GENERAL GYNECOLOGY

The levonorgestrel-releasing intrauterine system in human immunodeficiency virus–infected women: a 5-year follow-up study

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OBJECTIVE: We sought to assess the effects of long-term use and safety of the levonorgestrel-releasing (LNG)-intrauterine system (IUS) among human immunodeficiency virus (HIV)-infected women in comparison with HIV-infected women not using the device.

STUDY DESIGN: Fifteen women using the LNG-IUS and their 25 age- and $CD4^+$ lymphocyte count–matched control subjects with annual follow-up data were followed up for 5 years.

RESULTS: No unplanned pregnancies or pelvic infections occurred among the LNG-IUS users. Altogether, 12 (80%) of the LNG-IUS users continued its use up to 5 years. Annual $CD4^+$ lymphocyte counts were similar in the LNG-IUS users and control subjects throughout the follow-up period. The hemoglobin levels increased initially ($P < .005$) and remained higher among the LNG-IUS users ($P < .02$). Pap smears displayed non-squamous intraepithelial lesion cytology in ≥85% of cases in both groups.

CONCLUSION: No unfavorable effects on the course of HIV infection were noted during long-term use of the LNG-IUS. Dual protection by means of an LNG-IUS and condoms might be an ideal contraceptive strategy for HIV-infected women.

Key words: contraception, human immunodeficiency virus infection, intrauterine systems

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With an estimated >130 million users, intrauterine contraception is one of the most widely used methods of contraception worldwide.[1] The countries with the highest prevalence of intrauterine device (IUD) use, exceeding 40% among married or cohabiting women, are China, the Democratic People's Republic of Korea, and Kazakhstan. Women in sub-Saharan Africa show the lowest prevalence (0.5%) of IUD use globally.[1,2]

Infection with the human immunodeficiency virus (HIV) is a disease of reproductive-aged women.[3] Yet surprisingly little has been published on the topic of contraception and HIV infection. Research data concerning the use of intrauterine contraception in HIV-infected women are even more scarce. However, the safety of IUDs in HIV-infected women has been recently recognized, and their use in women living with HIV/AIDS has recently been classified as category 2 ("using the method generally outweighs the theoretical or proven risks") by the World Health Organization.[4]

We have previously assessed use of the levonorgestrel-releasing (LNG)-intrauterine system (IUS) in HIV-infected women in an extended case report[5] as well as in a prospective 1-year follow-up study.[6] In these studies use of the LNG-IUS was found to be safe, with effects similar to those seen in women not infected with HIV.

The use of hormonal contraception has been considered to be safe among HIV-infected women.[4] However, in a recent randomized study in which the safety of contraception in HIV-infected women not receiving antiretroviral (ARV) medication was assessed, it was reported, strikingly, that progression of HIV infection was more rapid among women randomized to hormonal contraception in comparison with those using an IUD.[7]

The purpose of the present study was to assess the effects of long-term use and the safety of the LNG-IUS among HIV-infected women in comparison with HIV-infected women not using the device.

Materials and Methods

Prior to initiation, the study was approved by the institutional review board of the Helsinki University Central Hospital. The study subjects and their controls were identified retrospectively among women attending a gynecological outpatient clinic for HIV-infected women living in the Helsinki metropolitan area. The total patient population at

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TABLE
Comparison of women using LNG-IUS and their controls

Variable	LNG-IUS (n = 15)	Controls (n = 25)	*P* value
Age (y; mean ± SD)	36.7 ± 7.0	35.6 ± 6.7	.57[a]
Nulliparous	5 (33%)	7 (28%)	.72[b]
Duration of HIV infection (y; mean ± SD)	5.1 ± 4.1	7.5 ± 4.0	.11[a]
Use of ARV medication at:			
• beginning of follow-up	8 (54%)	14 (56%)	.86[b]
• end of follow-up	11 (73%)	19 (76%)	.85[b]
$CD4^+$ lymphocyte counts ($\times 10^9$/L; mean ± SD) at:			
• beginning of follow-up	0.54 ± 0.23	0.56 ± 0.17	.90[a]
• end of follow-up	0.57 ± 0.24	0.59 ± 0.19	.60[a]

ARV, antiretroviral; *HIV*, human immunodeficiency virus; *LNG-IUS*, levonorgestrel-releasing intrauterine system.

[a] Mann-Whitney *U* test; [b] χ^2 test.

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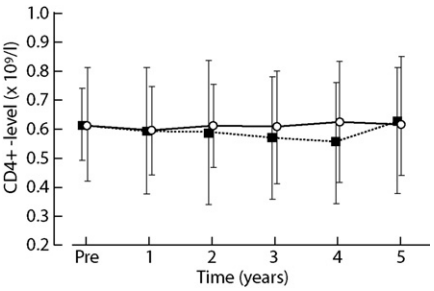
FIGURE 1
Circulating levels of CD4+ lymphocytes



Circulating levels of $CD4^+$ lymphocytes in levonorgestrel-releasing intrauterine system users (*open circles*) and controls (*black squares*). No statistically significant differences in $CD4^+$ lymphocyte counts were noted between 2 groups.

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the clinic is approximately 300 women. Gynecologic follow-up and Pap smear screening is organized at 6- to 12-month intervals at the department of obstetrics and gynecology, whereas treatment of HIV infection takes place at 3- to 6-month intervals at the department of infectious diseases.

For each subject using the LNG-IUS, 1 or 2 control subjects were identified. The subjects using the LNG-IUS had had at least 5 years of follow-up since insertion of the device, and the control subjects had had at least 5 years of follow-up. The LNG-IUSes (Mirena, Bayer-Schering Pharma AG, Turku, Finland) were inserted from April 2000 through January 2004. Seven of the women using the LNG-IUS also participated in a previously published prospective study assessing the safety of the device over 1 year.[6] Of the subjects in the LNG-IUS group 13 (87%) were at risk of pregnancy during the follow-up time. Three of them (20%) used the LNG-IUS mainly for the treatment of heavy menstrual bleeding.

For each subject using the LNG-IUS, 1 or 2 control subjects were identified. The subjects and controls were matched for year of birth (±2 years) and $CD4^+$ lymphocyte count ($\pm 0.1 \times 10^9$/L) at the beginning of follow-up (Table). In the control group 1 subject used contraceptive implant and 1 had undergone tubal sterilization. All women were systematically encouraged to use a condom during all intercourse.

The medical and laboratory records of our hospital were searched for the various outcome measures. Blood levels of $CD4^+$ lymphocyte counts analyzed within 3 months of the gynecologic follow-up visit were the primary outcome measure. The use of ARV medication, blood levels of hemoglobin, HIV-RNA measurements, and gynecological follow-up data such as annual Pap smear findings were secondary outcome measures.

Statistical analysis

Mann-Whitney *U*, χ^2, and *t* tests and analysis of variance (ANOVA) were used as appropriate. A *P* value $< .05$ was considered statistically significant. The statistical software used was StatView (SAS Institute Inc, Cary, NC).

RESULTS

Comparison of the women using the LNG-IUS and their matched controls is presented in the Table. The women using the LNG-IUS and the control women were similar regarding the use of ARV medication. The duration of HIV infection (as calculated from the first positive HIV antibody test result) was longer among the control women, but the difference did not reach statistical significance.

There were no unintended pregnancies in the LNG-IUS group. Of the 15 women fitted with the LNG-IUS, 12 continued use of the device for 5 years. The reasons for the 3 removals were desire for pregnancy (2 cases) and there was 1 case of increased bleeding at 4 years. Thus, the 5-year continuation rate was 80%. No cases of pelvic infection were seen in the LNG-IUS group.

Safety data

Figure 1 shows the $CD4^+$ lymphocyte counts in the 2 groups. The counts did not differ over time between the groups (ANOVA, $P = .97$). When the use or nonuse of ARV medication was taken into consideration, the $CD4^+$ counts were lower in the group not using it ($P = .001$). When stratifying for ARV medication use, the $CD4^+$ count did not differ between cases and controls ($P = .59$).

Of the women not using ARV medication at the beginning of the follow-up period, medication was started in 43% (3/7) and in 45% (5/11) in the LNG-IUS and control groups, respectively (χ^2 test, $P = .91$).

Blood HIV-RNA levels were below the detection limits of the assays used in women using ARV medication. In women not using ARV medication, the blood levels of HIV-RNA were highly variable. The levels of circulating HIV-