CONCISE COMMUNICATION

Impaired fertility in HIV-1-infected pregnant women: a clinic-based survey in Abidjan, Côte d'Ivoire, 1997

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Objective: Differences in fertility among HIV-1-positive and HIV-negative women tested in prenatal clinics were suspected by routine data collection in Abidjan, Côte d'Ivoire. This study was conducted on detailed fertility patterns among women at the same antenatal care centres, in order to assess these differences.

Method: The survey was carried out on 1201 consecutive women who agreed to be tested for HIV. Data collected included a detailed account of pregnancies, the time interval between the last two pregnancies, and the health status at the time of the survey. Blood samples were tested for HIV and syphilis with informed consent.

Results: Despite an earlier exposure to pregnancy risk, HIV-1-infected women aged 25 years and above, had, on the average, fewer pregnancies than uninfected women. An analysis of the interval between the last two pregnancies among multigravidae showed that, all things being equal, being HIV-1 positive decreased the risk of being pregnant by 17% (Cox regression, hazard ratio = 0.83, 95% confidence interval (CI): 0.69–0.99). This shift in the occurrence of the last pregnancy was more profound among HIV-1-positive women already at the symptomatic or AIDS stage, than among asymptomatic women.

Conclusion: These data confirm that women infected by HIV-1 would become pregnant less often than uninfected women, for an equal exposure to the risk of pregnancy. Therefore HIV-1-positive women could be under-represented at antenatal centres. Programmes involving such settings both for epidemiological surveillance and the reduction of mother-to-child transmission should take this observation into account.

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Keywords: fertility, HIV-1 infection, pregnant women, prenatal care centres, pregnancy interval

Introduction

Several studies have shown an increase in miscarriages among women infected with HIV [1–4] and a lower pregnancy incidence among infected than uninfected women [2]. A limited amount of evidence has, however, been produced to explain the adverse effects of HIV-1 on fertility, whereas this may have consequences both in terms of case management of HIV-infected women and surveillance of the epidemic.

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Indeed, surveillance sites set up to monitor the epidemiological trends are often located in antenatal care centres. If HIV-seropositive women have fewer pregnancies or more miscarriages than other women, this should imply that women who visit antenatal care centres are not representative of all women of child-bearing age as far as the AIDS epidemic is concerned, and that HIV infection prevalence is underestimated at these centres [5].

In the context of an intervention trial to reduce mother-to-child transmission of HIV conducted in Abidjan, Côte d'Ivoire, since 1995, it was shown that HIV-1-positive women have more frequently a history of abortion or stillbirth, compared with HIV-negative women [4]. In order to elucidate the relationship between HIV-1 infection and fertility, in 1997 more detailed data was collected on fertility among women who came for their first antenatal consultation in the same settings, according special attention to the interval between the last two pregnancies.

Methods

Since 1995, a clinical trial to reduce mother-to-child transmission of HIV (Essai Ditrame ANRS 049) has been ongoing in three urban health centres in Yopougon, Abidjan [6]. Before formal recruitment to the trial, HIV counselling and testing services are offered to all women coming for antenatal consultation with the following criteria: aged 18 years and above, planning to give birth in Abidjan, and with a pregnancy of less than 32 weeks. Following written consent, blood samples were tested for HIV (double enzyme-linked immunosorbent assay; ELISA) and syphilis (RPR, Reagine Plasma Reaction/TPHA, Treponema Pallidum Hemaglutination Assay) [6,7].

In 1997, a complementary survey was conducted during 3 months on the reproductive history of 1201 consecutive women who agreed to be tested for HIV. After the pre-test counselling, each woman who agreed to the test was asked to report her detailed pregnancy history. The maternal age, the pregnancy duration and outcome were collected for each pregnancy reported. Women were also asked details about contraception, breastfeeding, amenorrhea, and post-partum abstinence during the interval between the last two pregnancies. Finally, questions were asked on the women's health at the time of the survey, so that the stage of HIV infection was clinically determined on the basis of both major (severe weight loss, chronic diarrhoea, chronic fever, tuberculosis) and minor (persistent cough, oral candidiasis, pruritic dermatitis, herpes zoster, adenopathy) clinical signs [8,9].

A comparison was made between HIV-1-positive and HIV-negative women on the basis of all the available characteristics of their reproductive life (chi square test and Student's *t*-test). Then a Cox regression was used to analyse the interval between the last two pregnancies, to determine how HIV-1 influenced the period between the end of the last pregnancy and the beginning of the current pregnancy. A Cox model was also applied to estimate the effect of various factors on the period of occurrence of the current pregnancy among women infected by HIV-1, so as to observe the effect of the stage of HIV infection.

The 198 primigravidae (of whom 9.6% were HIV-1-infected) were excluded from the analysis of the interval between the last two pregnancies.

Results

Out of the 1201 women tested, 1013 were found to be HIV negative, 169 were HIV-1 positive (including dual reactive – HIV-1^+ and HIV-2^+); 19 were excluded from analysis because they were HIV-2 positive, or of indeterminate serological status, making a prevalence of 14.3% for HIV-1 in the sample tested. The prevalence of syphilis was 1.3% (16/1201), which is consistent with the prevalence of 1.1% observed in another study in Abidjan [10].

Early exposure to pregnancy risk was observed among HIV-1-positive women: thus, the mean age for first sexual intercourse was 16 years among HIV-positive and 17 years among HIV-negative-women; there were also fewer primigravidae among HIV-1-positive than HIV-negative women (Table 1). The mean number of pregnancies was higher among HIV-1-positive women under 20 years old than among non-infected women of the same age, but this trend reversed from the age of 25 years onwards (Table 1).

The interval between the last two pregnancies was longer among HIV-1-infected than among uninfected women (36.4 versus 33 months, $P = 0.14$, Table 1). This gap was rather high among 25–29-year-olds (51.8 versus 35.7, $P = 0.001$). In multivariate analysis, after adjustment for age, last pregnancy outcome, duration of post-partum amenorrhea, duration of post-partum abstinence, use of contraceptives during this interval, marital status and level of education, HIV-1 infection significantly delayed the occurrence of the current pregnancy (Cox model, hazard ratio = 0.83; 95% confidence interval (CI): 0.69–0.99, Table 2), i.e. being HIV-1 positive decreased the risk of being pregnant by 17%.

Table 1. Characteristics of the reproductive life and of the interval between the last two pregnancies for HIV-1-positive and HIV-negative women, Abidjan, Côte d'Ivoire, 1997

	Characteristics	HIV⁻	HIV-1⁺	*P**
Reproductive life (1013 HIV⁻, 169 HIV1⁺)	Age at first intercourse (years)	17.0 (SD = 7.6)	16.0 (SD = 1.8)	0.09
	Age at first pregnancy (years)	18.7 (SD = 3.1)	18.7 (SD = 3.2)	0.80
	Proportion of primigravidae (%)	17.7	11.2	0.05
	Mean number of induced abortions	0.47 (SD = 0.84)	0.48 (SD = 0.81)	0.94
	Mean number of miscarriages	0.21 (SD = 0.58)	0.17 (SD = 0.45)	0.38
	Mean number of pregnancies at age < 20	1.7 (SD = 0.8)	2.1 (SD = 1.1)	0.03
	Mean number of pregnancies at age ≥ 25	4.7 (SD = 2.2)	4.2 (SD = 2.1)	0.08
Last pregnancy interval characteristics Multigravidae only: (834 HIV⁻, 150 HIV-1⁺)	Mean length of the last pregnancy interval (months)	33.0 (SD = 25.9)	36.4 (SD = 28.8)	0.14
	Breast-feeding length (months)	16.2 (SD = 11.3)	17.8 (SD = 20.8)	0.25
	Post-partum amenorrhea length (months)	5.9 (SD = 7.9)	5.3 (SD = 5.8)	0.43
	Postpartum abstinence length (months)	9.6 (SD = 15.3)	9.6 (SD = 12.9)	0.99
	Contraceptive use (%)	16.1	20.0	0.45
	Modern contraceptive† use (%)	12.1	12.6	0.87

*Level of significance (eta test for comparison of means, chi square test for comparison of proportions).
†Pills, intrauterine device, preservative or depo-provera injection.

Table 2. Influence of predictor variables on the last pregnancy interval*. Cox regression (n = 984, multigravidae only), Abidjan, Côte d'Ivoire, 1997

Variable	Hazard ratio†	95% CI
Outcome of last pregnancy		
Stillbirth	1.06	(0.70–1.61)
Miscarriage	2.32	(1.71–3.14)
Abortion	1.42	(1.17–1.71)
Alive birth	ref	
Post-partum amenorrhea length (months)	0.99	(0.98–1.00)
Post-partum abstinence length (months)	0.99	(0.99–1.00)
Contraceptive use (yes/no)	0.56	(0.47–0.67)
Age (years)	0.87	(0.85–0.89)
Marital life/non-marital	1.11	(0.91–1.37)
Level of instruction		
Primary	0.95	(0.82–1.11)
Secondary	1.10	(0.91–1.32)
None	ref	
HIV-1⁺/HIV⁻	0.83	(0.69–0.99)
Total no. of pregnancies	1.36	(1.30–1.43)

*Interval between the last pregnancy and the present pregnancy.
†Factors presenting with a hazard ratio below 1 reduced the occurrence of the last pregnancy, and therefore extended the interval between the last two pregnancies. On the contrary, factors with a hazard ratio higher than 1 accelerated the occurrence of the last pregnancy, and therefore shortened the period between the last two pregnancies. CI, confidence interval; ref, reference category.

Among the 150 multigravidae HIV-1-positive women, eight were at the symptomatic stage, 24 at the AIDS stage, and the remainder were at the asymptomatic stage of HIV infection. The Cox model restricted to these HIV-1-positive women showed that being at the symptomatic or AIDS stage delayed the occurrence of the current pregnancy, but this trend was not statistically significant (hazard ratio = 0.78; 95% CI: 0.49–1.24).

Discussion

Two rather opposite characteristics of this survey have to be kept in mind when interpreting the results. On one hand, the major drawback of the data available for this study on the relationship between fertility and HIV infection is its retrospective nature. For HIV-1-positive women, all diagnosed at the time of the survey, because the date of infection was not known, it was not

possible to determine whether the pregnancies occurred before or after infection. This is the main reason why the study of the interval between the last two pregnancies was important, because it is very likely to shed light on the characteristics of the fertility of infected women in comparison with uninfected women. On the other hand, this study only considered pregnant women, as it was part of a clinical trial to prevent mother-to-child transmission. No observations were made on infertile women, who may be over-represented among HIV-1-positive women [11] if fertility is impaired by HIV, as has already been suggested.

Bearing in mind these two potential limitations, several conclusions can be drawn from these data on the relationship between HIV infection and fertility. First, despite a greater exposure to the risk of pregnancy (sexual intercourse at an early age, fewer first-time pregnancies at all ages), HIV-1-infected women experienced overall a lower total number of pregnancies than uninfected women, from 25 years onwards. Behavioural differences may account for HIV-1-positive women having a higher mean number of pregnancies than HIV-negative women before the age of 20 as documented in this study. Indeed, HIV-1-positive women were likely to have had more sexual intercourse than HIV-negative women, and were also more likely to become pregnant, because less than 10% of women among the population where the study was carried out used contraceptives [12]. Alternatively, the lower average number of pregnancies observed among HIV-1-positive women aged 25 years and above, cannot be explained by behavioural differences. The knowledge of being HIV-positive could not have influenced a change in reproductive behaviour, because all women were unaware of their HIV status before the survey. Most of the infected women were asymptomatic, and finally, no difference was observed when comparing the mean number of pregnancies among HIV-1-positive women at various clinical stages of the infection (data not shown). Therefore, the lower number of pregnancies could hardly suggest reduced sexual activity as a result of illness. It is likely that the lower number of pregnancies observed in HIV-1-positive women aged 25 years and over suggests a poorer physiological ability to become pregnant in relation to HIV infection.

The interval between the last pregnancy and the current one was considerably longer among HIV-1-infected women, taking into account all factors likely to influence this interval. Moreover, a longer interval was observed among symptomatic women or women with AIDS, than among asymptomatic women. The lack of significance in studying predictors of the last pregnancy interval among HIV-1-positive women is probably due to the limited sample size, because in this model, limited to HIV-1-positive women only, several factors such as the outcome of the last pregnancy, the length of post-partum abstinence or the use of contraceptives, which greatly affected the occurrence of the last pregnancy for the entire study sample, no longer seemed to be significantly associated with the length of the last pregnancy interval.

These two results, a fewer number of pregnancies among HIV-1-positive women and a longer interval between the last two pregnancies, may suggest lower fertility among HIV-1-positive women, in terms of their ability to become pregnant when exposed to the same risk of pregnancy as HIV-negative women. Difficulties in conceiving or excessive early miscarriages going unnoticed may also explain this lower fertility. This difference may very well be explained by sexually transmitted diseases (STD), often associated with HIV-1 [13]. Syphilis, gonococci and chlamydiae infections are the main STDs likely to cause sterility or materno-fetal complications. Sixteen out of the 1201 women tested were syphilis seropositive. Only one of these 16 women was HIV-positive, with no significant link between HIV serology and syphilis serology. Syphilis is therefore not a confounding factor in the relationship between HIV and fertility. No direct data is available in this study on other STDs.

Conclusion

Regardless of its causes, the lower fertility among HIV-1-infected women compared with HIV-1-negative women should be taken into account when monitoring the HIV epidemic, because sentinel surveillance can no longer be based solely on tests carried out at antenatal care centres [5]. As HIV-positive women have fewer pregnancies than HIV-negative women, they will pay fewer visits to these centres than HIV-negative women. The HIV prevalence assessed on the basis of these sites will therefore be underestimated in comparison with the prevalence in the general population. The prevalence assessed at antenatal care centres should therefore be adjusted, taking into account the fertility differences between HIV-1-positive and HIV-1-negative groups. This should provide a correct estimate of the HIV prevalence in the female population as a whole. Studies are currently under way to evaluate the effect of such a correction [14–16].

Finally, with regard to the prevention of mother-to-child transmission and HIV counselling and testing of women, because HIV-1-positive women are less likely to visit antenatal care centres than uninfected women, it would be advisable to make HIV testing and counselling services available to as many women of childbearing age as possible, even outside antenatal centres. Other avenues must be sought to reach women who do not visit these centres.

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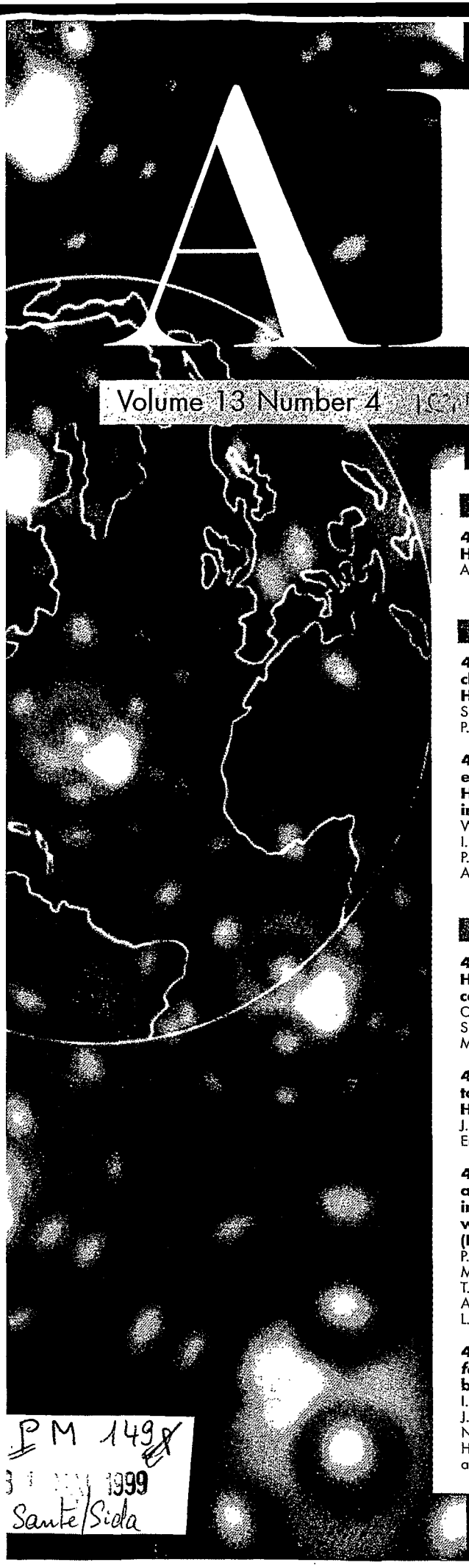

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