CONCISE COMMUNICATION

Frequency of Anovulation and Early Menopause among Women Enrolled in Selected Adult AIDS Clinical Trials Group Studies

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To obtain information on the prevalence of anovulation and early menopause and on pituitary-gonadal function among human immunodeficiency virus type 1–infected women, a study was undertaken that used stored serum samples from women aged 20–42 years who participated in selected Adult AIDS Clinical Trials Group protocols. Defined progesterone and follicle-stimulating hormone (FSH) levels were considered presumptive evidence of ovulation and of menopause, respectively. Anovulation occurred in 16 (48%) of 33 women for whom progesterone levels were tested; early menopause occurred in 2 (8%) of 24 women for whom FSH levels were tested. No statistically significant differences were seen in the demographic and clinical characteristics of anovulatory and ovulatory women, although women who ovulated had higher CD4 T cell counts and were less likely to have reported a recent change in menstrual periods. These data support the findings of prior studies of increased frequency of amenorrhea and/or irregular menstrual cycles, particularly among women with lower CD4 T cell counts.

Several studies have found decreased androgen levels associated with progressive immunosuppression among human immunodeficiency virus (HIV) type 1–infected men [1–3], but there is limited information on gonadal function among HIV-infected women. Anovulatory cycles occur in 5%–31% of healthy HIV-seronegative women with regular menses [4, 5] and are more common during the first few years after menarche and for several years before menopause [6]. In one small study that evaluated ovulation among HIV-1–infected women ($n = 14$) with regular menses [7], 4 women (29%) did not ovulate during a single cycle. Anovulatory women tended to be older (mean age, 38 vs. 31 years) and to have higher CD4 T cell counts (mean, 632 vs. 392 cells/mm^3) than women who ovulated.

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Informed consent for use of stored specimens for future testing was obtained from all subjects at entry into each clinical trial. Human experimentation guidelines of the US Department of Health and Human Services and those of the authors' institutions were followed in the conduct of the clinical research.

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There are considerably more data on menstrual functioning among HIV-1–infected women. Two studies found no association between HIV-1 infection or (in infected women) CD4 T cell count and menstrual dysfunction [8, 9]. Data from 2 additional cohort studies suggest that abnormalities of pituitary-gonadal function are related either directly to HIV-1 or to HIV-1–associated immune dysfunction [10, 11] and are relatively frequent. In one of these studies, 44% of HIV-1–infected women ($n = 248$) and 37% of HIV-seronegative women ($n = 87$) had irregular periods, defined as <26 days or >34 days between cycles [9]. Data on the frequency of anovulation were not included, but HIV-1–infected women were more likely to experience amenorrhea or intervals of >6 weeks without menstrual bleeding. They were also less likely to have typical premenstrual symptoms, suggesting that anovulatory cycles may be more common in this patient population [10].

A recent analysis of prospective data collected in the Women's Interagency HIV Study and HIV Epidemiology Research Study (802 HIV-1–infected women vs. 273 HIV-seronegative control subjects) showed that, although HIV serostatus did not affect menstrual cycle length, women with <200 CD4 T cells/mm^3 were more likely to have cycles of >40 days. After adjustment for age, body mass index, and substance use, a significant association also was seen between high virus loads and both cycle length (short and long) and cycle variability [11].

Premature ovarian failure is defined as menopause before age 40 years. Menopause is diagnosed by cessation of menses,

Table 1. Demographic and clinical characteristics of the total cohort and study sample populations.

Characteristic	Total cohort (n = 761)	Study sample (n = 52)
Median age, years	34	35
Race/ethnicity[a]		
White	35	40
Black	41	38
Hispanic	23	19
Other	1	3
History of injection drug use[a]	24	33
Median weight, kg	65.0	68.0
Median CD4 T cells/mm^3	279[b]	172[b]
Median Karnofsky score	90[c]	100[c]

[a] Data are percentage of subjects.
[b] $P < .001$ for difference.
[c] $P < .033$ for difference.

an increased follicle-stimulating hormone (FSH) level, and evidence of low estrogen levels [6]. A small survey study (n = 26) of postmenopausal HIV-infected women found that menopause (per the subject's impression) occurred relatively early (mean age, 47 years), but the data were based on recall and may have been subject to bias [12]. There is no information on the frequency of early ovarian failure among HIV-infected women.

Subjects and Methods

To better describe the prevalence of anovulation and early menopause among HIV-infected women, a study using stored serum samples from women who participated in selected Adult AIDS Clinical Trials Group (ACTG) protocols (nos. 175, 196, 200, and 866) was performed. Demographic information and gynecologic history data were collected from relevant case report forms for each study. Stored serum samples were used that had been obtained from nonpregnant, premenopausal, and amenorrheic (defined as absence of a menstrual period for ⩾90 days preceding sample collection) women, aged 20–42 years, who were not receiving hormonal therapies and had not undergone a hysterectomy. Samples must have been collected within the specified time windows, based on last menstrual period.

Progesterone and FSH levels were determined by standard assays in the Core Laboratory of the General Clinical Research Center, San Francisco General Hospital, California. A progesterone level of >3.1 ng/mL on cycle days 16–24 was considered to be presumptive evidence of ovulation, and an FSH level of >40 mIU/mL was indicative of menopause. Batch analysis of FSH was performed by immunoradiometric assay (Coat-A-Count; Diagnostic Products) and of progesterone by EIA (American Laboratory Products).

Of the 761 women enrolled in the 4 studies, samples from 622 women were not included because the women did not meet eligibility requirements, primarily because no information on last menstrual period was available. Another 87 women lacked blood samples matching the time windows required for the analyses. Fifty-seven samples from the remaining 52 women were acceptable for analysis (5 women had samples available for both progesterone and FSH testing). Twenty-four samples were acceptable for FSH testing (14 drawn on cycle days 2–5 and 10 drawn ⩾90 days from the last menstrual period), and 33 samples were acceptable for progesterone testing. Although descriptive data regarding menstrual function were not available for all subjects, all had responded to a query asking whether their periods had changed in the past 3 months. P values for unordered categorical variables were computed by Fisher's exact test and for ordered categorical variables by an exact Kruskal-Wallis test.

Results

Table 1 shows demographic and clinical characteristics for the total cohort (n = 761) and for the study sample (n = 52). The only differences between the 2 populations were a lower CD4 T cell count (median, 172 vs. 279 cells/mm^3; $P < .001$) and a higher Karnofsky score (median, 100 vs. 90; $P < .033$) in study sample subjects than in the total cohort. Table 2 shows results from tests for ovulatory status. In all, 48% of the women did not have evidence of ovulation, as previously defined, in the study time period. There were no statistically significant differences between anovulatory and ovulatory women, although women who ovulated had higher CD4 T cell counts and were less likely to have reported a recent change in menstrual periods.

Two (8%) of the 24 subjects whose samples were tested for FSH had elevated levels. Their ages, CD4 T cell counts, and body weights were 35 and 42 years, 266 and 16 cells/mm^3, and 61.3 and 73.2 kg, respectively. Neither woman had had a menstrual period within the past 90 days. Both had histories of injection drug use, but whether either woman was an active user was not known. Although no information was available regarding estrogen levels, the women were presumed to be menopausal on the basis of elevated FSH levels and cessation of menses.

FSH levels were assessed for 10 women in the group aged 20–35 years and 14 women in the group aged 36–42 years. Two (8%) of these 24 women were thought to have experienced early menopause (95% confidence interval [CI], 1%–27%), but only 1 (10%) of the 10 women in the group aged 20–35 years was presumed to have premature ovarian failure (95% CI, 0.3%–44%).

Table 2. Characteristics of the sample population, stratified by ovulatory status.

Characteristic	Anovulatory (n = 16)	Ovulatory (n = 17)	Total (n = 33)
Median age, years	32	33	33
Race/ethnicity[a]			
White	8 (50)	7 (41)	15 (45)
Black	4 (25)	8 (47)	12 (36)
Hispanic	3 (19)	2 (12)	5 (15)
Other	1 (6)	0	1 (3)
History of injection drug use[a]	4 (25)	4 (24)	8 (24)
Change in menstrual function in past 3 months[a]	6 (38)	2 (12)	8 (24)
Median weight, kg	69.9	68.6	69.0
Median CD4 T cells/mm^3	120	205	172

[a] Data are no. (%) of subjects.

Two (20%) of the women with amenorrhea had elevated FSH levels. The incidence of anovulation during a single cycle was higher in this study than in that of Greenblatt et al. [7]; however, the Greenblatt study was restricted to women with normal menses.

Discussion

In this study, we demonstrated a relatively high frequency of anovulation (48%) in a small subset of HIV-infected women participating in 4 large ACTG clinical trials. Although the number of subjects was small, trends suggested a relationship between lower CD4 T cell counts and anovulation. These data support the findings of other studies of increased frequency of amenorrhea and/or irregular menstrual cycles, particularly among women with lower CD4 T cell counts [10, 11]. CD4 T cell data were not consistent with those in the study of Greenblatt et al. [7], and the populations differed, in that our study subjects had lower median CD4 T cell counts. Eight percent of the subjects in our study had presumed early menopause, which may be compatible with the frequency in the general population.

Our results should be interpreted with caution, because the study was limited by its small sample size. Thus, the generalizability of our findings may be compromised by the relative differences in CD4 T cell counts among the full complement of women participating in the parent studies and those with samples eligible for testing in this study (i.e., women in this study had more advanced immunosuppression). There was also the potential for misclassification bias. It is possible that some subjects may have had nonmenstrual bleeding and thus were not timed correctly. In addition, specimens could have been taken before the luteinizing hormone surge, and a progesterone level of <3.1 ng/mL could subsequently occur in a woman who ovulated. This study evaluated only single hormonal values for presumptive evidence of both ovulation and early ovarian failure, and single values are imprecise measures of ovulation [13]. Information on current substance use, which can effect menstrual functioning [14], was not available for the 2 women with presumptive menopause, and no additional hormonal testing was done to confirm the diagnosis of early ovarian failure.

The data suggesting women with more advanced immunosuppression are less likely to ovulate are consistent with menstrual function information from other, large cohort studies of HIV-infected women. Our study expands on the menstrual function data by assessing progesterone and FSH levels, which helps better define the genesis of menstrual irregularities in this patient population. The information may be useful for both health care providers and HIV-infected women and underscores the need to further evaluate pathogenesis and interventions for treatment of hormonal dysfunction in HIV-infected women. Although there are known interactions between selected highly active antiretroviral therapies and hormones in oral contraceptive agents [15], the influence of such therapies on endogenous sex hormones has not been studied. Larger studies to gather additional data are warranted.

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