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Research

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

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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. Our objective was to compare the risk of maternal placental syndromes between women living with and without HIV infection in Ontario.

Methods: We conducted a population-based study using health administrative data from Ontario. We identified all pregnancies resulting in a live birth between Apr. 1, 2002, and Mar. 31, 2011; we identified women living with HIV using a validated case-finding algorithm. Our primary composite outcome was maternal placental syndromes, defined as a diagnosis of preeclampsia, 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 between HIV infection and maternal placental syndromes.

Results: Data from 1 132 871 pregnancies were available for analysis; 634 (0.06%) of the pregnancies were in women living with HIV. After multivariable adjustment, we found no difference in the risk of maternal placental syndromes between women living with HIV and those without HIV infection (5.8% v. 5.6%; AOR 0.85 [95% CI 0.59–1.21]). An increased risk of maternal placental syndromes was associated with pre-existing diabetes (AOR 1.47 [95% CI 1.39–1.54]), pre-existing hypertension (AOR 4.28 [95% CI 4.15–4.42]) and chronic kidney disease (AOR 1.83 [95% CI 1.61–2.08]).

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

Maternal placental syndromes, an inter-related group of disorders that includes preeclampsia, eclampsia, placental infarction and placental abruption, complicate 5.7% of pregnancies in Ontario.[1] However, whether HIV imparts a heightened risk of maternal placental syndromes among women in Ontario is unknown. These data are important for several reasons. First, women are increasingly represented among the population of persons with HIV who have entered care in Ontario, comprising about 20% of this population as of 2009.[2] Moreover, 82% of these women are of child-bearing age.[2] Second, maternal placental syndromes increase the risk of preterm delivery, fetal growth restriction and low-birth-weight infants,[3] adverse fetal outcomes that occur with greater frequency among women with HIV. Specifically, in an earlier study, we found that the proportion of births that were preterm (14.6% v. 6.3%; $p < 0.001$), small for gestational age (14.6% v. 10.3%; $p < 0.001$) and low birth weight (12.5% v. 4.6%; $p < 0.001$) were higher among Ontario women with than among those without HIV infection.[4] A finding of a higher risk of maternal placental syndromes among women with HIV could provide insight into the cause of the higher-than-expected rates of these adverse neonatal outcomes. Finally, in addition to fetal harm, maternal placental syndromes are associated with an increased risk (about 2-fold) of premature cardiovascular disease in affected women.[5–8] This association between maternal placental syndromes and future cardiovascular disease may reflect the effects of overlapping risk factors such as hypertension.[9] Alternatively, some evidence suggests that maternal placental syndromes precipitate a series of vascular changes in women that increase the risk of future cardiovascular impairment.[10–13] The association of maternal placental syndromes with maternal cardiovascular disease is augmented in women with pre-existing metabolic syndrome.

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In one study, the risk of future cardiovascular disease among women with maternal placental syndromes and 1 to 2 features of metabolic syndrome was increased 4-fold relative to women who had neither; this risk was increased more than 11-fold for women with 3 or 4 components of metabolic syndrome.[6] These findings are particularly concerning in the context of HIV infection, because the prevalence of metabolic syndrome is higher among women living with HIV than among those without HIV, thereby predisposing these women to both maternal placental syndromes and cardiovascular sequelae.[14–16]

Several studies have compared the risk of 1 or more placental disorders between women living with and without HIV, with conflicting results.[17–23] A recent meta-analysis found no difference in the risk of preeclampsia between women living with and without HIV but was unable to precisely estimate the association between HIV and eclampsia (odds ratio [OR] 2.56, 95% confidence interval [CI] 0.15–44.11).[24] Furthermore, with the exception of 1 large study involving a sample of 20% of all community hospitals in the United States,[23] existing risk estimates have been derived from single-centre studies with small samples. Many of these studies did not account for comorbid 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., before 2003) that predates 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 their pregnancies, contemporary estimates of the risk of maternal placental syndromes among these women are required.[25,26] We performed a population-based study to compare the risk of maternal placental syndromes between women living with and without HIV infection in Ontario between Apr. 1, 2002, and Mar. 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 analyzed at the Institute for Clinical Evaluative Sciences (ICES). We identified all pregnancies among Ontario women between the ages of 18 and 49 years during the study period using the MOMBABY database, which deterministically links the Canadian Institute for Health Information Discharge Abstract Database inpatient admission records of all mothers and their newborn infants from fiscal year 2002/03 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 that was generated using a previously validated case-finding algorithm.[27] The definition of 3 physician claims with an International Classification of Diseases, 9th revision code for HIV infection (042, 043, 044) within a 3-year period has a sensitivity of 96.2% (95% CI 95.2%–97.9%) and a specificity of 99.6% (95% CI 99.1%– 99.8%) for identifying people living with HIV.[27] We obtained demographic information from the Registered Persons Database, a registry of all Ontario residents eligible for provincial health insurance. We obtained data on hospital admissions from the Discharge Abstract Database, 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 that may influence the risk of maternal placental syndromes. We used validated disease registries to define the presence of diabetes and hypertension.[28,29] We used neighbourhood instability and deprivation as measures of maternal socioeconomic status based on the 2006 Canadian Census.[30] 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.[31] This method of case-mix adjustment has been studied among Ontario adults with HIV and found to have comparable discriminative performance for mortality and greater discriminative performance for hospital admission than other commonly used methods.[32] We determined the adequacy of prenatal care using the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX).[33] 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, because immigration status has been previously shown to be associated with maternal placental syndromes,[1] we determined immigration status and world region of origin using the Citizenship and Immigration Database, and categorized time since immigration to Ontario as recent (≤ 5 yr) or nonrecent (> 5 yr). These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used for population-based research examining pregnancy outcomes, including maternal placental syndromes.[1,4,34]

We obtained supplemental data regarding antiretroviral therapy, viral load and perinatal transmission from the Canadian Perinatal HIV Surveillance Program.

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

Outcome

Our primary composite outcome was maternal placental syndromes, defined as a diagnosis of preeclampsia, eclampsia, placental abruption or placental infarction during each hospital admission for a delivery. We determined the presence of each outcome from the maternal admission record in the MOMBABY database using the International Classification of Diseases, 10th revision coding system (Appendix 1, available at www.cmajopen.ca/content/3/4/E360/suppl/DC1).

Statistical analyses

We compared baseline characteristics of mothers living with and without HIV using a 2-sample t test for continuous variables, Cochrane–Armitage tests for ordinal variables and χ^2 tests for categorical variables. We compared the proportions of pregnancies complicated by maternal placental syndromes using multivariable generalized estimating equations with a logit link function and an

exchangeable correlation structure to account for multiple pregnancies in 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 comorbidity, pre-existing hypertension, diabetes (pre-existing and diagnosed during pregnancy), chronic kidney disease, dyslipidemia, immigration status, adequacy of prenatal care and socioeconomic status.[35] We used time-updated covariates for variables that could change with time (e.g., age, presence of comorbid conditions).[35] In a sensitivity analysis, we adjusted models for obesity and smoking, 2 variables that could influence the risk of maternal placental syndromes, but which are unlikely to be well captured in our databases. We used SAS version 9.3 (Cary, NC) for all analyses.

Results

We identified 1 133 505 pregnancies resulting in a live birth between Apr. 1, 2002, and Mar. 31, 2011, of which 634 (0.06%) were in women living with HIV. Relative to women without HIV, women with HIV were more likely to be immigrants to Ontario (48.1% v. 25.8%; $p < 0.001$) and have greater comorbidity, as shown by the median number of aggregated diagnosis groups in the preceding year (6 [interquartile range (IQR) 5.0–9.0] v. 4.0 [IQR 3.0–6.0]; $p < 0.001$) (Table 1). However, with the exception of chronic kidney disease in the 24 months preceding pregnancy, we saw no differences in the proportions of women living with and without HIV with known risk factors for maternal placental syndromes, including pre-existing diabetes (1.9% v. 1.8%; $p = 0.8$), diabetes diagnosed during pregnancy (5.8% v. 5.0%; $p = 0.4$), pre-existing hypertension (3.6% v. 2.6%; $p = 0.1$) and hypertension diagnosed during pregnancy (3.5% v. 4.4%; $p = 0.2$).

Supplemental data regarding antiretroviral therapy, viral load and perinatal transmission were extracted for 614 births to women living with HIV in Ontario for the period covered by our study, which show that 86.5% of women with HIV received combination antiretroviral therapy during their pregnancies, and only 8.5% received no antenatal therapy (Lindy Samson, co-chair Canadian Perinatal HIV Surveillance Program, personal communication). Of the women on combination antiretroviral therapy, most (78.9%) received protease inhibitors, and the risk of vertical transmission was 1.1%. Viral load data were available for 90.9% of women during the period encompassing 2006–2011, of whom 82.8% attained virologic suppression below the limits of detection (50 copies/mL), with a further 10.3% achieving suppression to less than 1000 copies per millilitre. The timing of when the viral load was obtained relative to delivery was recorded for 36.9% ($n = 146$) of women, with the median being 19.5 days before delivery (Canadian Perinatal HIV Surveillance Program, personal communication).

Overall, maternal placental syndrome developed in 63 217 (5.6%) women during the study. The proportions of women living with and without HIV in whom maternal placental syndromes developed during pregnancy were similar (5.8% v. 5.6%; $p = 0.8$). After multivariable adjustment, there was no significant difference in the risk of maternal placental syndromes between women living with and without HIV infection (adjusted OR 0.85, 95% CI 0.59–1.21) (Table 2). The results did not change in a sensitivity analysis adjusting for smoking and obesity (Appendix 2, available at www.cmajopen.ca/content/3/4/E360/suppl/DC1). The odds of maternal placental syndrome were lower among immigrants to Ontario relative to nonimmigrants, with the lowest risk being seen among recent (i.e., < 5 yr) immigrants from world regions outside of Africa or the Caribbean (Table 2). The risk of maternal placental syndromes was increased among women with established risk factors for these disorders, including pre-existing diabetes (adjusted OR 1.47, 95% CI 1.39–1.54), pre-existing hypertension (adjusted OR 4.28, 95% CI 4.15–4.42) and chronic kidney disease (adjusted OR 1.83, 95% CI 1.61–2.08) (Table 2).

Interpretation

We found no excess risk of maternal placental syndromes among women living with HIV relative to women without HIV infection. 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 most women with HIV during the prenatal period.

Our findings are in general agreement with previous studies;[19,20,23] but they differ from those of a cohort study that showed a nearly five-fold increase in the risk of preeclampsia in 82 women living with HIV relative to 8686 women without HIV.[22] However, that 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.

Strengths and limitations

Our study is strengthened by the population-based nature of the data, which allowed us to examine more than 1 million pregnancies during the study period. However, we could not determine births that occurred outside of a hospital, which account for about 1.1% of all births in Ontario.[36]

We did not have reliable data on some determinants of maternal placental syndromes, including smoking and body mass index, and because we used administrative data, outcome misclassification is possible. However, differential outcome 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 addition, although we adjusted for region of origin, residual confounding related to race was possible.

Finally, our databases do not include clinical information or reliable estimates of antiretroviral drug use. Although we were not able to capture CD4+ count at delivery, data from the Canadian Perinatal HIV Surveillance Program suggest that most women were receiving antiretroviral therapy, had achieved virologic suppression and were therefore appropriately managed in terms of their HIV infection.

Table 1: Baseline characteristics of included patients, by HIV status

Characteristic	HIV, no. (%)* n = 634	Non-HIV, no. (%)* n = 1 132 871	p value
Age, yr, mean ± SD	30.8 ± 5.2	30.1 ± 5.2	0.002
18–34 yr	470 (74.1)	895 675 (79.1)	0.002
35–49 yr	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)	0.8
Diabetes diagnosed during pregnancy	37 (5.8)	57 007 (5.0)	0.4
Pre-existing hypertension	23 (3.6)	29 789 (2.6)	0.1
Hypertension diagnosed during pregnancy	22 (3.5)	50 192 (4.4)	0.2
Hyperlipidemia	19 (3.0)	25 984 (2.3)	0.2
Obesity	17 (2.7)	30 659 (2.7)	1.0
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, region of origin			< 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 (least deprived)	68 (10.7)	296 868 (26.2)	
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 (most deprived)	261 (41.2)	183 836 (16.2)	
Residential instability quintile			< 0.001
1 (least instability)	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 (most instability)	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
Previous preterm birth†	n = 168	n = 338 276	< 0.001
	34 (20.2)	24 912 (7.4)	

Note: IQR = interquartile range, R-GINDEX = revised-graduated prenatal care utilization index, SD = standard deviation.
*Unless otherwise indicated.
†Among women in their second or subsequent pregnancy.

Table 2: Predictors of maternal placental syndrome

Covariate	OR (95% CI)	Adjusted OR (95% CI)*
HIV-infection	1.02 (0.72–1.45)	0.85 (0.59–1.21)
Age, yr		
18–34 (reference)	1.00	1.00
35–49	0.83 (0.82–0.85)	0.91 (0.89–0.93)
Pre-existing diabetes	2.05 (1.95–2.14)	1.47 (1.39–1.54)
Diabetes diagnosed during pregnancy	1.47 (1.42–1.51)	1.27 (1.23–1.31)
Pre-existing hypertension	5.15 (5.01–5.32)	4.28 (4.15–4.42)
Hyperlipidemia	1.27 (1.21–1.33)	1.03 (0.98–1.08)
Chronic kidney disease	3.78 (3.37–4.25)	1.83 (1.61–2.08)
Aggregated diagnosis groups		
0–5 (reference)	1.00	1.00
6–10	1.60 (1.57–1.62)	1.41 (1.38 t0 1.43)
11 or more	2.65 (2.52–2.79)	1.93 (1.82–2.03)
Adequacy of prenatal care (R-GINDEX)		
Adequate or intensive (reference)	1.00	1.00
Intermediate	0.58 (0.57–0.59)	0.65 (0.64–0.66)
Inadequate	0.60 (0.58–0.61)	0.70 (0.68–0.72)
Immigration status		
Non-immigrant (reference)	1.00	1.00
Non-recent immigrant, Africa or Caribbean	1.00 (0.95–1.06)	0.90 (0.85–0.95)
Non-recent immigrant, other world regions	0.72 (0.69–0.74)	0.70 (0.68–0.72)
Recent immigrant, Africa or Caribbean	0.83 (0.77–0.89)	0.79 (0.73–0.85)
Recent immigrant, other world regions	0.63 (0.61–0.64)	0.64 (0.62–0.66)
Material deprivation income quintile		
1 (least deprived; reference)	1.00	1.00
2	1.02 (1.00–1.05)	1.04 (1.01–1.06)
3	1.00 (0.97–1.02)	1.03 (1.00–1.05)
4	1.01 (0.99–1.04)	1.06 (1.03–1.09)
5 (most deprived)	1.00 (0.97–1.02)	1.06 (1.03–1.09)
Residential instability quintile		
1 (least instability; reference)	1.00	1.00
2	1.09 (1.07–1.12)	1.09 (1.06–1.11)
3	1.11 (1.09–1.14)	1.09 (1.06–1.13)
4	1.07 (1.05–1.10)	1.07 (1.04–1.10)
5 (most instability)	1.03 (1.01–1.06)	1.04 (1.01–1.07)
Multiple birth	2.45 (2.34–2.55)	2.06 (1.97–2.15)
Parity	0.62 (0.61–0.63)	0.61 (0.60–0.62)

Note: CI = confidence interval, OR = odds ratio, R-GINDEX = revised-graduated prenatal care utilization index.

Conclusion

Our population-based study suggests that HIV is not associated with an increased risk of maternal placental syndromes. In contrast, diabetes, hypertension and chronic kidney disease impart a substantial increase in the risk of these syndromes. Our data reinforce the importance of optimizing the management of these comorbid conditions during the prenatal period for all women, irrespective of HIV status.

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