HIV viral load and pregnancy loss: Results from a population-based cohort study in rural KwaZulu-Natal, South Africa

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Abstract

Objective: With ever-expanding antiretroviral therapy (ART) access amongst pregnant women in sub-Saharan Africa, it is more than ever important to address the gap in knowledge around ART effectiveness, as measured by HIV viral load (VL), and pregnancy loss.

Design: A population-based cohort study.

Methods: The study sample consisted of 3431 pregnancies from 2835 women living with HIV aged 16-35 years old. All women participated in a population-based cohort conducted between 2004 and 2018 in rural KwaZulu-Natal, South Africa. VL data was collected at prior surveys and an HIV care registry. The closest available VL to the date that each pregnancy ended was used and classified as either a pre- or post-conception VL. Logistic regression was used to investigate the association between high VL ($Log_{10}VL > 4.0$ copies/ml) and pregnancy loss, defined as either a miscarriage or stillbirth.

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Results: Pregnancy loss occurred at a rate of 1.3 (95% Confidence Interval, 95%CI: 1.0-1.8) per 100 pregnancies. There were 1451 pregnancies (42.3%) with post-conception VL measurements. The median time between the VL measurement and the pregnancy end date was 11.7 (Interquartile range: 5.0-25.4) months. We found a higher likelihood of pregnancy loss in women who had high VLs prior to the outcome of their pregnancy (adjusted odds ratio: 2.38, 95%CI: 1.10-5.18).

Conclusion: Given the significant relationship between high VL and pregnancy loss, our study lends further credence to ensuring effective ART through enrolment and retention of pregnant women living with HIV in ART programs, treatment adherence interventions, and VL monitoring during pregnancy.

Introduction

Women of reproductive age are a key population impacted by HIV in sub-Saharan Africa (SSA) [1, 2]. Although antenatal HIV prevalence is declining in the SSA region [3], South Africa (SA) still reports a high antenatal HIV prevalence of 30% [4]. HIV programs in SSA began championing antenatal HIV testing and antiretroviral therapy (ART) rollout in the late 2000's to reduce vertical HIV transmission through viral load (VL) suppression [1]. The success of these programs was evident during 2010-2018, when a dramatic increase in the proportion of pregnant women receiving ART and a concomitant decrease in vertical HIV transmission was observed [1].

However, a South African study by Mehta et al., found that ART exposure was associated with a 23% higher risk of adverse pregnancy outcomes, including pregnancy loss [5]. Nevertheless, all experts strongly contend that the benefits of ART in pregnancy outweigh the risks of adverse pregnancy outcomes [6, 7]. Interestingly, Mehta et al., did not include VL prior to the pregnancy outcome as a measure of ART effectiveness in their analysis [5], despite its reported association with pregnancy loss [8-11]. Furthermore, prior studies on ART and pregnancy outcomes have been facility-based, and the findings of these studies might not be entirely applicable to pregnant women living with HIV in the general population. With ever-expanding ART access amongst pregnant women, particularly in SSA, it is more than ever important to address the gap in knowledge around ART effectiveness and pregnancy loss. This was the impetus for our study.

Methods

Study design and setting:

This was a population-based cohort study. The study setting was a rural community within the Africa Health Research Institute (AHRI) HIV surveillance area, northern KwaZulu-Natal Province, SA. AHRI has used household and individual surveys (conducted 2-3 times a year) to prospectively follow this community for 20 years. A detailed description of the AHRI surveillance area and its general population are provided elsewhere [12]. HIV prevalence amongst pregnant women in this setting is >40% [13].

Data sources:

Pregnancy data was collected during the AHRI household surveys [14]. Pregnancy notification forms were completed for women who reported a pregnancy between survey periods and collected data on prior maternal history, conception date (based on last menses), pregnancy outcome date, and pregnancy outcomes [14]. Prepartum VL measurements and other variables relevant to pregnancy loss were established from existing AHRI surveys/ datasets [12, 13, 15-17]. We provide a description of these variables in Supplemental Digital Content 1.

Eligibility criteria:

We included all pregnancies during 2004-2018 from women aged 16-35 years old who had prepartum VL measurements recorded. Pregnancies ending in induced abortion and non-singleton pregnancies were excluded. The final study sample consisted of 3431 pregnancies from 2835 women.

Measures:

Pregnancy loss was defined as a pregnancy which ended in miscarriage or stillbirth. A detailed description of our definition for pregnancy loss is provided in Supplemental Digital Content 1. We used the closest VL measurement prior to the date of the pregnancy outcome in our analysis. A high VL was defined as a $Log_{10}VL > 4.0$ copies/ml [9, 10].

Data analysis:

Maternal characteristics of the pregnancies included in our study are presented descriptively. We used univariate and multivariate logistic regression to investigate the association between high VL and pregnancy loss. We identified potential confounders for inclusion in the multivariate model from the published literature. The results of the regression analyses are presented as unadjusted and adjusted odds ratios (uOR and aOR) with 95% confidence intervals (95%CI). We used R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) to perform the data analysis.

Ethical approval:

AHRI's population-based HIV surveillance platform was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, SA (Protocol BE290/16).

Results

The most important finding from our descriptive analysis (Table 1) was that maternal VL was high for 20.1% of pregnancies. Forty-five pregnancies ended in pregnancy loss (Rate: 1.3 per 100 pregnancies, 95%CI: 1.0-1.8 per 100 pregnancies), of which 37 (82.2%) were miscarriages and 8 (17.8%) were stillbirths. Table 2 shows the results of the logistic regression analyses. After controlling for confounders, a high VL was found to be associated with a two-fold higher likelihood of pregnancy loss (aOR: 2.38, 95%CI: 1.10-5.18). Multivariate associations were also noted between the following characteristics and pregnancy loss: increasing maternal age (aOR: 0.88, 95%CI: 0.80-0.97), a prior history of

pregnancy loss (aOR: 77.00, 95%CI: 25.38-233.68), a prior pregnancy which did not end in pregnancy loss (aOR: 0.32, 95%CI: 0.10-0.96), a post-conception VL measurement (aOR: 0.07, 95%CI: 0.03-0.20), and longer duration between VL measurement and pregnancy outcome (aOR: 0.94, 95%CI: 0.91-0.97).

Discussion

We found a two-fold higher likelihood of pregnancy loss in women who had high VLs prior to the outcome of their pregnancy. This highlights the importance of effective ART, rather than just ART exposure, in ensuring that HIV infection in pregnant women is adequately controlled. Maternal VL was high in 20% of pregnancies, suggesting a failure in the South African antenatal HIV care cascade. This failure might be attributed to one or a combination of the following: Problems with enrollment or retention in ART programs [18], treatment non-adherence [19, 20], or poor compliance with guidelines for antenatal VL monitoring [20].

Several factors negatively impact enrollment or retention of pregnant women in ART programs despite the current "test and treat" policy in SA [21], including breakdowns in linkage to HIV care; loss to follow-up of women enrolled in ART programs; and lack of treatment readiness [18]. The first two challenges could be mitigated through health systems strengthening, while lack of treatment readiness requires improved interventions for increasing pregnant womens' knowledge of HIV and ART. Based on previous studies, treatment non-adherence is a common reason for high VLs in pregnant women receiving ART, and is influenced by stigma, socioeconomic pressures, and lack of psychosocial support [22, 23]. It is imperative that interventions which seek to optimize treatment adherence, while accounting for these factors, be implemented in this population. Although SA has guidelines in place for antenatal VL monitoring [24], compliance with these guidelines is generally poor [25]. Poor compliance with the guidelines is also demonstrated in our study, wherein the median time between VL measurements and the pregnancy outcome was 11.7 months. This is likely explained by the lack of access to laboratory services in our rural South African setting [26]. Accordingly, point-of-care VL testing should be considered in our setting [27].

Our multivariate analysis yielded additional findings relevant to pregnant women living with HIV in our setting. Increasing maternal age was associated with a lower risk of pregnancy loss. This finding is in agreement with studies conducted in general populations that reported a higher risk of pregnancy loss in women aged <25 years old when compared with women aged 26-35 years old, with this risk increasing again at age >35 years [28, 29]. A longer duration between the VL measurement and the pregnancy outcome was associated with a lower risk of pregnancy loss. Thus, establishing ART effectiveness at an earlier stage might benefit women living with HIV who are considering having children. Our finding that post-conception VL measurements were associated with a lower risk of pregnancy loss confirms the importance of routine antenatal VL monitoring in our setting. Lastly, our finding that a prior history of pregnancy loss is a risk factor for subsequent episodes of pregnancy loss is congruent with the published literature [30, 31], and points to the potential usefulness of this characteristic for antenatal risk stratification in our setting.

The main limitation of our study was that the pregnancy outcomes data were obtained solely from AHRI household surveys, which were based on participant self-report. Although the data for stillbirth is robust, data for early miscarriage (which often goes unrecognized) and the date of last menses are subject to recall bias. We were unable to control for sexually transmitted/opportunistic infections, time since HIV diagnosis, WHO disease stage, or ART adherence in our multivariate analysis as this data was not available to us. We report a slightly lower rate of pregnancy loss when compared with urban South African women receiving ART [32], which reflects some underreporting of this outcome in our rural setting. We could not perform a sub-group analysis for miscarriage and stillbirth due to the low event rate for stillbirth in our study sample. Furthermore, pre-conception VLs used in our analysis might not necessarily reflect VLs at conception or during early pregnancy. We also acknowledge the long time period between VL measurements and pregnancy outcomes in our study.

In conclusion, a high VL is a risk factor for pregnancy loss in women living with HIV from rural KwaZulu-Natal, SA. One-fifth of pregnancies in our study were in women who had high VLs, suggesting a broader failure in the South African antenatal HIV care cascade which subsequently compromises ART effectiveness. This might include problems with enrolment or retention of pregnant women in ART programs; treatment non-adherence; or poor compliance with guidelines for antenatal VL monitoring. Priority should be given to strengthening these three components of the South African antenatal HIV care cascade.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1.

Description of maternal characteristics (N=3431)

Maternal characteristic	Summary statistic
Age at conception in years, median (IQR)	24.0 (20.0-29.0)
Prior pregnancy history, n (% N)	
No prior pregnancies	1280 (37.3)
Prior pregnancies, no history of pregnancy loss	2061 (60.1)
Prior pregnancies, history of pregnancy loss	90 (2.6)
Socioeconomic index, median (IQR)	2.7 (2.3-3.0)
Nearest clinic <5.0 km away, n (% of N)	
No	428 (12.5)
Yes	3003 (87.5)
History of tuberculosis infection, n (% of N)	
No	3282 (95.7)
Yes	149 (4.3)
Antiretroviral therapy at time of VL measurement, n (% of N)	
No	1104 (32.2)
Yes	2327 (67.8)
CD4 count <500 cells/mm^3, n (% of N)	
No	895 (26.1)
Yes	2536 (73.9)
Timing of VL in relation to conception, n (% of N)	
Pre-conception	1980 (57.7)
Post-conception	1451 (42.3)
Months between VL measurement and pregnancy outcome, median (IQR)	11.7 (5.0-25.4)
High VL, n (% of N)	
No	2741 (79.9)
Yes	690 (20.1)

VL: Viral load, IQR: Interquartile range.

Table 2.

Results of the univariate and multivariate logistic regression analyses investigating statistical associations between high VL, various covariates, and pregnancy loss

Maternal characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Independent variable under investigation		
High VL		
No	1.00	1.00
Yes	1.81 (0.96-3.42)	2.38 (1.10-5.18)
Covariates		
Age at conception, per year increase	0.99 (0.93-1.05)	0.88 (0.80-0.97)
Prior pregnancy history		
No prior pregnancies	1.00	1,00
Prior pregnancies, no history of pregnancy loss	0.18 (0.07-0.49)	0.32 (0.10-0.96)
Prior pregnancies, history of pregnancy loss	25.50 (13.00-50.01)	77.00 (25.38-233.68)
Socioeconomic index, per unit increase	1.10 (0.66-1.86)	1.23 (0.67-2.27)
Nearest clinic <5.0 km away		
No	1.00	1.00
Yes	0.93 (0.39-2.20)	0.73 (0.28-1.92)
History of tuberculosis infection		
No	1.00	1.00
Yes	1.59 (0.49-5.17)	2.19 (0.47-10.18)
Antiretroviral therapy at time of VL measurement		
No	1.00	1.00
Yes	0.65 (0.36-1.17)	0.92 (0.42-1.99)
Timing of VL in relation to conception		
Pre-conception	1.00	1.00
Post-conception	0.29 (0.14-0.63)	0.07 (0.03-0.20)
Months between VL measurement and pregnancy outcome, per month increase	0.72 (0.42-1.23)	0.94 (0.91-0.97)
CD4 count <500 cells/mm^3		
No	1.00	1.00
Yes	1.64 (0.76-3.54)	1.58 (0.63-3.94)

OR: Odds ratio, CI: Confidence interval, VL: Viral load. Reference category ORs set at 1.00.