Quinacrine non-surgical sterilisation: troubling questions

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Clinical trials of the quinacrine non-surgical sterilisation (QS) method raise a number of troubling ethical issues. This update on the quinacrine saga will present some of these dilemmas for discussion.

Quinacrine sterilisation has alternately been portrayed as an outstanding breakthrough for women in developing countries who die of pregnancy-related complications -- or as an unethical, covert experiment on 100,000 unsuspecting women in more than two dozen countries (1). Interest in the method had all but subsided because the promoters of the method were considered to be overzealous with a political agenda. However, Alix Freedman's article (2) critical of practices uncovered in the Vietnam clinical trials (3) generated a great deal of interest in the mass media and elsewhere. In 1999, the National Medical Committee (NMC) of the Planned Parenthood Federation of America (PPFA) decided to evaluate QS by reviewing the literature, and meeting with QS promoters and investigators. They also heard from a panel consisting of Dr. David Grimes, Family Health International (FHI); Ms Rachael Pine, AVSC International; Dr. Malcolm Potts and myself. The NMC committee recommended that a full-scale investigational study of the safety and efficacy of QS be conducted in the United States and that other similar studies be done in several foreign countries. However, the PPFA Board of Directors voted against it. This decision was influenced, at least in part, by a petition signed by women health advocates from around the world urging PPFA not to approve clinical trials. The petition cited several reasons, including the lack of basic animal toxicology studies, the unethical nature of the past clinical trials that lacked informed consent, and the potential for abuse.

It is unlikely that clinical trials will take place with the blessing of the PPFA Board, at least not until the Food and Drug Agency (FDA) approves toxicology studies being conducted by FHI. Proponents of QS are incensed that their plans for clinical trials in the USA were temporarily thwarted. Sarah Gamble Epstein circulated a "Dear Concerned Feminist" letter through various feminist listserves and by mail stating: "a fraud has been perpetrated on the Board of Directors of the Planned Parenthood Federation of America (PPFA). The quinacrine pellet method for non-surgical female sterilization (QS) is the most important development since the creation of the Pill... A group of four individuals, each with a long history of attacking other methods of contraception such as the pill, IUDs, Depo Provera and Norplant are the perpetrators of this fraud. They prepared the petition to the board that was circulated at the meeting and considerably alarmed the members" (5).

I will not waste energy engaging in a point by point refutation of this argument. However, there are many troubling issues with respect to QS. First, what motivates the promoters of quinacrine in their fervent pursuit of this method? Perhaps it is that many people accept dual standards, one for developed countries and another for developing countries. Some would go so far as to say that to do otherwise would be unethical (6). Others suggest that lives of 600,000 women who die annually due to pregnancy-related complications, including unsafe abortions would be saved if there were fewer pregnancies (7). They calculate risk: benefit ratios for the QS method by treating pregnancy as a disease (8). These arguments coupled to the promoters' anti-immigrant political agenda (2) explain why the method has support amongst the certain sections in the USA.

Second, if the method is so wonderful, why have the promoters not conducted animal studies for the drug's potential carcinogenicity and mutagenicity? They have argued that animal studies are not needed because thousands of soldiers during the Second World War used it prophylactically, without serious problem (9). Preliminary results from neonatal mouse studies were submitted to the FDA, who gave the go-ahead for a study with rats for reproductive toxicity and with neonatal mice for carcinogenicity. As far back as 1994, the World Health Organization had stated that these studies were essential before further clinical trials (10): FHI has also been involved with the follow up of women in Vietnam and in Chile. At the PPFA NMC meeting, Dr. Grimes said that the follow up of the original Vietnam study had uncovered some problems. During the QS procedure papaverine or ampicillin had been administered orally to some women but it was not reported in the original publication (4). Therefore, there were difficulties in interpreting the efficacy data. Most women were satisfied with the procedure but were concerned about failures and gynaecologic problems. They did not find any difference in the rates of tubal pregnancy between QS and surgical sterilisation. They also did not find any increase in rates of cancer (11); the follow up studies are ongoing.

Third, why do the main promoters of the method continue to publish "new data", collected under the pretext of providing a sterilisation service in different countries, knowing that it will always be suspect? Numerous papers essentially imply the same thing: that QS method must be good because (a) so many different groups have "confirmed" the results and (b) physicians from different countries get involved in the trials. Incidentally, these physicians become the first authors on papers, present "results" at international meetings and their travel expenses are paid for. These publications serve the propaganda campaign on behalf of the sterilisation method. The majority of papers on QS fail to describe whether informed consent was obtained; in fact there is evidence that women were not aware of that they were participating in a clinical trial (2,12,13). Follow-up of women in a vast majority of studies was

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about 12 months and in other instances it was sporadic or entirely lacking (12). Scientific analysis includes collection of data using ethical guidelines that includes approval of the protocol by an Institutional Ethics Board. Data obtained under any other circumstance are tarnished and must be discarded

QS literature helps develop support within United States for the method (14). The NMC's recommendation helps build credibility for the method despite the the PPFA Board's decision. It is important for QS's proponents to keep the method in the public eye and to win over different sectors in the regulatory process. Thus, they continue to make presentations at professional conferences; and they list upcoming conferences where they will have their information booths on their website (5).

President Bill Clinton's announcement that he will seek approval from Congress to impose fines on researchers and sponsoring universities who breach research ethics, to the tune of $ 250,000 and $ one million, respectively, does not address the issue of accountability (15). It does not deal with researchers who do not receive funding from US government agencies such as private foundations. Moreover, the Declaration of Helsinki (16) that governs clinical research in all countries does not have a mandatory monitoring process.

QS trials underscore the weaknesses in the guidelines to conduct clinical trials, especially in countries where procedures for human clinical trials may be weak or non-existent. It highlights how easy it is to by-pass the regulatory process altogether. Virtually all checks and balances seem to have failed in the majority of the studies on QS. No process has been built-in to ensure accountability and transparency in this process. There are no punitive measures against researchers violating ethical guidelines and the approved clinical protocols, other than through class-action suits for damages, an enormously difficult and expensive process inaccessible to most people, especially those in developing countries.

Even more troubling, there is considerable momentum to revise the Helsinki Declaration to weaken language on research conducted in developing countries. Although the proposed revisions strengthen the language concerning disclosure of conflict of interest (Clause 11, proposed revisions document 17C/ WW2/2000), Dr. Brennan (17) suggests "article 24 of the revised declaration would allow waiver of written informed consent if local ethics committees determined that the risks posed by the research are slight or if the procedures to be used in medical research are customarily used in medical practice without informed consent… It would be a matter to be decided by local ethics committees, guided by the local standard of care". This change can result in clinical research moving to countries that have the poorest regulatory process, just as manufacturing of goods under globalisation have moved to countries with very low wages to minimise costs of production and maximise profits with little regard for the health, safety and rights of workers. A human rights framework must be urgently introduced in the area of medical research (18) and accountability built in any undertaking in the clinical research enterprise.

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