



Quinacrine sterilization: a retrospective

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Abstract

Objective: To trace development of quinacrine sterilization (QS). **Methods:** Review of published reports. **Results:** The high prevalence of septic abortion among high parity women in Santiago, Chile, motivated Zipper to find a safe, inexpensive method of non-surgical female sterilization. Various cytotoxic drugs were tried in rats. Because quinacrine was already accepted for intrapleural injection it was chosen for the first clinical trial. A slurry consisting of quinacrine and xylocaine was instilled into the uterine cavity with a transcervical syringe. Reasonable efficacy was noted and a limited scar of the intramural tube demonstrated. However, a side effect of cortical excitation and reports of 3 deaths ended this approach. Zipper and Wheeler hypothesized that the difficulty was due to rapid absorption of quinacrine under pressure and designed a pellet form that dissolves slowly and could be delivered transcervically using a modified IUD inserter. A standard protocol of 252 mg in seven 36 mg pellets placed at the uterine fundus on two occasions a month apart has now been widely used with considerable evidence for safety and efficacy. Indeed, protection is greater than 98% at 2 years of use. **Conclusion:** QS is ready for widespread use, especially where surgical sterilization is not safely available or when women are poor candidates for surgery or have such a fear of surgery that they will not seek surgical sterilization.

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1. Introduction

The motivation for developing a non-surgical method of female sterilization was initially the high prevalence of septic abortion seen in government hospitals in Santiago, Chile [1]. A majority of these patients were of high parity; they occupied an important segment of female ward hospital beds and accounted for a significant proportion of maternal mortality in Chile [2], estimated as 38.8% in 1963. In this predominantly Catholic country, contraception was not legalized until 1967, at the time of an International Planned Parenthood Federation conference in Santiago;

but abortion remains illegal. Government hospitals to this day cannot accommodate the demand for an elective procedure such as surgical sterilization [3]. As a result, its prevalence in Chile remains low [4]. The same is true for such countries as Indonesia [5], Vietnam [6] and Egypt [7], for religious and political reasons despite their well-developed family planning programs. There is a great need for a less invasive method of female sterilization, especially one that could be safely performed in rural areas of developing countries at an affordable cost.

2. Early animal experiments

Although transcervical sterilization techniques have been investigated for over a century, using silver

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nitrate applied to the cornual angles of the tubal ostia [8] and electrocoagulation of the same areas [9], modern methods were initially described by Corfman in 1967 [10]. The experiments of Zipper and his coworkers [11] started with the use of cytotoxic compounds in rats. While some agents studied did have a pronounced effect on fertility, they were also known to be systemically toxic. Their research therefore turned to quinacrine [12] which, at a concentration of 200 mg/ml in distilled water, produced permanent occlusion of the uterine horn of rats. The fact that quinacrine was already clinically accepted for intrapleural injection for the treatment of repeated pleural effusion [13,14] led to a decision to try this compound clinically as a method of fertility control.

3. Quinacrine slurry studies

The first quinacrine slurry trial [15] used two concentrations of quinacrine of 125 mg/ml in 2 ml of distilled water for 85 cases and 250 mg/ml in 4 ml for 37 cases. Instillations were made during the proliferative phase of the menstrual cycle until there was evidence of tubal occlusion by CO₂ insufflation, or hysterosalpingogram. Three instillations were planned for the 125 mg/ml concentration and 2 for the 250 mg/ml slurry. An 88.2% tubal obstruction rate was seen for the 125 mg/ml group with a cumulative life-table pregnancy rate of 1.2% for obstructed cases at 31 months of use. The 250 mg/ml group had tubal occlusion of 84.3% and zero pregnancies among occluded cases. During this period, a few patients had hysterectomies and sections of their tubes were examined. These showed that the occlusive lesion was located in the intramural portion of the tube and extended for 2–4 mm. The muscular layer did not reveal important changes. No permanent damage to the endometrial mucosa was evident. The protective effect of zinc was also noted. A single complication of cortical excitation occurred in 150 quinacrine instillations. A few small quinacrine slurry trials were reported from Miami, Florida [16], Thailand [17], Jamaica [18] and Canada [19]. This experience was encouraging enough to pursue research on a larger scale, with potentiating agents to improve efficacy. Such a clinical trial by Zipper and his coworkers [20] suggested that xylocaine may improve efficacy.

This led them to conduct, in cooperation with the

International Fertility Research Program (IFRP) [21], a clinical trial of slurry instillations in xylocaine involving 300 Chilean women. They used 3 instillations, the first two a month apart and the third at six months, with 1.5 g of quinacrine suspended in 5 ml of 2% xylocaine delivered in a 4 mm cannula and 10 cc syringe. Of an initial 300 cases recruited, 114 completed the third instillation and were followed for 13 to 24 months with a pregnancy failure rate of 7.1%; most of these failures (80.4%) occurred before the third instillation. Zipper's 1976 report concluded that a revised quinacrine instillation schedule was needed to improve efficacy and such trials were planned. However, reports of 2 deaths were noted in other experiences and when a third death was reported in Bangladesh, no further cases of the quinacrine slurry method were performed.

4. Quinacrine pellet method

After the decision to discontinue quinacrine slurry instillations, discussions between Zipper and Wheeler of the IFRP led to the hypothesis that cortical excitation and possibly fatalities with the quinacrine slurry method were due to rapid absorption of the slurry through endometrial capillaries and that this could be avoided by preparation of quinacrine in pellet form for its slow release without pressure. Furthermore, they believed that in pellet form, the dose could be greatly reduced, from 1500 mg to 250 mg, which would also lessen the risk of cortical excitation. Wheeler designed a simple method for preparing the pellets [22] which was first used clinically by Zipper [23]. Cortical excitation did not appear with the pellet method. Several pre-hysterectomy studies confirmed Zipper's previous impression [15] that damage to the intramural tube was limited [24–27]. A further study [28] initiated in 1977 in Santiago, Chile, with pellets made at the Pharmacy Department of the University of North Carolina, showed additional promise by 3 monthly insertions of 252 mg of quinacrine as pellets with a 12-month pregnancy failure rate of 3.1%. Shortly thereafter, a trial was initiated in Baroda, India, with similar encouraging results. This trial, with support of the IFRP, was later reported with 4 years' follow-up [29].

With these encouraging results, three different initiatives were set in motion. The IFRP prepared a proposal

for a United States Food and Drug Administration (FDA) approved trial [30], which included pharmacologic and toxicologic studies [31–34] to be conducted at the Johns Hopkins University in the early 1980s. At the same time, the International Federation for Family Health (IFFH) arranged for manufacture of quinacrine pellets in Taiwan and later in Switzerland. Supported with this supply the IFFH mounted a large number of clinical trials in developing countries [35–41]. The largest of these was conducted by the Ministry of Health in Vietnam [41].

Finally, in a meeting of the authors in the early 1980s in Chapel Hill, North Carolina, it was decided that a field experience was needed in rural regions of a developing country to determine the suitability of QS for areas of greatest need. As IFFH had a long-standing experience with the Indian Rural Medical Association (IRMA) in Calcutta, that organization was encouraged to introduce a network of its active members to the procedure. These were primarily homeopathic physicians practicing outside the urban confines of West Bengal. The training proceeded in 3 phases; first, in IUD insertions, second, in menstrual regulation and finally, in QS. Dr. Biral Mullick, Secretary General of IRMA, an obstetrician/gynecologist who had published [42] his own experience in QS, supervised this preparation. Approximately 100 rural-based clinicians received this instruction, and it is estimated that over 30,000 QS cases were performed in their private practices without a reported mortality. Their early experience was under IRMA-approved protocols [42–45], even before IRMA had accepted a standard protocol [46] for their service programs. Their experience is considered the acid test of QS safety, which was clearly established with no reported deaths or hospitalizations required for complications in over 30,000 cases. A report in 1996 [47] summarized the international experience of the first 100,000 cases of QS. In the same vein, long-term follow-up of early QS experience in Chile showed no evidence of increased cancer risk [48]. The risk of birth defects with QS was also estimated to be remote [49] and ectopic pregnancy risk is not higher than for surgical sterilization [50].

5. Progress in efficacy of QS

The original insertion techniques of quinacrine pellets

followed IUD experience using a mid-intrauterine placement as for a Lippes Loop, or a vertical line of pellets from fundus to mid-uterine placement with the Copper T insertion technique. Hieu was the first to publish an insertion technique [41] that would place all pellets at the very top of the uterine fundus. Bairagi and his coworkers provided evidence for the superiority of the Hieu technique [45]. A wide experience since this report shows that almost all published reports using the Hieu technique have pregnancy failure rates below 2% at two years of use. Confusion occurred in the publication of an evaluation of the Vietnam field trial that showed a higher failure rate [51]; this was answered by Lippes in a letter to the editor [52]. It appears that pregnancy failure rates in the Vietnam trial were exaggerated by the availability of menstrual regulation for delayed periods, a recognized side effect of QS [35]. The true failure rate of the Vietnam experience remains unknown.

6. Future prospects

Despite a wide experience of QS demonstrating safety and reasonable efficacy using a standardized protocol [46], the method remains unaccepted by any government. It appears that without US FDA imprimatur of QS there is little chance of such sanction. For this reason, the IFFH and the Center for Research on Population and Security (CRPS) have encouraged FDA-approved trials in the USA, which have now been initiated by Dr. Jack Lippes as principal investigator. The need for QS as an option for American women has been described by Lippes [53], and certain American clinicians have begun to offer QS to their patients [54].

There is also current research [55] suggesting the possibility of identifying tubal closure after QS by ultrasound. This may not only improve efficacy but reduce the need for a second or third insertion in a high proportion of cases.

7. Conclusions

The original QS research in Chile continues to grow [56] and it has been joined by a wide international investigation. QS safety is thoroughly demonstrated

in long-term clinical experience in a wide variety of settings. There is a growing consensus [57] that the method should be made available to women where surgical sterilization is difficult to provide safely. Prospects for improved efficacy matching that of surgical sterilization appear likely. Final approval by the US FDA of QS is now the highest priority for contraceptive development.

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