whether QS causes cancer [29–33]. A study of all gynecologic cancers in 12 Vietnamese provinces during the period 2001–2006 found no increased risk with QS [31], and similar results were seen in a separate study from Chile [30]. When the number of individuals in each study is small the consistency of the results of these studies supports the conclusion of no effect of QS on cancer risk.

During this period, Dr. Claudia Ferreira and her colleagues at Minas Gerais University Hospital in Belo Horizonte, Brazil, made two significant contributions for understanding and improving QS. First, they provided QS to HIV+ women at a time when other physicians were fearful of treating these patients [34]. Second, they performed sonography on patients at 1-, 3-, 6- and 12-month intervals after receiving QS. This revealed that the endometrium returned to normal height within 2 to 4 weeks following a QS procedure suggesting normalization of the endometrium and no chronic inflammation [7]. Definitive evidence revealing no chronic inflammation was provided by biopsies taken by Dr. Lu in her examination of QS patients in Guizhou Province, China [12]. These observations are important because chronic inflammation is a known promoter of cancer [35].

In 2000, a Food and Drug Administration (FDA) Phase 1 study of QS was initiated at the Women and Children's Hospital of Buffalo, a teaching hospital affiliated with the State University of New York at Buffalo School of Medicine [36]. The hospital's investigational review board approved the clinical trial. Ten women who desired sterilization volunteered for QS and agreed to participate in the trial. This study was completed in 2003. There were no SAEs reported in this Phase 1 trial.

In October of 2003, the International Federation of Gynecology and Obstetrics (FIGO) devoted a half-day seminar to QS at its biannual international meeting in Santiago, Chile. Most of the presentations were published in a special supplemental issue of FIGO's journal, the International Journal of Gynecology & Obstetrics [37]. Twenty-five articles from 15 countries, covering 40,252 cases of QS, updated the QS literature. This collection of articles provides evidence for the safety of this method. All published clinical studies to date show that QS is not associated with an increased risk of reproductive tract cancer.

In 2001, Potts and Benagiano wrote, in an article entitled, *Quinacrine sterilization: a middle road*, "…we both wish to help broaden the range of fertility control options available, especially for low income women around the world. …. It always takes a decade or two to gather empiric evidence of safety, based on large-scale actual use." [38].

5. Animal safety studies

The WHO comments on quinacrine-prompted Family Health International to conduct animal (mouse and rat) studies to evaluate a possible risk of cancer from QS. These animal studies were initiated in the early 2000s. Quinacrine demonstrated no genotoxicity in a neonatal mouse assay, published in 2006 [39]. A 2-year rat carcinogenicity study (CaBio) used varying doses of quinacrine, which were placed in the rat uterus in an attempt to "mimic" the action of QS in the human situation [40]. However, for the following four reasons, the rat study did not mimic the human QS experience: (a) quinacrine was administered to rats in a slurry formulation while in women quinacrine is placed in the uterus in the form of solid pellets (use of the slurry formulation in women was abandoned in 1975 due to excessive toxicity); (b) methylcellulose (MC), a known tissue irritant that causes chronic inflammation [41], was added to the slurry of quinacrine (MC is not part of the quinacrine formulation administered to women); (c) the rats developed rare cancers that were preceded by chronic inflammation, and chronic inflammation is a known tumor promoter in cancer induction [35] (chronic inflammation has not been reported in women who received QS); and (d)

[1] Letter, Frank Webb, of the WHO Human Reproduction Programme, to Linda Demers, UNFPA representative for Vietnam, Dec. 7, 1993.

cancers in the rats developed only when doses of quinacrine exceeded the maximum tolerated dose (MTD). However, FDA/international conference on harmonization guidance states that the MTD in a study should be one that is minimally toxic and one that is tolerated without chronic dysfunction or pathological changes that would interfere with the interpretation and, therefore, the validity of the study [42].

These differences in formulation and dosing undermine the rat CaBio study's usefulness for an assessment of carcinogenicity with QS. One published interpretation of this rat CaBio concludes that quinacrine is not carcinogenic in rats at doses that do not exceed the MTD [43].

6. Comparison of QS to alternative methods of permanent contraception

Some critics of QS have proffered that alternative methods of contraception, like IUDs, might serve the same purpose as QS. While acceptance of long-acting reversible methods is growing in the United States, continuation rates may be lower in developing nations. Four IUDs were studied in a randomized controlled trial of 1905 women by the Indian Council of Medical Research. After 3 years, continuation of the levonorgestrel IUD was 38.8%, and the Cu T 200 IUD ranged from 45.4% to 50.4% [44]. Sterilization is the only method where the continuation rate approaches 100%. Essure™ (Bayer Healthcare), a device that is placed into the openings of the fallopian tubes using hysteroscopic guidance has been advanced as a minimally invasive method that is safer and more effective than traditional surgery. However, the technique still requires surgical facilities. Considerable surgical training is required, as failure of bilateral placement as high as 23% have been reported [45]. This is due to various reasons, including poor visualization, sclerosis and scarring of the oviduct. Due to these placement problems, and failure of some women to complete active follow up to confirm tubal occlusion, the failure rate for hysteroscopic sterilization may be higher than laparoscopy [46].

7. Conclusion

Like all methods of family planning and especially permanent methods, QS should always be offered in human rights frameworks of fully informed consent. Much is now known about QS. It is nonsurgical, there is no need for anesthesia, and studies have shown that it is safe. With the improved Hieu insertion technique, and two treatments, QS effectiveness (failure rate of 1.2% after 2 years) compares favorably, with surgical tubal ligation (0.7% at 2 years). The cost is low, and QS can be performed by nonphysicians [12]. It is time to reexamine the epidemiological and clinical data on the use of QS and reconsider its use in both developed and developing countries.

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