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SHORT COMMUNICATION

Rate, correlates and outcomes of repeat pregnancy in HIV-infected women

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Objectives

The aim of the study was to assess the rate, determinants, and outcomes of repeat pregnancies in women with HIV infection.

Methods

Data from a national study of pregnant women with HIV infection were used. Main outcomes were preterm delivery, low birth weight, CD4 cell count and HIV plasma viral load.

Results

The rate of repeat pregnancy among 3007 women was 16.2%. Women with a repeat pregnancy were on average younger than those with a single pregnancy (median age 30 *vs.* 33 years, respectively), more recently diagnosed with HIV infection (median time since diagnosis 25 *vs.* 51 months, respectively), and more frequently of foreign origin [odds ratio (OR) 1.36; 95% confidence interval (CI) 1.10–1.68], diagnosed with HIV infection in the current pregnancy (OR: 1.69; 95% CI: 1.35–2.11), and at their first pregnancy (OR: 1.33; 95% CI: 1.06–1.66). In women with sequential pregnancies, compared with the first pregnancy, several outcomes showed a significant improvement in the second pregnancy, with a higher rate of antiretroviral treatment at conception (39.0 *vs.* 65.4%, respectively), better median maternal weight at the start of pregnancy (60 *vs.* 61 kg, respectively), a higher rate of end-of-pregnancy undetectable HIV RNA (60.7 *vs.* 71.6%, respectively), a higher median birth weight (2815 *vs.* 2885 g, respectively), lower rates of preterm delivery (23.0 *vs.* 17.7%, respectively) and of low birth weight (23.4 *vs.* 15.4%, respectively), and a higher median CD4 cell count (+47 cells/μL), with almost no clinical progression to Centers for Disease Control and Prevention stage C (CDC-C) HIV disease (0.3%). The second pregnancy was significantly more likely to end in voluntary termination than the first pregnancy (11.4 *vs.* 6.1%, respectively).

Conclusions

Younger and foreign women were more likely to have a repeat pregnancy; in women with sequential pregnancies, the second pregnancy was characterized by a significant improvement in several outcomes, suggesting that women with HIV infection who desire multiple children may proceed safely and confidently with subsequent pregnancies.

Keywords: birth weight, HIV, HIV RNA, pregnancy, preterm delivery

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Introduction

The favourable changes produced by effective antiretroviral treatment in terms of life expectancy, clinical course, and mother-to child transmission of HIV have drastically changed perspectives relating to pregnancy and family planning among people with HIV infection [1,2]. Women with HIV infection may now undergo repeat pregnancies not just as a consequence of a lack of or ineffective contraception, but also as a result of the desire to have multiple children. Some studies have demonstrated a recent increase in repeat pregnancy among women with HIV infection [3], and further information is required to determine the demographics and health status of this particular population and to assess the possible risks associated with subsequent pregnancies. In order to explore this issue, we used data from a national study to determine the rate, correlates, and outcomes of repeat pregnancies in women with HIV infection.

Methods

Data from the Italian National Program for Surveillance on Antiretroviral Treatment in Pregnancy were used [4]. Women provided consent based on a patient information sheet approved by the competent Ethics Committee. General characteristics were summarized as medians with interquartile ranges (IQRs) and percentages. Preterm delivery was defined as delivery before 37 completed weeks, and low birth weight as < 2500 g; gender- and gestational age-adjusted *Z*-scores for birth weight were calculated according to recent national references [5]. Caesarean section was considered nonelective if performed after the rupture of membranes, onset of labour, or both. The distribution of quantitative variables was tested for normality using the Kolgomorov–Smirnov test. Categorical variables were compared using the -squared test for nonpaired samples and the McNemar test for paired samples, and quantitative variables were compared using the Mann–Whitney *U*-test for nonpaired samples, and the Wilcoxon two-sample signed rank test for paired samples. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. *P* values < 0.05 were considered statistically significant. All analyses were performed using the SPSS software, version 21 (IBM, Somers, NY, USA).

Results

As of 3 March 2016, among 3007 women with at least one pregnancy reported to the programme between 2001 and 2016, 488 (16.2%) had two or more pregnancies reported (two, 387; three, 73; more than three, 28). These women, compared with those with a single pregnancy reported, were younger [median age at first pregnancy reported: 30 years (IQR: 27–34 years) *vs.* 33 years (IQR: 29–37 years), respectively; $P < 0.001$], more recently diagnosed with HIV infection [median interval from HIV diagnosis to current pregnancy: 25 months (IQR: −2 to 87 months) *vs.* 51 months (IQR: −1 to 117 months), respectively; $P < 0.001$], and more frequently of foreign origin (OR: 1.36; 95% CI: 1.10–1.68; $P = 0.004$), diagnosed with HIV infection in the current pregnancy (OR: 1.69; 95% CI: 1.35–2.11; $P < 0.001$), and at their first pregnancy (OR: 1.33; 95% CI: 1.06–1.66; $P = 0.012$). The two groups had similar HIV clinical and immunological characteristics, with a history of symptomatic HIV disease present in 13.7% and 14.8% of women with and without subsequent pregnancies reported, respectively ($P = 0.545$), and first CD4 counts in pregnancy of 434 (IQR: 281–597) and 442 (IQR: 299–630) cells/μL, respectively ($P = 0.208$).

Compared with women with no subsequent pregnancies reported, women with subsequent pregnancies had (for the first pregnancy reported) a significantly higher rate of pregnancy ending in no live birth (miscarriage, voluntary pregnancy termination or stillbirth): 10.8 *vs.* 18.4%, respectively (OR: 1.86; 95% CI: 1.38–2.50; $P < 0.001$). The occurrences of preterm delivery and low birth weight were similar in the two groups: 21.6 *vs.* 21.8%, respectively, for preterm delivery (OR: 1.01; 95% CI: 0.76–1.36; $P = 0.919$), and 21.7 *vs.* 23.0%, respectively, for low birth weight (OR: 1.07; 95% CI: 0.80–1.44; $P = 0.642$).

Among 488 women with multiple pregnancies reported, 297 (60.8%) had available outcome information for two or more sequential pregnancies. The median interval between the first two pregnancies was 109 weeks (IQR: 70–182 weeks) and the median CD4 count change was +47 cells/μL (IQR: −52 to +223 cells/μL). Among women with a CD4 count > 350 cells/μL in the first pregnancy and available subsequent information ($n = 95$), 14.7% showed a decline in CD4 count to < 350 cells/μL in the second pregnancy. Only one (0.3%) progression to Centers for Disease Control and Prevention (CDC) stage C was observed between the two pregnancies. Clinical, immunological and virological outcomes in subsequent pregnancies are shown in detail in Table 1.

Discussion

Overall, the information collected in this study on repeat pregnancy among women with HIV infection confirms some of the findings obtained by others and offers new insights: as already shown by others, repeat pregnancy in women with HIV infection was associated with younger age [3,6–9], foreign country of origin [3], and parity (no prior pregnancies) [3]. We also showed that women with subsequent pregnancies were more likely to have been diagnosed with HIV infection in the current pregnancy, but also more likely to have a first pregnancy ending in no live birth, a finding common to the study by Kreitchmann *et al.* [9], which may indirectly indicate a desire for children and family planning following a first pregnancy with a negative outcome. With respect to the controversial issue of a potentially better

Table 1 Clinical, immunological and virological outcomes in sequential pregnancies (first two reported)

	First pregnancy	Subsequent pregnancy	*P*-value*
Pregnancy planned [% (*n*/total)]	38.5 (95/247)	40.3 (106/263)	0.213
On ART at conception [% (*n*/total)]	39.0 (112/287)	65.4 (187/286)	< 0.001
Weight at start of pregnancy (kg) [median (IQR)]	60 (53–68)	61 (54–70)	< 0.001
First CD4 count in pregnancy (cells/mL) [median (IQR)]	432 (284–598)	443 (302–612)	< 0.001
Undetectable plasma HIV RNA at third trimester [% (*n*/total)]	60.7 (111/183)	71.6 (131/183)	0.021
Pregnancy ending in no live birth [% (*n*/total)]	20.2 (60/297)	20.9 (62/297)	0.920
Fetal demise (spontaneous abortion or stillbirth) [% (*n*/total)]	14.1 (42/297)	9.4 (28/297)	0.082
Voluntary termination [% (*n*/total)]	6.1 (18/297)	11.4 (34/297)	0.034
Preterm delivery [% (*n*/total)]	23.0 (53/230)	17.7 (40/226)	0.041
Caesarean section [% (*n*/total)]	97.0 (223/230)	96.9 (222/229)	1.000
Nonelective caesarean section [% (*n*/total)]	18.9 (42/222)	20.3 (46/222)	1.000
Delivery complications [% (*n*/total)]†	8.5 (19/224)	6.2 (14/225)	0.093
Birth weight (g) [median (IQR)]‡	2815 (2527–3082)	2885 (2616–3240)	0.002
Low birth weight [% (*n*/total)]‡	23.4 (50/214)	15.4 (32/208)	0.014
Intrauterine growth restriction (BWZ < 10th centile) [% (*n*/total)]‡	13.4 (28/209)	12.5 (26/208)	1.000
HIV transmission [% (*n*/total)]	2.7 (5/187)	0.6 (1/173)	0.625

ART, antiretroviral therapy; IQR, interquartile range; BWZ, birth weight *Z*-score (adjusted for gender and gestational age).
*McNemar test for categorical variables; Wilcoxon two-sample signed rank test for quantitative variables.
†Usually represented by surgical wound infections and fever.
‡Singletons only: three (first pregnancy) and five (subsequent pregnancy) pairs of twins were excluded from paired comparisons that included birth weight.

health status in women with subsequent pregnancies [3,6], we did not observe any difference in HIV clinical or immunological status between women with and without subsequent pregnancies. In the subgroup of women with subsequent pregnancies, however, several outcomes improved significantly in the second pregnancy, with increased CD4 counts, better maternal weight, a higher rate of being on antiretroviral therapy at conception, a higher rate of undetectable plasma HIV RNA at the end of the pregnancy, and significantly lower rates of preterm delivery and low birth weight. Taken together, these observations indicate that stable antiretroviral therapy provides significant benefits regarding maternal status, with no adverse consequences in terms of pregnancy outcomes in the case of a subsequent pregnancy. Rates of preterm delivery and low birth weight actually declined significantly from the first to a subsequent pregnancy. This reassuring finding indicates that women with HIV infection who remain on treatment may safely proceed with sequential pregnancies, also supporting the currently endorsed World Health Organization (WHO) approach [10]. The observed lower rate of preterm delivery in subsequent pregnancies, in the presence of a higher rate of antiretroviral therapy coverage at conception, does not exclude *per se* an association between antiretroviral therapy and preterm delivery, but highlights the importance of the timing of the start of antiretroviral therapy, consistent with the hypothesis of a higher risk of preterm delivery with antiretroviral therapy started in pregnancy compared with treatment started before pregnancy [11]. Clinical HIV progression to AIDS, during or between pregnancies, was almost absent (0.3%), and immunological decline (to < 350 cells/mL) between two sequential pregnancies was also infrequent (14.7%), and even lower than in other studies (25.9% in a recent UK/Ireland study) [12]. A new finding of our study was that voluntary pregnancy termination was significantly more common in the second pregnancy. This occurrence was not attributable to a higher presence of elective terminations because of fetal anomalies (four of 34 terminations in the second pregnancy *vs*. seven of 18 terminations in the first pregnancy), or to sequential pregnancy terminations because of no desire for children (only one of 34 women had two consecutive terminations). Conversely, almost all terminations in the second pregnancy (32 of 34; 94.1%) followed a first pregnancy with a live birth, suggesting different intentions between the first and second pregnancies, with issues related to family size potentially involved. Although we showed a high rate of unplanned pregnancy in both first and subsequent pregnancies, we were unable to explore in detail the women's intentions regarding childbearing, contraception, family planning and family size, a subject that should be further addressed. Estimates of pregnancies ending in no live births should also be considered cautiously, given the possibility of an underreporting of such events, particularly when they occur in early pregnancy. Despite these limitations, the study provided new information on the rate, correlates and outcomes of repeat pregnancy in women with HIV infection, showing that younger and foreign women are more likely to have a repeat pregnancy, indicating that women with HIV infection who desire multiple children may confidently proceed with subsequent pregnancies.

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Details of ethics approval

Approval was obtained on 28 September 2001 from the Ethics Committee of the Istituto Nazionale per la Malattie Infettive (INMI) Lazzaro Spallanzani in Rome (ref. deliberation n. 578).

Appendix: The Italian Group for Surveillance of Antiretroviral Treatment in Pregnancy

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