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Commentary

Quinacrine sterilization: a middle road

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Discussion of female sterilization using the trans-cervical application of quinacrine hydrochloride (quinacrine sterilization; QS) has become highly polarized [1,2]. We feel the unreasoned passion about QS is making evidence-based decisions difficult to reach.

We have both had executive responsibility for clinical trials on new drugs and devices, with particular reference to developing countries. In the case of QS, we have in the past taken somewhat different policy stands, although always sincerely respecting each other's points of view. Although we are no longer directly engaged in research in this area, we both wish to help broaden the range of fertility control options available, especially for low income women around the world. We think it would be useful to summarize where we agree, and to invite others also to look for common ground in this area.

We both recognize that introducing a new drug or device is a difficult. complex process that demands careful, sincere judgments. Experts do not always like to recognize that they are fallible, and the public does not like to accept an element of uncertainty. However, the introduction of any new drug must necessarily take place on the basis of balanced judgment and, almost inevitably, incomplete information. It always takes a decade or two to gather empiric evidence of safety, based on large-scale actual use. During this interval there are endless opportunities for nonobjective forces to surface.

1. Animal testing can demonstrate whether it is likely that there are more benefits than risks in introducing a new method or device, but it cannot prove human safety. Occasionally, animal tests produce results that are qualitatively different from those subsequently found in humans, as occurred with Depo-Provera.
2. Clinical trials in human volunteers can demonstrate the efficacy and can measure relatively common risks, but such trials cannot prove that rare, adverse side effects (including deaths) will not occur. We all know that, with rare exceptions, infrequent, adverse side effects do not occur in clinical trials.
3. Epidemiologic surveillance of large scale use of any new drug or device is prudent and has often provided additional valuable information about side effects, unexpected benefits, and optimum clinical use.
4. Parallel information available on the use of any given drug for other purposes can be relevant and valuable to the decision to make that drug available for a new use, but it cannot by itself be the deciding factor of whether the drug is safe or is not safe to be used for a new purpose.

QS is equivalent in clinical complexity to inserting an intrauterine device (IUD). Food and Drug Administration (FDA)-approved animals studies of QS were conducted in rodents and in primates in the 1980s [3,4], and additional tests are underway at present. A small series of pre-hysterectomy cases were studied in an FDA-approved trial in the USA in the 1980s [5], and an FDA-approved Phase I trial began in the US in 2000.

We feel the experience to date has shown that QS has a low risk of serious, immediate side effects. We recognize, however, that as with all new family planning methods at this stage of development, there are insufficient data to answer all possible questions about rare but potentially important long-term risks. We are also aware that decisions about QS can be easily misinterpreted as involving a "double standard," because it can appear that QS is being promoted in developing countries because it is low-cost and easy to use. However, we suggest that the differences are quantitative not qualitative. For example, there are heavy smokers in the USA for whom QS is a safer choice than surgery, just as there are women in India for whom QS is a safer choice than surgery. In India, where anemia is common, QS also has the potential to be a life-saving option for those women who are not fit for surgical, voluntary sterilization, but whose lives would be threatened by additional pregnancies [6].

We look forward to the ongoing documentation of large-

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scale use of QS in Chile and Vietnam, although we suspect that the number of cases is likely to be too small to provide a definitive answer about rare, long-term side effects (particularly cancer). We also look forward to the results of repeated and expanded animal tests now being conducted, although here again we suspect the results may be equivocal in some areas. Such animal tests can help answer the question, is it responsible to use this drug? But they can never answer the question, is this method safe to use? Until we have a very large scale of controlled use, we can never know that answer. We are glad that Phase I, FDA-approved trials are underway in the USA, and we believe that if they prove satisfactory then Phase II and III trials should be strongly supported.

We do not find problems and questions surrounding QS to be qualitatively different from those occurring with other methods in the past, such as IUDs or injectables. We would not be surprised if different countries were to treat the approval of this drug in different ways, according to the needs, conditions, and other options widely available in their respective environments.

We deplore hasty judgements and biased comments, and we ask all those who are interested in the welfare of women around the world to recognize the difficulty and inevitable uncertainty surrounding the introduction of any new method of fertility regulation.

We therefore urge those who favor the large-scale use of this method to proceed cautiously. At this stage, QS should be limited to those women who ask for sterilization and for whom existing methods are not available or present unacceptable risks.

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