Maternal placental syndromes among women living with HIV: a population-based study

Short title: Maternal placental syndromes in women with HIV

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Abstract

Background

Maternal placental syndromes are associated with adverse fetal outcomes and maternal cardiovascular disease. However, whether HIV infection increases the risk of maternal placental syndromes is unknown.

Methods

We conducted a population-based study using health administrative data from Ontario, Canada. We identified all pregnancies resulting in a live birth between April 1, 2002 and March 31, 2011, and identified women living with HIV using a validated case-finding algorithm. Our primary composite outcome was maternal placental syndromes, defined as a diagnosis of pre-eclampsia, eclampsia, placental abruption or placental infarction. We used generalized estimating equations with a logit link function to derive adjusted odds ratios (aORs) and 95% confidence intervals (CI) for the association of HIV infection with maternal placental syndromes.

Results

A total of 1,132,871 pregnancies were available for analysis, of which 634 (0.06%) were among women with HIV. Following multivariable adjustment, there was no difference in the risk of maternal placental syndromes between women living with and without HIV infection (5.8% versus 5.6%; aOR 0.85, 95% CI 0.59 to 1.21). An increased risk of maternal placental syndromes was associated with pre-existing diabetes (aOR 1.47, 95% CI 1.39 to 1.54), chronic hypertension (aOR 4.28, 95% CI 4.15 to 4.42) and chronic kidney disease (aOR 1.83, 95% CI 1.61 to 2.08).

Interpretation

Women with HIV are not at increased risk of maternal placental syndromes. Our results underscore the importance of optimizing the management of co-morbid illness associated with maternal placental syndromes during the prenatal period for all women, irrespective of HIV status.

INTRODUCTION

Maternal placental syndromes are an inter-related group of disorders which include pre-eclampsia, eclampsia, placental infarction and placental abruption.[1] In affected pregnancies, maternal placental syndromes are associated with adverse fetal outcomes such as preterm delivery, fetal growth restriction and fetal death.[1] In addition to fetal harm, maternal placental syndromes are associated with an approximately two-fold increased risk of premature cardiovascular disease in affected women.[2-5] This association between maternal placental syndromes and future cardiovascular disease may reflect the effects of overlapping risk factors such as hypertension.[6] Alternatively, some evidence indicates that maternal placental syndromes precipitate a series of vascular changes in women that increase the risk of future cardiovascular impairment.[7-10] The association of maternal placental syndromes with maternal cardiovascular disease is augmented in women with pre-existing metabolic syndrome. In one study, the risk of future cardiovascular disease among women with maternal placental syndromes and one to two features of the metabolic syndrome was increased four-fold relative to women who had neither; this risk was increased more than 11-fold for women with three or four components of the metabolic syndrome.[2] These findings are particularly concerning in the context of HIV infection because the prevalence of metabolic syndrome is higher among women living with HIV relative to HIV-negative women, thereby predisposing these women to both maternal placental syndromes and cardiovascular sequelae.[11-13]

Several studies have compared the risk of one or more placental disorders between women living with and without HIV, with conflicting results.[14-20] A recent meta-analysis found no difference in the risk of pre-eclampsia between women living with and without HIV but was unable to precisely estimate the association between HIV and eclampsia (odds ratio 2.56, 95% confidence interval 0.15 to 44.11). [21] Furthermore, with the exception of one large study conducted in a sample of 20% of all community

hospitals in the United States,[20] existing risk estimates have been derived from single-center studies with small sample sizes. Notably, many studies did not account for co-morbid diseases known to influence the risk of maternal placental disorders, such as hypertension, diabetes and chronic kidney disease. In addition, the existing literature reflects a time period (i.e. prior to 2003) that pre-dates the widespread use of ritonavir-boosted protease inhibitor therapy among pregnant women with HIV. Because protease inhibitors may increase the risk of metabolic syndrome and are currently used by almost 80% of women living with HIV during pregnancy, contemporary estimates of the risk of maternal placental syndromes among these women are required.[22,23] Accordingly, we compared the risk of maternal placental syndromes between women living with and without HIV infection in a population-based study in Ontario, Canada between April 1, 2002 and March 31, 2011.

METHODS

Data sources

We used Ontario's administrative health databases, which were held securely in linkable files without any direct personal identifiers, and analysed at the Institute for Clinical Evaluative Sciences (ICES). Specifically, we identified all pregnancies among Ontario women between the ages of 18 and 49 during the study period using the MOMBABY database, which deterministically links the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) inpatient admission records of all mothers and their newborn infants from 2002/3 onward. Within this cohort, we identified births to women living with HIV using the Ontario HIV Database, an administrative data registry of Ontario residents with diagnosed HIV infection which was generated using a previously validated case-finding algorithm.[24] We obtained demographic information from the Registered Persons Database, a registry of all Ontario residents eligible for provincial health insurance. We obtained hospitalization data from the

CIHI-DAD, which contains detailed clinical information regarding all hospital admissions in Ontario. We used the Ontario Health Insurance Plan database to identify claims for physician services and pre-existing medical conditions which may influence the risk of maternal placental syndromes. We used validated disease registries to define the presence of diabetes and hypertension.[25,26] We used ecologic measures of neighborhood instability and deprivation as measures of maternal socioeconomic status using the 2006 Canadian Census.[27] We adjusted for differences in comorbidity by calculating the number of Aggregated Diagnosis Groups for each woman, using the John Hopkins Adjusted Clinical Group system.[28] We determined the adequacy of prenatal care using the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX).[29] The R-GINDEX is a summary measure of prenatal care, and is calculated on the basis of the number of visits for prenatal care and the trimester care began, taking gestational age into account. Finally, we ascertained immigration status and world region of origin using the Citizenship and Immigration Database, and categorized time since immigration to Ontario as recent (i.e. $\leq$ 5 years) or non-recent (i.e. >5 years). These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used for population-based population-based research examining pregnancy outcomes, including maternal placental syndromes.[30-32]

Outcome

Our primary composite outcome was maternal placental syndromes, defined as a diagnosis of pre-eclampsia, eclampsia, placental abruption or placental infarction during each hospital admission for a delivery. We ascertained the presence of each outcome from the maternal admission record in the MOMBABY database using the International Classification of Diseases 10 revision (ICD-10) coding system (Supplementary material).

Statistical analyses

We compared baseline characteristics of mothers living with and without HIV using one-way analysis of variance for continuous variables, Cochrane-Armitage tests for ordinal variables and chi-square tests for categorical variables. We compared the proportions of pregnancies complicated by maternal placental syndromes using multivariable general estimating equations with a logit link function and an exchangeable correlation structure to account for multiple pregnancies from the same woman during the follow-up period. We adjusted models for variables known to influence the risk of maternal placental syndromes, including age, parity, multiple versus singleton birth, maternal co-morbidity, hypertension, diabetes (pre-existing and diagnosed during pregnancy), chronic kidney disease, dyslipidemia, immigration status, adequacy of prenatal care and socioeconomic status.[33] All analyses were performed using SAS version 9.3 (Cary, NC).

Ethics

This project was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

RESULTS

We identified 1,133,505 pregnancies between April 1, 2002 and March 31, 2011, of which 634 (0.06%) were among women living with HIV. Relative to women without HIV, women living with HIV were more likely to be immigrants to Ontario (48.1% versus 25.8%; $p < 0.001$) and have a greater co-morbidity burden, as demonstrated by the median number of Aggregated Diagnosis Groups in the

preceding year [6 (interquartile range 5.0 to 9.0) vs. 4.0 (interquartile range 3.0 to 6.0); p< 0.001] (Table 1). However, with the exception of chronic kidney disease in the 24 months preceding pregnancy, no differences were observed in the proportions of women living with and without HIV with known risk factors for maternal placental syndromes, including pre-existing diabetes (1.9% versus 1.8%; p = 0.84), diabetes diagnosed during pregnancy (5.8% versus 5.0%; p = 0.36), pre-existing hypertension (3.6% versus 2.6%; p = 0.12) and hypertension diagnosed during pregnancy (3.5% versus 4.4%; p = 0.24).

Overall, 63,217 (5.6%) women developed maternal placental syndrome during the study. The proportions of women living with and without HIV who developed maternal placental syndromes during their pregnancy was similar (5.8% vs. 5.6%; p = 0.78). Following multivariable adjustment, there was no significant difference in the risk of maternal placental syndromes between women living with and without HIV infection [adjusted odds ratio 0.85, 95% confidence interval (CI) 0.59 to 1.21] (Table 2). The odds of maternal placental syndrome were lower among immigrants to Ontario relative to non-immigrants, with the lowest risk being observed among recent (i.e. < 5 years) immigrants to the province (Table 2). The risk of maternal placental syndromes was increased among women with established risk factors for these disorders, including pre-existing diabetes (adjusted odds ratio 1.47, 95% CI 1.39 to 1.54), chronic hypertension (adjusted odds ratio 4.28, 95% CI 4.15 to 4.42) and chronic kidney disease (adjusted odds ratio 1.83, 95% CI 1.61 to 2.08) (Table 2).

DISCUSSION

We found no excess risk of maternal placental syndromes among women living with HIV relative to HIV-negative women. Our study provides a contemporary population-based estimate of the risk of

maternal placental syndromes in women living with HIV and is reflective of a period during which protease inhibitor-based antiretroviral therapy was used by the majority of women during the prenatal period. Data from the Canadian Perinatal HIV Surveillance Program indicates that during the study period, 86.5% of pregnant women with HIV in Ontario received combination antiretroviral therapy, of whom 78.9% received protease inhibitors (personal communication).

Our findings are in general agreement with previously conducted studies,[16,17,20] but differ from those of a cohort study which demonstrated a nearly five-fold increase in the risk of preeclampsia in 82 women living with HIV relative to 8,686 HIV-negative women.[19] However, this study differed from ours in several important respects, including being conducted in a single referral centre and a lack of control for important confounders in the association between HIV-infection and preeclampsia, including diabetes, hypertension and chronic kidney disease.

Although the difference in risk for maternal placental syndromes between women living with and without HIV in our study did not reach statistical significance, the estimate for this association suggest that women living with HIV may be at slightly lower risk for these outcomes. This interpretation may provide some support for the notion that HIV-associated immune dysfunction prevents the excessive maternal inflammatory response to paternal antigens and pregnancy thought to provoke the development of preeclampsia.[34-36] Alternatively, the lower risk of maternal placental syndromes among women living with HIV may partially reflect a healthy immigrant effect, a premise supported by our finding of lower risk among recent immigrants and previous work documenting a progressively lower risk of maternal placental syndromes associated with recency of immigration.[32]

Our study is strengthened by the population-based nature of the data, thereby allowing us to study over one million pregnancies during the study period. However, some limitations of our study merit

emphasis. First, we could not ascertain births that occurred outside the hospital, which accounts for approximately 1.1% of all births in Ontario.[37] Second, we had no data on some determinants of maternal placental syndromes, including smoking and body mass index. Finally, we used administrative data and outcome misclassification is therefore possible. However, differential outcomes misclassification is unlikely because maternal placental syndromes are recorded for all women at the time of delivery in mandatory fields of the Ontario birth record by the attending physician or midwife.

In conclusion, our population-based study indicates that HIV is not associated with a heightened risk of maternal placental syndromes. In contrast, diabetes, hypertension and chronic kidney disease impart a substantial increase in the risk of these outcomes. These data reinforce the importance of optimizing the management of these co-morbid conditions during the prenatal period for all women, irrespective of HIV status.

Competing interests

None of the authors have competing interests related to this work.

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Author contributions

All authors contributed to the concept and design of the study. Tony Antoniou, Ryan Ng and Erin Macdonald acquired the data, and all authors were involved in the analysis and interpretation of the data. Ryan Ng and Tony Antoniou drafted the manuscript, and all authors were involved in critical revision of the manuscript. All authors approved the manuscript submitted for publication. Tony Antoniou, Erin Macdonald and Ryan Ng provided administrative, technical or material support. Tony Antoniou is the guarantor for the manuscript.

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Table 1: Baseline characteristics of pregnancies according to HIV status

Characteristic	HIV (n = 634)	Non-HIV (n = 1,132,871)	p-value
Mean age ± SD (years)	30.8 ± 5.2	30.1 ± 5.2	0.002
18 to 34 years	470 (74.1%)	895,675 (79.1%)	0.002
35 to 49 years	164 (25.9%)	237,196 (20.9%)	
Aggregated Diagnosis Groups			
Median (IQR)	6.0 (5.0 – 9.0)	4.0 (3.0 – 6.0)	< 0.001
Pre-existing diabetes	12 (1.9%)	20,211 (1.8%)	0.84
Diabetes diagnosed during pregnancy	37 (5.8%)	57,007 (5.0%)	0.36
Pre-existing hypertension	23 (3.6%)	29,789 (2.6%)	0.12
Hypertension diagnosed during pregnancy	22 (3.5%)	50,192 (4.4%)	0.24
Hyperlipidemia	19 (3.0%)	25,984 (2.3%)	0.24
Obesity	17 (2.7%)	30,659 (2.7%)	0.97
Chronic kidney disease	8 (1.3%)	2,046 (0.2%)	< 0.001
Adequacy of prenatal care (R-GINDEX)			< 0.001
Adequate	175 (27.6%)	428,867 (37.9%)	
Intensive	54 (8.5%)	61,597 (5.4%)	
Intermediate	304 (47.9%)	484,055 (42.7%)	
Inadequate	101 (15.9%)	156,982 (13.9%)	
Immigration Status			< 0.001
Non-immigrant	329 (51.9%)	840,609 (74.2%)	
Non-recent immigrant, Africa or Caribbean	97 (15.3%)	23,814 (2.1%)	
Non-recent immigrant, other world regions	28 (4.4%)	108,480 (9.6%)	
Recent immigrant, Africa or Caribbean	157 (24.8%)	15,412 (1.4%)	
Recent immigrant, other world regions	23 (3.6%)	144,556 (12.8%)	
Material Deprivation Income Quintile			< 0.001
1 (lowest)	68 (10.7%)	296,868 (26.2%)	

Characteristic	HIV (n = 634)	Non-HIV (n = 1,132,871)	p-value
2	72 (11.4%)	233,052 (20.6%)	
3	98 (15.5%)	213,667 (18.9%)	
4	117 (18.5%)	190,959 (16.9%)	
5	261 (41.2%)	183,836 (16.2%)	
Residential Instability Quintile			< 0.001
1 (lowest)	77 (12.1%)	303,577 (26.8%)	
2	72 (11.4%)	228,844 (20.2%)	
3	69 ((10.9%)	168,458 (14.9%)	
4	145 (22.9%)	214,871 (19.0%)	
5	253 (39.9%)	202,632 (17.9%)	
Multiple birth	19 (3.0%)	19,849 (1.8%)	0.02
Preterm birth	100 (15.8%)	81,047 (7.2%)	< 0.001

SD, standard deviation; IQR, interquartile range

Table 2: Regression models of predictors of maternal placental syndrome

Covariate	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)*
HIV-infection	1.02 (0.72 to 1.45)	0.85 (0.59 to 1.21)
Pre-existing diabetes	2.05 (1.95 to 2.14)	1.47 (1.39 to 1.54)
Diabetes diagnosed during pregnancy	1.47 (1.42 to 1.51)	1.27 (1.23 to 1.31)
Pre-existing hypertension	5.15 (5.01 to 5.32)	4.28 (4.15 to 4.42)
Hyperlipidemia	1.27 (1.21 to 1.33)	1.03 (0.98 to 1.08)
Chronic kidney disease	3.78 (3.37 to 4.25)	1.83 (1.61 to 2.08)
Immigration Status		
Non-immigrant	1.00	1.00
Non-recent immigrant, Africa or Caribbean	1.00 (0.95 to 1.06)	0.90 (0.85 to 0.95)
Non-recent immigrant, other world regions	0.72 (0.69 to 0.74)	0.70 (0.68 to 0.72)
Recent immigrant, Africa or Caribbean	0.83 (0.77 to 0.89)	0.79 (0.73 to 0.85)
Recent immigrant, other world regions	0.63 (0.61 to 0.64)	0.64 (0.62 to 0.66)

*Models also adjusted for age, parity, world region of birth, maternal comorbidity (using Aggregated Diagnosis Groups), hyperlipidemia, chronic kidney disease, adequacy of prenatal care and neighborhood instability and deprivation

Supplementary Materials

Table 1: Codes to define maternal placental syndrome

	Ontario Health Insurance Plan (OHIP) Databse	Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD)
Pre-eclampsia or eclampsia	642.4 to 642.7	O11, O13, O15
Placental abruption	641.2	O45
Placental infarction	656.7	O43.1, O43.8, O43.9