Original Article

Pregnancy Loss in Women with HIV is not Associated with HIV Markers: Data from a National Study in Italy, 2001-2018

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Abstract. *Background*: **There is limited information on pregnancy loss in women with HIV, and it is still debated whether HIV-related markers may play a role.**
Objectives: To explore potential risk factors for pregnancy loss in women with HIV, with particular reference to modifiable risk factors and markers of HIV disease.
Methods: **Multicenter observational study of HIV-positive pregnant women. The main outcome measure was pregnancy loss, including both miscarriage (<22 weeks) and stillbirth (≥22 weeks). Possible associations of pregnancy loss were evaluated in univariate and multivariate analyses.**
Results: **Among 2696 eligible pregnancies reported between 2001 and 2018, 226 (8.4%) ended in pregnancy loss (miscarriage 198, 7.3%; stillbirth 28, 1.0%). In multivariate analyses, only older age (adjusted odds ratio [AOR] per additional year of age: 1.079, 95% confidence interval [CI] 1.046-1.113), HIV diagnosis before pregnancy (AOR: 2.533, 95%CI 1.407-4.561) and history of pregnancy loss (AOR: 1.625, 95%CI 1.178-2.243) were significantly associated with pregnancy loss. No significant association with pregnancy loss was found for parity, coinfections, sexually transmitted diseases, hypertension, smoking, alcohol and substance use, CD4 cell count, HIV-RNA viral load, and CDC HIV stage.**
Conclusions: **Older women and those with a previous history of pregnancy loss should be considered at higher risk of pregnancy loss. The severity of HIV disease and potentially modifiable risk factors did not increase the risk of pregnancy loss.**

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Introduction. HIV infection, when appropriately treated, has currently a much less severe impact on the quality of life and life expectancy. This more favorable prognosis, together with the possibility to have healthy and uninfected children, has determined among women with HIV an increased desire for pregnancy, a more confident family planning, and increasing use of fertility treatments and services.[1-8] In this context, miscarriage and stillbirth represent severe events that may have adverse consequences on parenting desire and family planning. It is therefore important to define determinants of pregnancy loss, identify pregnancies at risk, and implement targeted preventive measures that may increase the probability of delivering live and healthy newborns in this particular population. Large multinational projects,[9] systematic reviews,[10] and smaller regional studies[11-13] have identified risk factors in the general population, but data in HIV-infected women are still sparse and often inconsistent, particularly with respect to the potential predictive role of some HIV-specific markers such as viral load and CD4+ cell levels.[14-18] In order to further explore this issue, we used data from a national study to define determinants of pregnancy loss in a large cohort of pregnant women with HIV.

Methods. We studied all miscarriages and stillbirths reported to the National Program on Surveillance on Antiretroviral Treatment in Pregnancy. This is a national observational study of pregnant women with HIV established in Italy in 2001.[19] The study (currently not funded) was supported in the past by public, peer-reviewed research grants (ref.: H85E08000200005) from the Italian Medicines Agency (AIFA), with no role of the funder in study design, data collection, data analysis, manuscript preparation and/or publication decision. The study is structured as a prospective cohort, with reporting recommended before pregnancy outcome. Retrospective reports are also allowed but represent roughly 20% of total cases in the project. Laboratory and clinical data are collected from hospital records of Obstetrics, Infectious Diseases and Paediatrics departments following women's consent. Both the study protocol and patient information sheet were approved by the competent Ethics Committee (National Institute for Infectious Diseases L.

Spallanzani, Rome). Information on past and recent (less than one year) substance use and on the HIV status of the current partner is based on the women's reports. Status and level of smoking (with no smoking defined by less than one cigarette per day [CPD], light smoking by one to nine CPD and moderate to heavy smoking by 10 or more CPD)[20] are defined at first visit in pregnancy. Hypertension, diabetes, and alcohol consumption were defined according to national guidelines for the management of pregnancy.[21] Gestational age is determined on the basis of the last menstrual period, ultrasound biometry, or both. Preterm and very preterm delivery are defined as delivery before 37 and 32 completed weeks of gestation, respectively, and low and very low birth weight by values below 2500 and 1500 g, respectively. Cesarean section is considered elective if performed before the rupture of membranes and the onset of labor, and nonelective if performed after the rupture of membranes, the onset of labor, or both.

For the present analysis we considered all the centres who reported at least one case of pregnancy loss (miscarriage, before 22 weeks of gestation; stillbirth, at or after 22 weeks) from December 2001 (study start) to October 2018, and compared the pregnancies ending in a pregnancy loss with all the pregnancies with a live birth concurrently reported from the same centres. Voluntary terminations and cases with a diagnosis of HIV during the third trimester of pregnancy were excluded. The study period (2001-2018) was divided into three intervals of six years each (2001-2006, 2007-2012, 2013-2018). The possible role of HIV-related variables was evaluated considering periconception values of CD4 cell count and plasma HIV-RNA as potential predictors of pregnancy loss. We considered for this analysis as periconception values all available CD4 cell counts and HIV-RNA values with a time distance no greater than 13 weeks before or after the date of the last menstrual period. HIV-RNA was categorized at a threshold of 50 copies per ml and CD4 cell levels at two different thresholds, of 200 cells/mm^3 and 500 cells/mm^3, respectively. Quantitative variables were summarized as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U-test. Categorical variables were compared using the chi-square test, with odds ratios

(OR) and 95% confidence intervals (CI) calculated. Temporal trends were analyzed using the chi-square test for trend. In order to adjust for potential confounders, pregnancy loss was also evaluated as a dependent variable in multivariable logistic regression analyses, and sensitivity analyses were conducted individually valuating miscarriage and stillbirth as dependent variables and introducing other possibly relevant covariates as independent variables. P values below 0.05 were considered statistically significant. All analyses were performed using the SPSS software, version 25.0 (IBM Corp, 2017, Armonk, NY, USA).

Results. As of October 2018, 2696/4132 pregnancies in the study database (65.2%) were eligible for analysis. Among those pregnancies, 226 (8.4%) ended in either miscarriage (198, 7.3%) or stillbirth (28, 1.0%). The rate of pregnancy loss remained substantially unchanged across the study period (7.4% in 2001-2006, 10.3% in 2007-2012, 6.8% in 2013-2018; p=0.772, chi-square for trend). No temporal trends were observed also analyzing separately miscarriage and stillbirth (data not shown).

The general characteristics of the population studied according to pregnancy loss are shown in **Table 1**. The main markers of HIV disease, represented by CD4 cell count, HIV-RNA viral load, and CDC HIV stage, showed no differences between the two groups of women with and without pregnancy loss. Additional analyses conducted on CD4 levels categorized at different thresholds confirmed this finding: rates of pregnancy loss were 6.8% for CD4<200/mm^3 and 8.2% for CD4 $\geq$200/mm^3 (OR 0.822, 95%CI 0.436-1.550, p=0.545), 8.2% for CD4$\geq$500/mm^3 and 8.0% for CD4 <500/mm^3 (OR 1.018, 95% CI 0.740-1.400, p=0.912).

Women with pregnancy loss were significantly older, HIV-infected from a longer time, more frequently diagnosed with HIV and on antiretroviral treatment before pregnancy, had received more frequently preconception counseling, and were more

Table 1. Population characteristics at entry in pregnancy in women with and without pregnancy loss.

Characteristic	% (N) or median (IQR)			OR, 95%CI	P value #
	All	Pregnancy loss	No pregnancy loss		
Age (years) (n: 2695)	33 (29-36)	35 (31-39)	32 (28-36)	n.a.	<0.001
Body mass index (Kg/m^2) (n: 1968)	22.3 (20.2-25.3)	22.2 (20.3-24.5)	22.3 (20.1-25.3)	n.a.	0.690
Months from HIV diagnosis (n: 2595)	56 (12-116)	75 (33-136)	55 (10-114)	n.a.	<0.001
CD4 cell count at entry in pregnancy (cells/mm^3) (n: 2054)	476.5 (340-665)	474.5 (350-650)	476.5 (340-666.5)	n.a.	0.885
HIV already diagnosed before pregnancy (n: 2595)	79.1 (2052/2595)	92.2 (202/219)	77.9 (1850/2376)	3.378 (2.040-5.594)	<0.001
Preconception counselling § (n: 2332)	36.1 (843/2332)	49.8 (101/203)	34.9 (742/2129)	1.851 (1.386-2.472)	<0.001
African provenance (n: 2644)	35.0 (926/2644)	33.6 (74/220)	35.1 (852/2424)	0.935 (0.698-1.252)	0.653
History of intravenous drug use (n: 2628)	9.4 (247/2628)	6.3 (14/224)	9.7 (233/2404)	0.621 (0.356-1.085)	0.091
Partner without HIV infection (serodiscordant couple) (n: 1906)	63.5 (1210/1906)	65.5 (110/168)	63.3 (1100/1738)	1.100 (0.789-1.534)	0.574
HIV symptomatic disease (CDC disease stage B or C) (n: 2615)	11.4 (297/2615)	12.9 (29/224)	11.2 (268/2391)	1.178 (0.782-1.776)	0.433
HIV-RNA <50 copies/ml at conception (n: 1140)	53.4 (864/1933)	58.9 (66/112)	52.8 (543/1028)	1.282 (0.863-1.904)	0.219
Antiretroviral-naïve (n: 2618)	31.4 (822/2618)	21.4 (48/224)	32.3 (774/2394)	0.571 (0.410-0.794)	0.001
On antiretroviral treatment at conception (n: 2620)	55.7 (1459/2620)	67.1 (151/224)	54.6 (1308/2396)	1.721 (1.286-2.301)	<0.001
HBV-coinfected (n: 2504)	11.2 (280/2504)	7.1 (14/197)	11.5 (266/2307)	0.587 (0.336-1.026)	0.059
HCV-coinfected (n: 1861)	20.2 (376/1801)	16.6 (27/163)	20.6 (349/1698)	0.767 (0.499-1.179)	0.226
Hypertension (n: 2623)	2.2 (59/2623)	3.2 (7/221)	2.2 (52/2402)	1.478 (0.663-3.295)	0.339
History of sexually transmitted diseases * (n: 2472)	18.8 (464/2472)	19.1 (40/209)	18.7 (424/2263)	1.027 (0.716-1.472)	0.887
Recent substance use (n: 2540)	5.7 (144/2540)	2.9 (6/209)	5.9 (138/2331)	0.470 (0.205-1.077)	0.068
Alcohol abuse (n: 2266)	1.2 (27/2226)	0 (0/188)	1.3 (27/2078)	n.a.	0.116
Primiparous (n: 2618)	25.2 (659/2618)	22.6 (50/221)	25.4 (609/2397)	0.858 (0.618-1.192)	0.362
Twin pregnancy (n: 2679)	1.8 (48/2679)	1.9 (4/209)	1.8 (44/2470)	0.930 (0.331-2.613)	0.890
History of pregnancy loss (n: 2559)	22.3 (571/2559)	32.1 (70/218)	21.4 (501/2341)	1.737 (1.286-2.347)	<0.001
Smoking, any (n: 2445)	25.3 (619/2445)	26.1 (52/199)	25.2 (567/2246)	1.047 (0.753-1.457)	0.783
Smoking, heavy (10 or more cigarettes per day) (n: 2445)	12.2 (298/2445)	12.6 (25/199)	12.2 (273/2246)	1.038 (0.670-1.609)	0.866

IQR: interquartile range; OR: odds ratio; CI: confidence interval; N.A.: not applicable.
Chi-square test or Mann-Whitney U test. *Chlamydia, Gonorrhea, Genital condylomatosis, Genital herpes, Syphilis, Trichomonas. § defined as preconception advice on health issues regarding pregnancy and HIV.

Table 2. Multivariable analysis of possible determinants of pregnancy loss.

	Adjusted odds ratio (AOR)	95% CI	p value
Age (adjusted odds ratio per each additional year of age)	1.079	1.046-1.113	<0.001
On antiretroviral treatment at conception	0.971	0.680-1.386	0.871
Diagnosis of HIV before pregnancy	2.533	1.407-4.561	0.002
African provenance	1.238	0.898-1.705	0.192
Multiple (twin) pregnancy	0.524	0.124-2.204	0.378
History of pregnancy loss	1.625	1.178-2.243	0.003

likely to have experienced previous pregnancy losses. No differences were observed between the two groups in other possible risk factors for pregnancy loss, such as parity, coinfections, sexually transmitted diseases, hypertension, smoking, alcohol, and substance use.

The above analyses were also conducted separately for miscarriage and stillbirth. For miscarriage, the results substantially overlapped those of the common analysis (data not shown). For stillbirth, the results showed significant associations with African nationality (odds ratio [OR]: 2.728, 95%CI 1.261-5.904, p=0.011) and with twin pregnancy (OR: 4.356, 95%CI 1.004-18.898, p=0.049).

The associations found in the above univariate analyses were evaluated in a multivariable logistic regression analysis that included as dependent variable (outcome) pregnancy loss, and as independent (predictive) variables age, African provenance, HIV diagnosis before conception, being on antiretroviral treatment (ART) at conception, twin pregnancy, and history of pregnancy loss. Other variables significantly associated in univariate analyses with pregnancy loss were excluded being considered either redundant compared to others already included in the model (months since HIV diagnosis, antiretroviral status at entry in pregnancy) or reflecting spurious associations (preconception counseling, apparently increasing risk of pregnancy loss). The results of the multivariable analysis are shown in **Table 2**. After adjusting for covariates, only older age, the timing of HIV diagnosis and history of pregnancy loss remained significantly associated with pregnancy loss. Sensitivity analyses that included additional covariates in the model consistently confirmed the above results (data not shown).

Discussion. This large study explored the determinants of pregnancy loss in a large series of roughly three thousand pregnancies with HIV. Our sample was entirely represented by HIV-positive women, and we were, therefore, unable to assess the role of HIV infection, that was reported as a significant risk factor in other studies.[9] We were also unable to assess the role of other potentially relevant variables such as socioeconomic and marital status,[9] placental and amniotic status.[12]

As expected, most of the cases (198/226) of pregnancy loss were represented by miscarriages. The ratio between pregnancy loss and live birth remained relatively constant over time, with no significant change across the study period. In general, the observed rate (around seven percent of pregnancies) was lower compared to data reported for the general population in Italy (14% of all pregnancies in 2015),[22] and for pregnant women with HIV by others (15 and 20% in the studies by Hoffman and Stringer, respectively),[18,17] suggesting underreporting or missed enrolment of women with miscarriage in this surveillance. This occurrence might be favored by preferential access of women with early pregnancy loss to other structures, such as emergency departments. The observed rate of stillbirth (1.0%) is consistent with other studies, that usually showed rates between 0.8% and 4%.[17,18,23]

The main objective of this study was to identify preventable determinants of pregnancy loss among women with HIV. In this large series, the two major determinants of pregnancy loss were represented by two non-modifiable risk factors, represented by older age and history of a previous pregnancy loss. Both these associations have already been described.[9-12]

We found an association, apparently paradoxical, between pregnancy loss and preconception counseling. Our interpretation is that preconception counseling acted here as a proxy for the previous pregnancy losses or pregnancy at risk, with women with such a history more likely to seek preconception advise. The absence of a positive effect of preconception counseling in preventing pregnancy loss is nonetheless important, because is consistent with the absence of modifiable factors among the determinants found. Importantly, no significant role was found for smoking, alcohol, and recent substance use. This finding was confirmed in sensitivity analyses that included such variables in the main multivariable model (data not shown). We also found no effect of BMI, another potentially modifiable risk factor for pregnancy loss,[10] also when the risk was assessed specifically for the presence of overweight and/or obesity (data not shown). Finally, we found no significant role of smoking, in discordance with the observations by Flenady et al in the general population[10] and by Westreich et al in women with

HIV.[16] We also found no association of pregnancy loss with hypertension and parity, that represented risk factors in larger studies evaluating the general population.[9,10] In univariate analysis twin pregnancy represented a predictor of stillbirth, as reported by others.[9] Although this association did not persist in the multivariable analysis, this lack of significance could be due to the limited number of stillbirth events, and we think that multiple pregnancy should be still considered as a potential risk factor for this adverse outcome.

This study also contributed information to the debate on the potential role of severity of HIV disease in increasing the risk of pregnancy loss. We did not find any role for clinical or laboratory markers of HIV, confirming the findings by Stringer et al. for CD4 and HIV-RNA,[17] but in discordance with the significant associations between pregnancy loss and HIV disease indicators (CD4, plasma HIV-RNA levels and clinical HIV stage) found in a previous study conducted in Zambia,[4] while another study had found conflicting results, with a small absolute increase in risk of pregnancy loss for the highest viral load category compared to the lowest category, and a simultaneous paradoxical protective effect of increased cumulative viremia against pregnancy loss.[15] Presence of ART at conception showed in the present series no association with pregnancy loss in multivariable analyses, confirming the findings of other studies and systematic reviews.[17,18, 23,24]

The interpretation of the study should take into account some limitations. Study population may have been selected because of different reasons, that include missing outcome information (the main reason for patient ineligibility), exclusion of women diagnosed with HIV in late pregnancy (that might have higher viral load and lower CD4), and referral bias (with specialized centres more likely to participate in this surveillance). The patient's desire of acceptability may also have influenced the accurate reporting of personal risk factors/behaviors (e.g., smoking, substance use), and ascertainment of outcomes (particularly for miscarriage) is usually problematic. The low rate observed, actually, suggests incomplete coverage or underreporting of this outcome. Information on periconception HIV-RNA levels was also missing in a substantial number of cases, and this should prompt caution in the interpretation of the findings. Such a high rate of missing information, however, includes more than 500 cases in which HIV infection was diagnosed during pregnancy, and HIV-RNA analyzed for the first time at second or third trimester. This occurrence is also likely to have influenced through selection bias the finding of a higher risk of pregnancy loss in women diagnosed before current pregnancy, that should therefore also be considered cautiously.

Conclusions. In conclusion, despite the above caveats, our findings show that pregnancy loss is a multifactorial outcome. Older women and those with a previous history of pregnancy loss should be considered at high risk of pregnancy loss, and twin pregnancy should be considered a risk factor for stillbirth. Our data indicated that modifiable factors, such as excess body weight, smoking, alcohol, and substance abuse, have a limited role in pregnancy loss. The degree of severity of HIV disease apparently did not increase the risk of pregnancy loss in general and of miscarriage in particular. Larger, possibly multinational studies may be necessary to define more accurately the determinants of stillbirth in women with HIV, given the low prevalence of this condition.

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