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Antiretroviral therapy during pregnancy and risk of preterm birth☆

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ABSTRACT

Background: Antiretroviral therapy use in pregnancy, and specifically regimens containing protease inhibitors (PIs), has been associated with adverse infant outcomes including preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) infants. However, there are conflicting results in the literature with respect to the degree of risk. These results may be related to demographic factors and confounding of maternal HIV infection and degree of immune suppression.
Objective: The primary objective of our study was to assess the risk of PTB in HIV-positive pregnant women on ART compared to HIV-negative pregnant women. Secondary objectives included: comparing the risks of LBW and SGA infants in HIV-positive women on ART to HIV-negative pregnant women; comparing the risks of PTB, LBW and SGA in HIV-positive women on PI-based regimens compared to HIV-negative women.
Methods: A retrospective matched cohort study of 384 women was conducted between 2007 and 2012 comparing outcomes of HIV-positive women on ART to HIV-negative women. Univariate and multivariable logistic regression models were used, adjusting for potential confounding factors, to compare the two groups on adverse infant outcomes.
Results: Unadjusted odds ratios revealed a >2-fold increase in rates: PTB OR 2.6 [95% CI 1.3–5.1]; LBW OR 2.9 [95% CI 1.4–6.3]; SGA OR 2.5 [95% CI 1.3–4.7]. Once odds ratios were adjusted to account for race ($p < 0.01$), our results were no longer statistically significant as this study was underpowered to detect smaller differences: PTB aOR 1.4 [95% CI 0.5–3.6]; LBW OR 1.9 [95% CI 0.6–5.5]; SGA OR 1.8 [95% CI 0.8–4.6].
Conclusion: Our preliminary results show an increase in PTB, LBW and SGA but due to lack of power, our adjusted results are not statistically significant. A larger prospective follow-up study is needed to further explore these findings in this population.

Introduction

More than 50% of people living with the human immunodeficiency virus (HIV) worldwide are women and girls [1]. Each year, about 1.5 million HIV-positive women become pregnant and in 2013, 62% of these women received antiretroviral therapy (ART) during pregnancy [1–4]. In North America, over 97% of women are tested for HIV during pregnancy and appropriately identified as infected, leading to nearly universal use of ART during pregnancy to prevent perinatal transmission [1–5]. In 2012, perinatal transmission rates were estimated at 1.7% in Canada and the United States [5].

There is ongoing concern about the related toxicity of ART to the mother and the developing fetus [8–26]. Possible adverse effects include an increased rate of preterm births (PTB) among patients on combination therapy, and specifically regimens including protease inhibitors (PIs) [8–23]. There have been conflicting results from American and European studies investigating the relationship between different types of ART regimens and PTB [8–21]. Early European observational studies showed an increased rate of PTB with the use of ART during pregnancy [8–10]. In contrast, most American studies from the same era showed no increased rate in PTB [13–15]. A meta-analysis of 14 studies showed no overall increased

☆ This study was conducted in Toronto, Ontario, Canada at St. Michael's Hospital, University of Toronto, Department of Obstetrics and Gynecology.

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rate of PTB on ART during pregnancy but did detect an increased rate of PTB in women who were on PI-based regimens compared to non-PI-based regimens and in women where ART was initiated before pregnancy or in the first trimester compared to initiation in the second trimester and beyond [11]. Subsequent studies have continued to lead to conflicting results [12,16–23,27].

To further investigate the relationship between ART in pregnancy and PTB, we sought to undertake a study looking at the rates of PTB in a cohort of HIV-positive Canadian women. We attempted to overcome issues with confounders by selecting a group of HIV-positive women on ART and matching them to HIV negative women. In addition, we collected information on potential confounders that could bias associations.

The primary objective of our study was to assess the risk of PTB in HIV-positive pregnant women on ART compared to HIV-negative pregnant women in our center. Secondary objectives included: comparing the risks of low birth weight (LBW) and small for gestational age (SGA) infants in HIV-positive women on ART to HIV-negative pregnant women; comparing the risks of PTB, LBW and SGA in HIV-positive women on PI-based regimens compared to HIV-negative women. Additionally, we attempted to reduce outcome misclassification by distinguishing spontaneous from indicated PTBs and by identifying the pregnancy complications that led to these outcomes.

Methods

Study design, setting and participants

This was a single-center retrospective matched cohort study conducted in a tertiary referral center in Toronto, Canada. Information was collected through a chart review. HIV-infected women were included in the study if they: received prenatal care at our center, were diagnosed with HIV prior to pregnancy or during antenatal screening, received antiretroviral therapy during the pregnancy, gave birth between January 1, 2007 and December 31, 2012, gave birth after 20 weeks and carried a singleton pregnancy. The protocol for this study was approved in August 2012 by the Research Ethics Board at University of Toronto (REB 12-165).

Variables, data measurement and bias

The primary outcome was PTB. Secondary outcomes included LBW and SGA. We compared the odds of PTB, LBW and SGA in HIV-positive women versus HIV-negative women and among women on PI-based regimens versus HIV-negative women. The exposure variable was HIV disease treated with ART.

To minimize bias, information was collected on risk factors for preterm birth including race, smoking status, illicit drug use, sexually transmitted infections, stage of HIV disease, obstetric history of premature birth. These confounding variables were then adjusted for in our analysis.

PTB was defined as birth before 37 completed weeks of gestational age. LBW was defined as birth weight less than 2500 g [33]. SGA was defined as birth weight less than the 10th percentile for gestational age according to the Brenner growth chart [34]. Reason for preterm birth was recorded and these were classified as spontaneous preterm births or indicated preterm births. The indicated preterm births were classified as (1) possibly related preterm birth (diagnosis leading to a delivery possibly related to ART use) and (2) unrelated preterm births (delivery with cause unrelated to ART). The classifications were circulated to four obstetricians and a consensus was obtained. An initial analysis was conducted excluding unrelated preterm births. If this analysis showed a statistically significant association, a sensitivity analysis including only spontaneous preterm births would be carried out.

Gestational age at delivery was determined using obstetrical estimates. We confirmed the gestational age recorded in the chart with first trimester ultrasound or conception date by assisted reproduction if these were available. If the date was discordant by more than a week, we used first trimester ultrasound dating. If a first trimester ultrasound was not performed, we used the date recorded in the chart.

With the available number of HIV-positive women ($N = 96$), we performed a series of sample size calculations to find an acceptable trade-off between effect size and number of non-exposed women. Our calculations indicated that 288 non-exposed women would be needed to obtain an unadjusted odds ratio of 2.55 or higher for preterm birth, assuming an incidence of 8% among HIV-negative women, at alpha = 0.05 and power = 80%. Each HIV-positive woman was therefore matched to three random HIV-negative women based on year of delivery (same year), parity (primiparous or multiparous) and maternal age (same). Both groups of women were restricted to singleton pregnancies.

Statistical methods

We computed frequencies and cross-tabulations. Differences in proportions between groups were assessed with the Chi-Square analyses. A two-sided p-value < 0.05 denoted a statistically significant difference. In an effort to control for various confounding factors, a conditional multivariable logistic regression model was performed to calculate adjusted odds ratios and 95% confidence intervals. All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

Results

Between 2007 and 2012, 14,813 deliveries took place in our center (2007–08: 2642 births; 2008–09: 2981 births; 2009–10: 2991 births; 2010–11: 3000 births; 2011–12: 3199 births). Of the 14,813 deliveries that took place, 97 were by HIV-infected women. One delivery was a multiple birth and was excluded from the study.

Ninety-six HIV-positive pregnant women on ART were identified and matched with 288 HIV-negative women in a 1:3 ratio. All of these women were included in the final analysis. Baseline characteristics of the HIV-positive women on ART and the HIV-negative subjects are included in Table 1. Despite matching, there were a few differences between the groups. The HIV-positive group had significantly more black women, women with a history of preterm birth, and women with medical illnesses compared to the HIV-negative women. 84% of black women were of African origin, 30% of HIV-positive women were above age 35 and only 1% of HIV-positive women reported illicit drug use. Disease characteristics of the HIV-positive women including information about their ART regimens are presented in Table 2. 81% of HIV-positive women had undetectable viral loads at delivery, 93% had CD4 counts above 200, and 77% were on PI-containing ART regimens.

After outcome review of the 19 preterm births in the HIV-positive cohort, 68% of the preterm births were classified as spontaneous preterm births, 32% were classified as possibly related preterm births and no preterm births were classified as unrelated (Table 3). The different diagnoses and definitions associated with each of these categories are described in Table 3.

In the HIV-positive group, mean birth weight (g) ± (SD) was 3005 g ± (651 g), and was 3334 g ± (587 g) ($p = 0.02$) in the HIV-negative group. The mean gestational age (GA) (weeks) ± (SD) at birth was 38.2 weeks (±2.6 weeks) for the HIV-positive women and 38.9 weeks (±2.2 weeks) ($p = 0.02$) in the HIV negative cohort.