

Premature Ovarian Deficiency in HIV-infected women

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Background

With the introduction of efficient antiretroviral therapy, HIV infection is now a chronic disease. Dramatic improvements in life expectancy have been reported. Little is known about the impact of highly active antiretroviral therapy (HAART) or HIV infection itself on the ovarian function. Reports of menstrual dysfunction, increased miscarriage rates and elevated basal follicle-stimulating hormone (FSH) level suggest premature ovarian insufficiency.

Aim of the study

The aim of the current study was to collect ovarian function markers in HIV-infected women and to compare them with normal ranges. A secondary objective was to find a possible connection between changes in these markers and CD4 cell counts, HIV viral load and antiretroviral therapy.

Materials and Methods

The study obtained approval by the Ethics Committee in September 2003; four HIV clinics in Eastern France participated.

Inclusion criteria: all women aged 18 to 45 with documented HIV infection, attending the clinic for regular visits, regardless of current antiretroviral therapy.

Exclusion criteria: pregnancy, ongoing hormonal therapy and endocrine disease.

Blood sample was taken between days 2 and 4 of the cycle (in the fasting state). The hormonal assessment was performed centrally and included plasma FSH, LH, estradiol, prolactin and TSH, testosterone, inhibin B and antimüllerian hormone (AMH). Blood CD4 cell counts and plasma HIV-RNA levels were measured simultaneously.

Between days 7 and 10, a trained gynaecologist measured the antral follicular count (AFC) by vaginal ultrasonography; AFC was defined as the sum of the numbers of follicles of less than 10 mm visualized in both ovaries.

Four parameters (those accepted as markers of the stock of remaining primordial follicles in non HIV-infected women) have been chosen as ovarian markers: **FSH, inhibin B, AMH and AFC**.

Statistical analysis: For quantitative variables, results were expressed with mean and standard-error of mean, median, quartiles and ranges. For qualitative variables, results were expressed as percentages with 95 % confidence intervals. Means comparisons were computed with Kruskal-Wallis test. Associations between quantitative variables were computed with Spearman correlation coefficient.

Population

A total of 82 patients consented to participate. Four were excluded from the analyses for the following reasons: ongoing oral contraception (2), missing blood sample and missing AFC result (2).

Characteristics of included patients:

Number	78
Mean age (years)	34.5 ± 0.6
Mean BMI (kg/m ²)	24.4 ± 0.5
Mean menstrual cycle duration (days)	27.9 ± 0.3
Number of women with history of pregnancy (%)	66 (85%)
Mean duration of HIV infection (months)	68.6 ± 7.1
Number of women in CDC stage C	11 (14%)
Number of women on HAART (%)	49 (63%)
Number of women with undetectable viral load (%)	48 (62%)
Mean CD4 count (cells/μl)	437 ± 29

Results

Parameters	n	Mean	(± SE)	Normal values	% abnormal [95 % CI]
FSH	75	10.3	(± 0.7)	≤10.0 IU/l	36 [25;47]
AMH	71	22.4	(± 2.8)	≥7.4 pmol/l	23 [13;33]
Inhibin B	75	52.9	(± 5.6)	≥45.0 ng/l	57 [46;68]
AFC	72	7.6	(± 0.6)	≥10.0	63 [52 ;74]

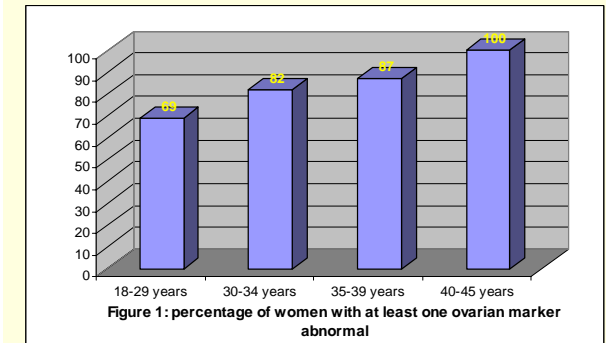
Table 1: ovarian features

	n	AFC Mean ± SE	p	FSH (IU/l) Mean ± SE	p	
<35 years	HAART	20	10.8 ± 1.3	0.59	8.8 ± 0.6	0.61
	no HIV therapy	16	10.1 ± 1.1		9.0 ± 1.1	
35-45 years	HAART	23	5.8 ± 0.9	0.43	11.1 ± 1.0	0.06
	no HIV therapy	16	4.8 ± 1.3		12.5 ± 2.8	

Table 2: AFC and FSH according to age and anti-HIV treatment

Results

Testosterone, TSH, estradiol and prolactin values were within normal ranges. At the opposite, 85% of the patients had at least one marker of ovarian function, FSH, inhibin, AMH and AFC outside the normal range (table 1). Rates were 69, 82, 87 and 100 for the age 18-29, 30-34, 35-39 and 40-45 respectively (figure 1). There was a trend for lower AFC and higher FSH in women without HAART compared with those with treatment at all ages (table 2). There was no impact of the treatment status on inhibin B and AMH values. No obvious difference in any ovarian markers between disease categories according to CD4 counts and viral load was noted.



Conclusion

Our descriptive study in HIV positive women shows premature ovarian deficiency based on changes in four different ovarian function markers. Alterations were severe and occurred surprisingly early, noticeable from the age of thirty onwards. This is important to keep in mind when following these women, particularly when discussing family planning matters. Pregnancy should probably not be delayed due to a higher risk of failure with age. Special attention should be exercised for early diagnosis of premature menopause and its potential consequences.