Quinacrine sterilization for human immunodeficiency virus–positive women

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Objective: To evaluate the safety of nonsurgical quinacrine sterilization for HIV-positive (HIV+) women.
Design: An open trial of quinacrine sterilization was carried out in women infected with HIV and women who were HIV negative (HIV−). Comparison of the results with the two groups provided an assessment of the safety and effectiveness of quinacrine sterilization for HIV+ women.
Setting: University Medical School outpatient services.
Patient(s): A total of 258 women who desired sterilization were offered quinacrine sterilization as a means of limiting family size. Sixty-four were HIV+, and 194 were HIV−. Women who were HIV+ had CD4 counts >200 and were otherwise healthy.
Intervention(s): A modified Copper T intrauterine device inserter was used to place 252 mg of quinacrine, divided into seven pellets (36 mg each) into the uterine cavity. Three insertions of this formulation were performed, 1 month apart. Viral load and CD8 and CD4 lymphocytes were measured both before and after quinacrine sterilization and at follow-up visits. Pregnancies and adverse events were recorded carefully. A decrement life table was made to statistically analyze results.
Result(s) and Main Outcome Measure(s): No serious adverse event occurred in any patient in this study. Adverse effects related to quinacrine sterilization were abdominal cramping, vulvar itching, nausea, and vaginal bleeding. Vaginal bleeding was the only short-term side effect noted to occur more frequently in HIV-infected women after quinacrine sterilization. Among HIV+ women, 35.9% had complaints of increased bleeding, whereas only 8.2% of those who were HIV− had such complaints, which probably were insertion related. Viral load and the CD4+ and CD8+ lymphocyte measures displayed no statistically significant difference after quinacrine sterilization.
Conclusion(s): Quinacrine sterilization is a safe method for the sterilization of HIV-infected women and has no short-term effect on the pathology of the disease. (Fertil Steril® 2009;92:108–15. ©2009 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, QS, HIV, CD4+, CD8+, lymphocytes, viral load, ART

An increase in the world population of HIV-positive (HIV+) women in the reproductive age (between 15–49 years of age) to 18 million was reported in 2006 (1). Life expectancy for such women has improved because of the advances in antiretroviral therapy. Women infected with HIV are exposed to the same chance of becoming pregnant as those who are HIV negative (HIV−). Obviously, there is a need to educate all women and men about contraception (2). In spite of the increasing epidemic of AIDS, there is no consensus about the best method to control reproduction for HIV-infected women (2).

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Quinacrine nonsurgical sterilization was introduced by Zipper et al. (1970) (3). Subsequent research sought the best dose, the optimum number of quinacrine applications, and possible adjuvants to enhance efficacy (4–8). Today, quinacrine when used for sterilization is given in the form of slow-releasing pellets to avoid rapid absorption of the drug (9). Since the 1970s, experiments have been conducted to evaluate the efficacy and safety of quinacrine sterilization in >175,000 women of unknown serologic findings (10–14). Extensive literature has been published on the simultaneous use of aminoacridines and antiretroviral drugs in HIV-infected women in malaria-endemic areas, during pregnancy and breastfeeding periods, without any evidence of negative drug antagonisms (15–21).

This investigation addresses pursuant questions: Does quinacrine affect HIV pathophysiology? Conversely, does HIV alter the pharmacology of quinacrine, especially its effect in

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scarring the oviduct? Furthermore, will antiviral drug therapy enhance or inhibit quinacrine sterilization? Are adverse events of quinacrine sterilization different in HIV+ women, both those given and those not given antiretroviral therapy?

MATERIALS AND METHODS

This open clinical trial was carried out from February 2005 to August 2006 at the Family Planning Clinic, School of Medicine of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil. The research design, protocol, and informed consent were approved by the UFMG Ethics and Research Committee (the Brazilian equivalent of a US institutional review board). The women who volunteered to participate in this research freely signed the informed consent. Quinacrine pellets (Sipharm, Sisseln, Switzerland), already sterilized and packed in modified Copper T intrauterine device inserters, were used in this trial. Each inserter held seven 36-mg quinacrine pellets, a total of 252 mg for each of the three monthly insertions. Two hundred fifty-eight women were involved, of whom 194 were HIV− and 64 were HIV+. The HIV+ women were further divided into two subgroups: 42 patients who received antiretroviral therapy and 22 who did not. All subjects were sexually active. Each requested definitive contraception or sterilization. Their demographic characteristics are shown in Table 1. The women were advised to use an alternative contraceptive method after their first quinacrine insertion and for as long as 12 weeks afterwards, allowing time for subsequent inflammation and cicatrization of the lumens of the fallopian tubes. Women infected with HIV were included only if CD4 lymphocyte counts were >200 cells/mm^3 and without opportunistic infection. As required by the School of Medicine of the UFMG, women younger than 25 years or mothers with fewer than two living children were excluded. However, exceptions were made when there was a formal recommendation for sterilization from other clinics. Further exclusion criteria were pregnancy, being <60 days post partum, uterine bleeding, alcoholism, use of primaquine, being a carrier of psoriasis or porphyria, glucose-6-phosphate dehydrogenase deficiency, pelvic tumors, and pelvic inflammatory disease.

Seven quinacrine pellets, 36 mg each for a total of 252 mg, were inserted transcervically, high into the uterine cavity during the follicular phase of the menstrual cycle under aseptic conditions as described by Hieu et al. (22). After the procedure, the participants rested in a supine position for 1 hour. Quinacrine insertions were performed three times about 4 weeks apart. Six women received a fourth insertion because of bleeding that occurred immediately after or during quinacrine sterilization. Three of these women were HIV−, and three were HIV+. Another woman had an arcuate uterus found by ultrasound examination and had two simultaneous quinacrine insertions of 252 mg inserted into each uterine cornu for a total dose of 504 mg (Fig. 1).

Follow-up visits were scheduled for 1, 3, 6, and 12 months after the last quinacrine sterilization insertion. Short-term adverse effects (AEs) were considered those events that occurred during the procedure or 1 hour after insertion or that were obtained by history during the follow-up 1-month visit. Transvaginal ultrasonography searched for echogenic spots (scars) in the oviducts during the second visit after quinacrine sterilization.

The biologic monitoring by viral load and CD4+ and CD8+ lymphocyte counting was done before quinacrine sterilization and 4 to 6 months after the last quinacrine sterilization procedure. Blood for these tests was always drawn in the morning, with use of the MultiSET program at laboratories supervised by the Sistema de Controle de Laboratórios (Laboratory Test Control System), Belo Horizonte, Brazil. The viral load was determined with use of the branched DNA HIV-1–RNA method (version 3.0 VERSANT; Bayer S.A., São Paulo, Brazil), with detection sensitivity of 50 copies per milliliter (1.69 log) and maximum detection limit of 500,000 copies per milliliter (5.699 log). The T-CD4+ and -CD8+ lymphocytes were quantified by flow cytometry. Differences between two consecutive results of viral load >0.5 log or >70% of the absolute value of the number of copies per milliliter were considered significant (real differences). With CD4+ and CD8+ counting, variations >25% of the absolute value were considered significant (real differences). The sampling calculation was based on the type I α error of 5% and type II β error of 90%. Statistical calculations were done by Minitab (version 14.0; Minitab, State College, PA) and SPSS programs (version 12.0; SPSS, Inc., Chicago, IL). The χ^2 test was used to detect meaningful differences in qualitative variables inside the same group (homogeneity test, users or nonusers antiretroviral therapy). The Student's *t*-test was used to compare the groups according to quantitative variable means. The comparison of AEs was defined for significance by using the *z* test. Statistical evaluation for the presence of oviductal scars between groups that were HIV+ and HIV−, as well as the subgroups of HIV+, that is, those receiving antiretroviral therapy and those not receiving antiretroviral therapy, was calculated with the *z* test for proportions. The 95% confidence interval (CI) was applied, and the acceptably significant level for the hypothesis was $P<.05$.

RESULTS

The frequency of short-term AEs is presented in Table 2. Adverse events were abdominal cramping, nausea, yellow discharge, vulvar itching, and uterine bleeding. All women reported yellow vaginal discharge lasting from 3 to 20 days. In women who had four quinacrine insertions, AEs were similar to those in women who had three insertions. These AEs were managed easily as follows. Patients complaining of cramps were prescribed acetaminophen, which was taken only when needed. The yellow discharge was prevented or diminished by patients who douched with water for 1 or 2 days after quinacrine sterilization. Patients who douched also avoided vulvar itching. Uterine bleeding was the only AE with a higher frequency rate (23 [35.9%] vs. 16 [8.2%], $P<.001$) in HIV-infected women (Table 2).