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8-Year follow-up in a randomized trial of one vs two transcervical insertions of quinacrine pellets for sterilization in Indonesia

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Abstract

Objective: To evaluate the efficacy of one vs two insertions of quinacrine and the long-term safety of quinacrine sterilization (QS) 8 years after the procedure in Indonesia. *Methods:* Between March 1993 and September 1995, a randomized trial was conducted in 6 academic centers in Indonesia. In February 2003, a follow-up study was undertaken in Bandung, one of those centers. This survey required a home visit of each woman. A questionnaire was designed to elicit information regarding current general health status, method failure, pregnancy outcomes and other contraceptive methods now used by women who experienced failures. Among the 70 patients receiving a single insertion of quinacrine pellets, 14.3% had become pregnant. There were no pregnancies among the 30 who received 2 insertions. All the women were found to be in good health. No long-term side effects or complications were identified. *Conclusion:* The two-insertion protocol is unmistakably superior to the single insertion. This study provides further evidence that QS is a safe contraceptive method.

Keywords: quinacrine sterilization, nonsurgical sterilization, female sterilization

1. Introduction

The Indonesian government's formal efforts at family planning began in 1970, and by 1994 the prevalence of modern methods of contraception had exceeded 50%. Despite this success, there are shortcomings in the country's health status in general and in its family planning program in particular. In 1994, maternal mortality was reported to be 326 per 100,000 live births. Yet, in the contraceptive mix in Indonesia, female surgical sterilization accounted for only 2.9% of users. Research in both Indonesia [1,2] and elsewhere [3–5] had shown quinacrine sterilization (QS) to be both safe and reasonably effective. Delivery of quinacrine pellets is remarkably similar to IUD insertion. In Indonesia, we have a great resource in that we have a large cadre of well-trained paramedics who are experienced in IUD placement. These personnel are strategically located throughout the country. With minimal additional training, they can safely and effectively perform QS.

The potential for QS to increase the prevalence of female sterilization led the National Family Planning Coordinating Board (NFPCB), with the approval of its ethics committee, to conduct a trial of this method in 6 academic centers located throughout the country. We viewed the requirement for 2 insertions as disadvantageous. A single insertion would be preferable in our circumstances. For this reason, the Board decided to evaluate the differences in one- and two-insertion protocols in a randomized trial. The financial cost of this evaluation was an important consideration, as

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it would be for any developing country. However, we recognized from the outset that to definitively demonstrate that the one- and two-insertion protocols were comparable in safety and efficacy was beyond our means.

Of particular interest to us were the single-insertion protocol and center variation in efficacy. We chose a study design using 6 centers, with 100 subjects each, divided into a group of 70 for single insertion and another of 30 to receive two. The original plan called for an expanded trial based on results of this initial research. A single venue with clinical trial experience was chosen from Bandung, Denpasar, Jakarta, Semarang, Surabaya and Yogyakarta. Since I had undertaken a clinical trial of QS in the 1980s, I was appointed principal investigator, to be responsible for the training program. All insertions were performed by obstetricians. The specifics of the study design, as well as the results of this trial, are described in an article on the first-year follow-up [6]. All women entered this 6-center clinical trial between April 1993 and September 1995. There were 2 pregnancies at one year among the 180 receiving 2 insertions (1.1%) but 31 failures after one year among the 420 women with only one (7.4%). Both two-insertion pregnancies and 11 of the 31 among single-insertion cases occurred at the clinic in Denpasar.

The current report is based on the results of an 8-year follow-up of the 100 women who elected QS in Bandung only. At one year, this clinic had a single-insertion failure rate of 2.8% but no two-insertion pregnancies.

2. Materials and methods

For the purpose of conducting an 8-year follow-up of the 100 women electing QS in Bandung, a questionnaire was designed to elicit information regarding their current health status, pregnancy, including pregnancy outcomes and the method of contraception chosen by the women who experienced a failure with QS. Home visits, where the questionnaire was administered, were conducted in February 2003.

3. Results

In the group of 70 patients who had a single insertion of quinacrine, 9 were lost to follow-up. We were unable to locate one of the 30 women who had 2 insertions. In all cases, those lost to follow-up had changed addresses in the 6 years since the 1-year monitoring. Thus 90 of the 100 women were interviewed for a follow-up rate of 90%.

The ages of the women at the time of the home visit ranged from 41 to 50 years. All of them were found to be healthy. None of the 29 who had had 2 insertions became pregnant. Ten of those with only a single insertion had become pregnant, for a crude failure rate of 14.3%. The distribution of these pregnancies over time is shown in Table 1.

Table 1
Time interval of pregnancies following a single insertion of 252 mg of quinacrine, Bandung, Indonesia, March 1993 to September 1995 ($N = 10$)

Years	Pregnancies (No.)
<1	2
1 to 2	3
2 to 3	2
3 to 4	0
4 to 5	1
5 to 6	1
6 to 7	1
Total	10

The outcomes of the 10 pregnancies were as follows: 4 women decided on menstrual regulation followed by surgical sterilization; 6 chose to continue their pregnancies to term and had normal deliveries. Two of these 6 patients requested surgical sterilization after delivery, while 3 selected the IUD and one selected OCs for their method of contraception.

4. Discussion

The distribution of pregnancies as shown in Table 1 suggests that the body continues indefinitely to try to repair the injury to the one-cell thick lining of the fallopian tube caused by only a few hours of exposure to the antibiotic, quinacrine. Sometimes, it succeeds. In most, if not all of the 10 cases, the tubes were blocked and then, with the passage of time, they became unblocked. Somehow, the second insertion reinforces the first in the formation of the

scar. This is an important research question for the future. If the mechanism for this reinforcement could be determined, then perhaps an adjuvant could be developed to be administered at the time of the first insertion, thus eliminating the need for a second one. But this experience clearly demonstrates that two insertions of quinacrine are more effective than one.

That 6 of the 10 women decided to seek surgical sterilization after their QS procedure failed suggests that permanent contraception is highly desirable. Yet, sterilization accounts for only 2.9% of the contraceptive mix of Indonesia. There may be considerable frustrated demand for sterilization services in our country. During home visits for this follow-up study, we encountered many other women who knew about QS and wanted this procedure for themselves.

As noted earlier, the NFPCB had planned to undertake another clinical trial of 600 women that would involve paramedics. But it never took place. With a letter from the World Health Organization to the NFPCB, dated 27 January 1994, containing the statement, "WHO experts and FDA officials have said that they would be surprised if quinacrine did not turn out to be carcinogenic", began a period of international pressure to halt research on this promising new method. After the 600-case clinical trial was completed and the data analyzed, the NFPCB decided in 1997 to ignore the external opinions and proceed with the planned 600-case trial at the health center level with paramedics. After all, the claim that quinacrine might be carcinogenic at the dose required for QS was not credible. Quinacrine had been used clinically for treatment and prophylaxis, even in Indonesia, for 60 years at doses of 36,000 mg per year without any hint that it might cause cancer.

I was invited to present the findings of this study at the 2000 FIGO meeting in Washington, DC and authorized to inform the gathering that we had been given verbal approval to proceed with the second trial of 600 cases. As a part of my presentation I proudly made this announcement. But this approval was short-lived. The international pressure to stop this research was then renewed, possibly due to several factors, including my announcement. In an interview with *Wall Street Journal* reporter, Alix Freedman, in Jakarta on January 19, 1998, our Minister of Population informed her that "Indonesia simply cannot fly in the face of world opinion" (Personal communication, Stephen D. Mumford, Dr.P.H., January 19, 1998). No further action has been taken on this second trial. We hope that FIGO will act to counter the opposition to further research of this method. Then when women ask how they may obtain a QS for themselves, we will be able to respond in a satisfactory manner.

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