Quinacrine nonsurgical female sterilization*

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Sterilization is currently the most prevalent contraceptive method in the world; the demand for female sterilization, especially in developing countries, is likely to sharply rise in the remainder of this decade[1]. The need for a safe, inexpensive and effective method of female sterilization to meet this need is a high priority for fertility research. The acceptable nonsurgical female sterilization method has been described as one that is safe, 95% effective, that can be performed by nonphysicians on an outpatient basis after a brief training period, and that requires only a single visit by the woman.

The transcervical quinacrine pellet method developed by Zipper and co-workers[2], which utilizes an intrauterine device inserter to deposit 252 mg of quinacrine hydrochloride as pellets in the uterine cavity, has potential for meeting this description. Prehysterectomy studies of the quinacrine method in women showed that quinacrine produces inflammation and fibrosis that is confined primarily to the intramural portion of the fallopian tube[3].

This method can be performed by nonphysicians on an outpatient basis after a brief training period or by any personnel capable of performing an intrauterine device insertion. In the studies of the quinacrine pellet method for female sterilization reported to date[4–11], the method appears to be safer than surgical sterilization.

Major complications of the quinacrine method reported in a large field trial in Vietnam[11] of 0.03% is remarkably lower than major complications for laparoscopic sterilization of 1.7% (refs. 12, 13). Smaller clinical trials of the quinacrine method[4–10] support its safety as far as early major complications are concerned. Side effects of the quinacrine method are also reported as mild and transient in these studies. There have been no deaths reported in 80,000 quinacrine method procedures whereas in Bangladesh[14] and in Gujarat State, India[15] case fatality rates of 19 and 20 per 100,000 female surgical sterilizations, respectively, have been reported.

The greatest benefit of the quinacrine method is its ability to raise contraceptive prevalence among high risk women of developing countries with high maternal mortality. Many expensive but needed interventions are being considered to lower maternal mortality[16], but the quinacrine method is the most cost-effective.

Risks of the quinacrine method

The risk of ectopic pregnancy for the quinacrine method in Vietnam has been reported as 0.89 per 1000 woman-years of use in two insertion studies, similar to that of IUD users[11]. Ectopic pregnancy risk is highest among noncontracepting women[17].

Reversibility of the quinacrine method, being a proximal occlusion, is expected to be more difficult and less successful than for surgical tubal occlusion. In developing countries the comparative risk is for disappointment among a relatively small group of women who fail to have a reversal and a much larger number of women whose lives are saved by avoiding maternal mortality[18]. Newer methods of treating proximal occlusions by transcervical catheterization of the tube might also apply to the quinacrine method[19].

The risk of toxic effects of accidental perforation of the uterus and intraperitoneal administration of 252 mg quinacrine must be considered. In the two cases reported[20] hospitalization was not required and no permanent sequelae occurred. Quinacrine has been administered intraperitoneally in cancer patients to treat recurrent effusions. Doses of 400 mg produce relatively mild toxicity[21].

The risk of cancer of the uterus or tubes of two insertions of 252 mg of quinacrine must be considered. A retrospective cohort study of 1,492 women in Chile who received the quinacrine method between 1977 and 1989 showed no excess cancer risk for the quinacrine method (Sokal, D., submitted for publication). A large clinical experience and toxicology studies of quinacrine for prophylaxis and treatment of malaria[22] has not shown evidence of cancer for the doses used for sterilization. The main concern in this regard stems from quinacrine being mutagenic by the Ames test[23]. Approximately 60% of chemicals showing mutagenicity in such bacterial systems are shown to be carcinogenic in rodents[24]. But these rodent carcinogenicity tests are carried out at the maximum tolerated dose for the life of the rodent which shows carcinogenicity for most substances tested, including some commonly used in human diets.

Toxicology studies conducted by Johns Hopkins University in the 1970s were acceptable in the United States Food and Drug Administration to grant to Family Health International (FHI) an Investigational Exemption for a New Drug (IND) and a Phase I study involving 10 American women volunteers scheduled for a hysterectomy was conducted.

There are now plans to repeat and possibly extend the toxicology studies conducted at Johns Hopkins University and to reapply for an IND. This will be costly and time-consuming and the question arises as

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to whether clinical trials and even field trials should be conducted concurrently with these toxicology studies. In a consultant report prepared for FHI[26] to assess the risk of cancer by the quinacrine method, toxicologists express the opinion that 'the lack of positive *in vivo* data and considering the extent of medicinal use, the lack of relevant human data suggests that the risk for cancer may be quite small'. It is necessary to balance this small risk with the need for further information from clinical trials, in light of the demonstrated safety of the quinacrine method to date.

Need for clinical trials

Most developing countries will need to conduct clinical trials required by their own regulations to confirm safety and effectiveness of the quinacrine method in their local circumstances. If these studies can be initiated now, the potential benefits of the method, including saving of lives of women of reproductive age, can be realized earlier.

Three approaches to improving efficacy of the quinacrine method are in need of controlled clinical trials. Merchant and her coworkers[27] have shown in prehysterectomy studies that the longer the insertion to hysterectomy interval the higher the tubal closure rate by histological examination. She recommends at least six weeks additional contraception from last insertion of quinacrine pellets. In a study by Mullick[28] it appears that depoprovera may be the contraceptive of choice.

In the large Vietnam field trial[11] great variation was noted in efficacy of individual studies and between inserting clinicians. We hypothesized that insertion technique was responsible and recommend a technique that assured all pellets are deposited at the fundus, which is not the case if a Copper T IUD insertion technique is used. This hypothesis needs testing.

Finally, Zipper[29] and coworkers have suggested antiprostaglandins might improve efficacy when inserted along with quinacrine. There is some evidence (Bashir, A., paper in preparation) that oral ibuprofen given before quinacrine insertion can improve efficacy. From both this work of Bashir and the use of depoprovera 150 mg IM (ref. 28), it appears that high efficacy in the range of 98% to 99% at 12 months can be achieved with a single insertion.

The choice for south countries

Official trials of the quinacrine pellet method have been initiated in China, India, Indonesia, the Philippines and Vietnam, and additional trials are underway in government facilities in Bangladesh, Chile, Costa Rica, Croatia, Egypt, Malaysia, Pakistan and Venezuela. Trials in private clinics are underway in India, Pakistan and Iran.

One of the research contrasts between North and South countries in contraceptive research is that the North has the resources and technical capabilities to conduct preclinical toxicology studies that the South can ill afford, while the South can more economically document efficacy, acceptability and early safety in trials of a new contraceptive method. The main contraceptive methods in use today and approved by North regulatory agencies, such as the hormonal methods, including orals, injectables and implants, and intrauterine devices, have all had their efficacy, safety and acceptability documented in clinical trials in developing countries before pharmaceutical companies or foundations went to the expense of completing toxicology studies or clinical trials required by North regulatory agencies.

Any organization attempting to develop a new contraceptive method entirely within a North regulatory framework will be faced with high resource commitments and long time delays before reasonable assurance of clinical safety and efficacy of the method.

The only logical global standard is a risk-benefit one which will vary by circumstances of the country involved in the research. A simple guide to determining benefits is the estimate for rural areas of South countries that each sterilization prevents two births. If maternal mortality is, say, 3.8 per 1,000 live births as estimated for Vietnam[11], then each 1,000 additional sterilizations performed by a new method such as the quinacrine pellet method will prevent 7.6 maternal deaths. No one is suggesting that this method could kill that number of women. In over 80,000 procedures performed to date there has not been a case-fatality reported whereas there were three case-fatalities for a similar number of surgical sterilizations in Vietnam.

Lessons learned from the field trial

The main lessons learned from the field trial[11] can be summarized as follows.

1. No case fatalities were reported in 31,781 procedures, whereas two case fatalities were reported for a similar number of surgical female sterilization procedures in 1992 in Vietnam.
2. Early serious complications of 0.03% was considerably lower than that reported in the literature for surgical female sterilization.
3. The Q Method was more acceptable to Vietnamese women than surgical sterilization.
4. Ectopic pregnancies in Namha Province studies (N = 4511) were 6 or 3.5% of all pregnancies in these studies, which comes to 0.89 per 1000 woman-years of use. The rate of ectopic pregnancies per procedure was 0.14%, which was similar to that for IUD users

Family planning in Vietnam

A trial of nearly 32,000 quinacrine pellet female sterilisations in Vietnam needs to be seen in the context of a country in transition. Working in Vietnam since 1987 for various United Nations agencies I have witnessed the country's rapid transition from a centrally planned to a market-oriented economy. From being a rice importer, Vietnam has now emerged as a major exporter. After a period of political isolation it is now forming links with the international community. Sadly, the US embargo continues to hinder some investments needed to modernise, and the gross national product is still only around $200 per head. It is within this context of low budgets and an increasing population of reproductive age, that the country has forged its population and family planning policies. The main objectives are small family size (preferably a two child family), a lower infant mortality rate, from 45 to 25 per 1000, lower child malnutrition rates from 50% to 25%, reduced maternal mortality from 120 to 50/100,000, increase in contraceptive use by 20% from its present rate of 33%, and reduction in fertility rate from 4.0 to below 3 by the end of the century.

There is a strong awareness that, without voluntary but vigorous family planning, the population could double to 170 million within 30 years. The government has trebled its population and family-planning budget, but this still amounts to only 15 US cents a head, while neighbouring countries are said to spend 6–10 times as much. Vietnam may need to spend 60 cents per head to achieve its goals. Even with international donor support Vietnam's budget for population and family planning is tiny.

The search is on to broaden the range of family planning methods currently in use. In 1990 there were reported to be about 1 million abortions, another million insertions of intrauterine devices, around 223,000 pill users, and 23,000 sterilisations. Menstrual regulation is legal and free, and is available in communes where there is a three-year trained health worker. Research is in progress in Ho Chi Minh City on injectable and implanted contraceptives. Acceptance of male sterilisation is said to be increasing. Longer term government policy emphasises increased local production of some contraceptives, including condoms.

The context in which field trials of quinacrine pellet non-surgical female sterilisation have been carried out in Vietnam is multifaceted. In the study by Hieu and co-workers, physicians and midwives trained in IUD insertion were used. Vietnam is currently in the throes of a major overhaul of health manpower and health facilities. It may in future be possible to have one full-time health professional to act as family planning focal point at every commune health station. If quinacrine pellet sterilisation were to be offered on a wide scale, there would, theoretically be no shortage of health staff trainable in such a procedure. However, there are weaknesses in district level health services, including family planning, and problems also in providing health staff with continuing education. Another issue is standard of sterility in the health facilities where this procedure would be done. Further research is also required – for example, on the effects of insertion technique, on the efficacy of quinacrine pellet sterilisation, and on concentration of quinacrine in the uterine cavity in relation to placement and efficacy.

It is thus within a complex web of issues that Vietnam is exploring the use of quinacrine pellet female sterilisation. Financially, this method is attractive. The cost of quinacrine and supplies for two insertions is reported to be less than $1. The field trial also suggests that around 242 maternal deaths may have been averted during the study. Hieu *et al.* estimate that 1300 clinicians doing 100 or so quinacrine pellet insertions sterilisations a month could meet Vietnam's unmet need for female sterilisation. That could be an important contribution to the country's family planning needs in an era of economic development and modernisation.

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in Namha Province of 0.13% among 18,000 IUD users.

5. There was variation in pregnancy failure rates between studies for those using two insertions, ranging from 0.95 ($N = 105$) to 4.54 ($N = 710$) per 100 women at 12 months. For all two insertion studies, which were censored to have at least 50 cases at risk at 12 months, the rate was 2.63 ($N = 9461$).
6. Further analysis of pregnancy failures by operator experience in two Namha Province studies ($N = 4010$) showed that while small experience with quinacrine pellet insertions resulted in higher failure rates, those clinicians who had experience of more than 10 insertions who had failures had mean failure rates that were similar regardless of experience.

This suggested that there was something about their insertion technique or patient selection that contributed to pregnancy failures. We believe two insertion techniques were mainly used. Our recommended procedure was to pass the inserter to the fundus, withdraw it 1/2 cm and then push the inserter plunger. This would deposit all pellets at the fundus. The other technique was the copper T insertion technique which would result in a column of pellets from the fundus extending toward the lower uterine segment. We suspect this difference in insertion technique may account for variation in failure rates among studies.

7. Assistant doctors and the midwife among inserting clinicians had a crude pregnancy failure rate lower