Adverse Neonatal Outcomes Among Women Living With HIV: A Population-Based Study

Erin M. Macdonald, MSc,[1] Ryan Ng, MSc,[1] Ahmed M. Bayoumi, MD, MSc,[1,2,3,4,5] Janet Raboud, PhD,[1,6,7] Jason Brophy, MD, MSc,[8] Khatundi-Irene Masinde,[9] Wangari E. Tharao,[10] Mark H. Yudin, MD, MSc,[2,5,11] Mona R. Loutfy, MD, MPH,[1,3,4,9] Richard H. Glazier, MD, MPH,[1,2,3,5,7,12] Tony Antoniou, PhD[1,2,12,13]

[1]Institute for Clinical Evaluative Sciences, Toronto ON

[2]Li Ka Shing Knowledge Institute, Toronto ON

[3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto ON

[4]Department of Medicine, University of Toronto, Toronto ON

[5]Centre for Research on Inner City Health, St. Michael's Hospital, Toronto ON

[6]Toronto General Research Institute, University Health Network, Toronto ON

[7]Dalla Lana School of Public Health, University of Toronto, Toronto ON

[8]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa ON

[9]Women's College Research Institute, Women's College Hospital, Toronto ON

[10]Women's Health in Women's Hands Community Health Centre, Toronto ON

[11]Department of Obstetrics and Gynecology, St. Michael's Hospital and University of Toronto, Toronto ON

[12]Department of Family and Community Medicine, St. Michael's Hospital and University of Toronto, Toronto ON

[13]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto ON

Abstract

Background: There have been few population-based studies describing the risk of adverse neonatal outcomes among women living with HIV in Canada. Accordingly, we compared the risk of preterm birth (PTB), low birth weight (LBW) and small for gestational age births among Ontario women aged 18 to 49 years living with and without HIV infection.

Methods: We conducted a population-based study using Ontario health administrative data. Generalized estimating equations with a logit link function were used to derive adjusted odds ratios (aORs) and 95% confidence intervals for the association of HIV infection with adverse neonatal outcomes.

Results: Between 2002–2003 and 2010–2011, a total of 1 113 874 singleton live births were available for analysis, of which 615 (0.06%) were to women living with HIV. The proportion of singleton births that were SGA (14.6% vs. 10.3%; $P < 0.001$), PTB (14.6% vs. 6.3%; $P < 0.001$), and LBW (12.5% vs. 4.6%; $P < 0.001$) were higher among women living with HIV than among women without HIV. Following multivariable adjustment, the risks of PTB (aOR 1.76; 95% CI 1.38 to 2.24), SGA (aOR 1.43; 95% CI 1.12 to 1.81), and LBW (aOR 1.90; 95% CI 1.47 to 2.45) were higher for women living with HIV than for women without HIV.

Conclusion: Women with HIV are at higher risk of adverse neonatal outcomes than HIV-negative women. Further research is required to develop preconception and prenatal interventions that could reduce the excess burden of poor pregnancy outcomes among women living with HIV.

Key Words: Preterm birth, small for gestational age, low birth weight, HIV, pregnancy

Competing Interests: None declared.

Received on July 28, 2014

Accepted on October 7, 2014

Résumé

Contexte : Peu d'études en population générale ont décrit le risque d'issues néonatales indésirables chez les femmes vivant avec le VIH au Canada. Par conséquent, nous avons comparé les risques d'accouchement prétermе (APT), de faible poids de naissance (FPN) et d'hypotrophie fœtale (HF) chez des Ontariennes de 18-49 ans vivant ou non avec le VIH.

Méthodes : Nous avons mené une étude en population générale au moyen de données administratives sur la santé en Ontario. Des équations d'estimation généralisées comptant une fonction Logit ont été utilisées pour en venir à des rapports de cotes corrigés (RCc) et à des intervalles de confiance à 95 % en ce qui concerne l'association entre l'infection au VIH et des issues néonatales indésirables.

Résultats : Entre 2002–2003 et 2010–2011, 1 113 874 naissances vivantes issues de grossesses monofœtales étaient disponibles aux fins de l'analyse, 615 (0,06 %) desquelles mettaient en jeu

des femmes vivant avec le VIH. La proportion de naissances issues de grossesses monofœtales qui présentaient une HF (14,6 % vs 10,3 %; P < 0,001), un APT (14,6 % vs 6,3 %; P < 0,001) et un FPN (12,5 % vs 4,6 %; P < 0,001) était plus élevée chez les femmes vivant avec le VIH que chez les femmes n'étant pas infectées par ce dernier. À la suite d'une correction multivariée, les risques d'APT (RCc, 1,76; IC à 95 %, 1,38 - 2,24), d'HF (RCc, 1,43; IC à 95 %, 1,12 - 1,81) et de FPN (RCc, 1,90; IC à 95 %, 1,47 - 2,45) étaient plus élevés chez les femmes vivant avec le VIH que chez les femmes n'étant pas infectées par ce dernier.

Conclusion : Les femmes vivant avec le VIH sont exposées à des risques d'issues néonatales indésirables plus élevés que les femmes séronégatives pour le VIH. La tenue d'autres recherches s'avère requise pour que l'on puisse élaborer des interventions préconceptionnelles et prénatales qui pourraient atténuer le fardeau supplémentaire que doivent assumer les femmes vivant avec le VIH en matière de piètres issues de grossesse.

J Obstet Gynaecol Can 2015;37(4):302–309

INTRODUCTION

In 2011, women constituted 23.3% of people living with HIV in Canada. The vast majority (87.6%) of these women were of reproductive age.[1–3] These statistics are similar in Ontario, which is home to over 40% of the national population of persons living with HIV.[1] Women of reproductive age also represent the fastest growing group of persons living with HIV in Ontario,[1,2] and motherhood is both important to and desired by many of these women.[4,5] In addition, pregnancies among women living with HIV in Ontario account for one third of the total in Canada, with gradual but significant increases in the number of HIV-affected pregnancies over time.[6] In this context, studies examining the risk of adverse birth outcomes among women living with HIV are essential for the design and evaluation of services to optimize the health of these women and their children.

However, despite the increase in the number of women living with HIV who are considering motherhood and becoming pregnant, there are no population-based data describing infant outcomes among HIV-infected women in Canada apart from those arising from surveillance of vertical transmission rates.[6] Previous risk estimates of adverse neonatal outcomes among women with HIV have been derived largely from cohorts that were not population-based in nature, and have additional limitations which render their findings non-generalizable to the Canadian setting. These limitations include variability in maternal health insurance status and a lack of controlling for important determinants of neonatal outcomes, such as immigration status, maternal comorbidity, socioeconomic status, and adequacy of prenatal care.[7–14]

In view of the lack of Canadian estimates of adverse neonatal outcomes among women living with HIV and the limitations of earlier studies, we conducted a population-based study comparing the risk of preterm birth, low birth weight, and small for gestational age births among women living with and without HIV infection in Ontario. We selected these outcomes because they are commonly used indicators of perinatal health, thereby facilitating comparisons across jurisdictions and various time periods.[7–16]

ABBREVIATIONS

aOR	adjusted odds ratio
GEE	generalized estimating equations
LBW	low birth weight
PTB	preterm birth
R-GINDEX	Revised-Graduated Prenatal Care Utilization Index

METHODS

We conducted a population-based study of the outcomes of deliveries in women living with HIV who were residing in Ontario between April 1, 2002, and March 31, 2011. Ontario has a universal single-payer, government-administered health care system. All permanent residents are therefore eligible to receive publicly funded physician and hospital care.

We obtained data from Ontario's administrative health databases. These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. We identified all singleton live births to all Ontario women between the ages of 18 and 49 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 within this cohort, we identified 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.[17] The definition of three physician claims with an International Classification of Diseases, Ninth Revision code for HIV infection (042, 043, 044) within a three-year period has a sensitivity of 96.2% (95% CI 95.2% to 97.9%) and a specificity of 99.6% (95% CI 99.1% to 99.8%) for identifying persons living with HIV.[17]

We obtained hospitalization data from the Canadian Institute for Health Information 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 such as prenatal care, and used validated disease registries to define the presence of diabetes and hypertension.[18,19] We obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. We used the Ontario Mental Health Reporting System database to identify admissions to adult-designated inpatient mental health beds in psychiatric and non-psychiatric facilities in Ontario. We adjusted for differences in comorbidity by calculating the number of Johns Hopkins Aggregated Diagnosis Groups for each woman, using the Johns Hopkins Adjusted Clinical Group system.[20] We derived ecologic measures of neighbourhood instability and deprivation (two dimensions of the Ontario Marginalization Index) using the 2006 Canadian Census.[21] We determined the adequacy of prenatal care using the Revised-Graduated Prenatal Care Utilization Index.[22] 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 in which care began, taking gestational age into account. Finally, we used the Citizenship and Immigration Canada Database to identify women who had immigrated to Ontario. These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used for population-based research examining maternal and neonatal outcomes.[23–26]

The primary outcomes were SGA, LBW, and PTB among all singleton births during the study period. Infants considered to be SGA were those with a birth weight below the tenth percentile appropriate for gestational age, ethnicity, and sex.[27] We classified infants weighing less than 2500 grams as LBW. Finally, any birth that took place before 37 completed weeks was considered preterm.

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 used multivariable generalized estimating equations with a logit link function and an exchangeable correlation structure to derive adjusted odds ratios and 95% confidence intervals for the association of HIV infection with adverse neonatal outcomes. We used GEE models to account for multiple pregnancies from the same woman during the follow-up period. We adjusted all models for variables known to influence the risk of adverse neonatal outcomes, including age, parity, world region of birth, time since immigration, mode of delivery, maternal comorbidity, adequacy of prenatal care, and neighbourhood instability and deprivation. Because the GEE method is not a likelihood-based method, we used the quasi-likelihood under the independence model criterion both to ascertain the appropriateness of the exchangeable correlation structure relative to other working correlation matrices and to assess the fit of our regression models.[28] In all analyses, the reference group was HIV-negative women. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

We obtained ethics approval for this study from the Research Ethics Board of Sunnybrook Health Sciences Centre.

RESULTS

We identified 1 113 874 singleton live births between 2002–2003 and 2010–2011, of which 615 (0.06%) were to women living with HIV. Relative to HIV-negative women, more women living with HIV were between 34 and 49 years of age (25.5% vs. 20.8%; $P = 0.004$) and were immigrants to Ontario (48.3% vs. 25.9%; $P < 0.001$). Women living with HIV were less likely to have had adequate prenatal care (27.6% vs. 37.7%; $P < 0.001$), but more likely to have a prior mental health hospitalization in the preceding five years (3.7% vs. 0.9%; $P < 0.001$), and a previous Caesarean section (37.6% vs. 27.2%; $P < 0.001$) (Table 1). There was no difference between women living with and without HIV in terms of the prevalence of selected comorbidities that may influence the risk of adverse neonatal outcomes, including diabetes, gestational diabetes, and hypertension (Table 1). Women living with HIV and their infants had longer mean lengths of hospital stay, and a greater proportion of infants born to women with HIV required admission to NICU (20.0% vs. 11.9%; $P < 0.001$) (Table 1).

The proportion of singleton births that were SGA (14.6% vs. 10.3%; $P < 0.001$), PTB (14.6% vs. 6.3%; $P < 0.001$), and LBW (12.5% vs. 4.6%; $P < 0.001$) were higher in women living with HIV than in women without HIV. Following multivariable adjustment, the risks of PTB (aOR 1.76; 95% CI 1.38 to 2.24), SGA (aOR 1.43; 95% CI 1.12 to 1.81), and LBW (aOR 1.90; 95% CI 1.47 to 2.45) remained higher for women living with HIV than for women without HIV (Table 2).

DISCUSSION

We found an increased risk of adverse neonatal outcomes among women living with HIV relative to women without HIV. Although the rate of vertical HIV transmission among women living with HIV in Canada is very low,[6] this

Table 1. Baseline characteristics

Characteristic	HIV pregnancy n = 615	Non-HIV pregnancy n = 1 113 259	*P*
Mother's age at delivery, years			
18 to 34	458 (74.5)	881 796 (79.2)	0.004
35 to 49	157 (25.5)	231 463 (20.8)	
Neighbourhood income quintile			
1 (lowest)	297 (48.3)	245 424 (22.0)	< 0.001
2	136 (22.1)	221 795 (19.9)	
3	64 (10.4)	226 430 (20.3)	
4	70 (11.4)	229 961 (20.7)	
5	44 (7.2)	185 342 (16.6)	
Missing	≤ 5	4307 (0.4)	
Time since immigration, years			
0 to 4	155 (25.2)	138 437 (12.4)	< 0.001
5 to 9	88 (14.3)	75 359 (6.8)	
≥ 10	54 (8.8)	74 471 (6.7)	
Non-immigrant	318 (51.7)	824 992 (74.1)	
Region of birth			
Africa	222 (36.1)	22 169 (2.0)	< 0.001
Caribbean	26 (4.2)	16 433 (1.5)	
Other regions	49 (8.0)	249 665 (22.4)	
Canada	318 (51.7)	824 992 (74.1)	
Comorbidities			
Diabetes	12 (2.0)	19 847 (1.8)	0.752
Gestational diabetes	34 (5.5)	55 680 (5.0)	0.549
Hypertension	22 (3.6)	29 149 (2.6)	0.137
Pregnancy-induced hypertension	22 (3.6)	48 443 (4.4)	0.347
Mental health hospitalization	23 (3.7)	9691 (0.9)	< 0.001
Median weeks of gestation at delivery (IQR)	38 (37 to 40)	39 (38 to 40)	< 0.001
Median parity (IQR)	0 (0 to 1)	0 (0 to 1)	0.064
Mode of delivery			
Caesarean section	231 (37.6)	302 504 (27.2)	< 0.001
Induced labour	111 (18.0)	234 315 (21.0)	0.068
Sex of infant, male	306 (49.8)	571 552 (51.3)	0.432
Median birth weight, g (IQR)	3180 (2810 to 3550)	3420 (3090 to 3750)	< 0.001
NICU admission	123 (20.0)	132 238 (11.9)	< 0.001
Median (IQR) maternal LOS, days	3.0 (2.0 to 4.0)	2.0 (1.0 to 3.0)	< 0.001
Median (IQR) infant LOS, days	3.0 (2.0 to 3.0)	2.0 (1.0 to 3.0)	< 0.001
Aggregated diagnosis groups			
Median (IQR)	6 (4 to 9)	4 (3 to 6)	< 0.001
R-GINDEX category			
Adequate	170 (27.6)	419 153 (37.7)	< 0.001
Inadequate	94 (15.8)	156 172 (14.0)	
Intensive	50 (8.1)	56 332 (5.1)	
Intermediate	298 (48.5)	480 246 (43.1)	
Missing	0 (0.0)	1356 (0.1)	

continued

Table 1. *Continued*

Characteristic	HIV pregnancy n = 615	Non-HIV pregnancy n = 1 113 259	*P*
Material deprivation quintile			
1 (least deprived)	66 (10.7)	290 837 (26.1)	< 0.001
2	70 (11.4)	228 756 (20.5)	
3	90 (14.6)	210 132 (18.9)	
4	117 (19.0)	188 042 (16.9)	
5	254 (41.3)	181 208 (16.3)	
Missing	18 (2.9)	14 284 (1.3)	
Residential instability quintile			
1 (least instability)	72 (11.7)	297 877 (26.8)	< 0.001
2	67 (10.9)	224 601 (20.2)	
3	67 (10.9)	165 539 (14.9)	
4	141 (22.9)	211 395 (19.0)	
5	250 (40.7)	199 563 (17.9)	
Missing	18 (2.9)	14 284 (1.3)	

IQR: interquartile range; LOS: length of stay

All data are n (%), unless otherwise stated.

Table 2. Association between HIV and preterm birth, low birth weight, and small for gestational age

Neonatal outcome	HIV pregnancy n (%)	Non-HIV pregnancy n (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Preterm birth	90 (14.6)	70 178 (6.3)	2.48 (1.96 to 3.14)	1.76 (1.38 to 2.24)
Low birth weight	77 (12.5)	51 353 (4.6)	2.90 (2.26 to 3.72)	1.90 (1.47 to 2.45)
Small for gestational age	90 (14.6)	114 192 (10.3)	1.49 (1.17 to 1.90)	1.43 (1.12 to 1.81)

*Models adjusted for age, parity, world region of birth, time since immigration, delivery method, induced labour, maternal comorbidity (using Aggregated Diagnosis Groups), adequacy of prenatal care and neighbourhood instability and deprivation

study reveals substantial non-infectious neonatal morbidity in the context of HIV infection. Our results indicate that at least one in seven pregnancies to women with HIV is complicated by SGA or PTB.

Our findings of increased risk of PTB, LBW, and SGA infants in women living with HIV compared to women without HIV are similar to those of other studies conducted in different settings.[7–14,29–32] However, there are several factors that preclude the generalizability of these findings to the Canadian setting. First, most previous studies did not include the entire target population of women with HIV or have access to the entire population of non-HIV infected mothers for comparison, as they were not population-based. In addition, few cohorts of HIV-infected pregnant women described in the literature approximate the ethnic diversity found within Ontario. In our previous study, we found that the proportion of HIV-infected mothers originally from Africa and the Caribbean increased from 26.7% in 2002 to 2003 to 51.6% in 2009 to 2010.[33] These women may face several challenges when accessing prenatal care, including lack of familiarity with the health care system, inadequate housing, financial barriers for child care and travelling to prenatal appointments, and language barriers.[34,35] Finally, several studies were confounded by variation in health insurance status, an important determinant of obstetrical care,[9,14,31,36,37] whereas in Canada these services are covered by universal health insurance for all women eligible for health care.

The mechanisms responsible for the increased risk of adverse neonatal outcomes among women living with HIV are poorly understood. PTB and LBW may be explained by protease inhibitor-mediated disruptions in progesterone synthesis.[38] In addition, antiretroviral associated immune reconstitution may elicit changes in circulating cytokine levels that induce the premature onset of labour.[39,40] However, an association between adverse neonatal outcomes and antiretroviral therapy has not been uniformly endorsed in the literature, with several studies discounting a causal role for these drugs.[36,37,41] Furthermore, women living with HIV require antiretroviral therapy during pregnancy to prevent

perinatal HIV transmission and maintain their own health. Consequently, not taking these drugs during pregnancy is not a feasible option for women living with HIV. Several placental abnormalities associated with LBW and PTB have been observed with greater frequency in women living with HIV than in non-infected women, including fibrotic lesions, intervillous thrombi, villous immaturity, succenturiate lobes, and velamentous insertions.[42] In addition, social determinants of maternal health such as stigma, racism, stresses of immigration, and residence in marginalized neighbourhoods may augment the negative effect of underlying HIV infection in our population of women living with HIV. Ultimately, it is likely that biologic and social factors are components of causal pathways that result in adverse neonatal outcomes among women with HIV, and further research will be required to identify those factors amenable to intervention.

The findings of this study are strengthened by the population-based nature of the data, thereby allowing us to include all women who delivered a baby in an Ontario hospital over the nine-year study period. In addition, unlike previous studies, we were able to derive risk estimates that were adjusted for maternal region of birth, adequacy of prenatal care, maternal comorbidity, and neighbourhood characteristics that could influence maternal and neonatal health. However, our study has some limitations. We did not have data from births that occurred outside a hospital or among women without provincial health insurance. However, it is estimated that this only accounts for approximately 1.1% of all births in Ontario.[43] Our databases do not include clinical information or reliable estimates of antiretroviral drug use. However, we obtained supplemental data regarding antiretroviral therapy and perinatal transmission from the Canadian Perinatal HIV Surveillance Program (extracted for 614 births to women living with HIV in Ontario for the period covered by our study), which indicates that 86.5% of women with HIV received combination antiretroviral therapy, and only 8.5% received no therapy during their pregnancy (Canadian Perinatal HIV Surveillance Program, personal communication). Of the women on combination antiretroviral therapy, the majority (78.9%) received protease inhibitors, and the risk of vertical transmission was 1.1%. Viral load data were available for 91% of women during the period encompassing 2006 to 2011, and among these 82.8% attained virologic suppression below the limits of detection (50 copies/mL), with a further 10.3% being suppressed to less than 1000 copies/mL. The time when the assessment of viral load was obtained relative to delivery was recorded for 37% of women (n = 146), with the median being 19.5 days before delivery (Canadian Perinatal HIV Surveillance Program, personal communication). We cannot be certain of the generalizability of our findings to other countries. However, it is possible that our results are contextually transferable to other settings with single-payer universal health care systems. Finally, we had no data on important determinants of adverse neonatal outcomes, including smoking, alcohol consumption, and drug use, and maternal BMI. It is therefore possible that residual confounding could account for some of our findings.

While the long-term health of infants born to women with HIV is a topic for future research, it is known that preterm infants are at an increased risk of short-term complications following delivery such as perinatal asphyxia, hypothermia and hypoglycaemia, and mortality.[44] Further, infants who are small at birth have increased rates of cardiovascular disease and non-insulin-dependent diabetes as adults.[45,46] Consequently, it is imperative that clinicians, social scientists, and basic scientists work together to develop and examine pre-conception and pregnancy services tailored to mitigating the effects of biological, behavioural, and social determinants of adverse neonatal outcomes in women living with HIV.

CONCLUSION

Our population-based study indicates that the risk of LBW, PTB, and SGA are higher among women living with HIV than among HIV-negative women. Our findings have important implications for the management of pregnant women living with HIV.

ACKNOWLEDGEMENTS

We would like to thank the investigators of the Canadian Perinatal HIV Surveillance Program for providing data regarding antiretroviral therapy and risk of vertical transmission for mother–infant pairs in Ontario.

This project was supported by a research operating grant from the Ontario HIV Treatment Network (grant number ROG G768) and by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. Tony Antoniou is supported by a New Investigator Award from the Canadian Institutes for Health Research-Ontario HIV Treatment Nework. Mona Loutfy is the recipient of salary support from Women's College Hospital, the University of Toronto and the Women's College Research Institute. Ahmed M. Bayoumi is supported by a Canadian Institutes for Health Research/Ontario Ministry of Health and Long-Term Care Applied Chair in Health Services and Policy Research. Janet Raboud is supported by an Ontario HIV Treatment Network Chair in Biostatistics and the Skate the Dream Fund, Toronto and Western Hospital Foundation.

REFERENCES

1. Public Health Agency of Canada. Population specific HIV/AIDS status report women, 2012. Ottawa: PHAC; 2010.
2. Remis RS, Swantee C, Liu J. Report on HIV/AIDS in Ontario. Toronto: Ontario HIV Epidemiologic Monitoring Unit; April 2010.
3. Antoniou T, Zagorski B, Bayoumi AM, Loutfy M, Strike C, Raboud J, et al. Trends in HIV prevalence, new diagnoses and mortality in Ontario, 1996 to 2009: a population-based study. Open Med 2013;7:98–106.
4. Kennedy VL, Serghides L, Raboud JM, Su D, Blitz S, Hart TA, et al. The importance of motherhood in HIV-positive women of reproductive age in Ontario, Canada. AIDS Care 2014; 26:777–84.
5. Loutfy MR, Hart TA, Mohammed SS, Su D, Ralph ED, Walmsley SL, et al. Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study. PLoS One 2009;4:e7925.
6. Forbes JC, Alimenti AM, Singer J, Brophy JC, Bitnun A, Samson LM, et al. A national review of vertical HIV transmission. AIDS 2012;26:757–63.
7. Martin F, Taylor GP. Increased rates of preterm delivery are associated with the initiation of highly active antiretroviral therapy during pregnancy: a single-center cohort study. J Infect Dis 2007;196:558–61.
8. Stratton P, Tuomala RE, Abboud R, Rodriguez E, Rich K, Pitt J, et al. Obstetric and newborn outcomes in a cohort of HIV-infected pregnant women: a report of the women and infants transmission study. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:179–86.
9. Schulte J, Dominquez K, Sukalac T, Bohannon B, Fowler MG. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: pediatric spectrum of HIV disease, 1989–2004. Pediatrics 2007;119:e900–6.
10. Martí C, Peña JM, Bates I, Madero R, de José I, Pallardo LF, et al. Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003. Acta Obstet Gynecol Scand 2007;86:409–15.
11. Baroncelli S, Tamburrini E, Ravizza M, Pinnetti C, Dalzero S, Scatà M, et al. Pregnancy outcomes in women with advanced HIV infection in Italy. AIDS Patient Care STDs 2011;25:639–45.
12. Azria E, Moutafoff C, Schmitz T, Le Meaux JP, Krivine A, Pannier E, et al. Pregnancy outcomes in women with HIV type-1 receiving a lopinavir/ritonavir-containing regimen. Antivir Ther 2009;14:423–32.
13. Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M, et al. The AmRo study: pregnancy outcome in HIV-1 infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG 2007;114:148–55.
14. Machado ES, Hofer CV, Costa TT, Noqueira SA, Oliveira RH, Abreu TF, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. Sex Transm Infect 2009;85:82–7.
15. Ontario Ministry of Health and Long-Term Care. Initial Report on Public Health. Toronto, ON: Ontario Ministry of Health and Long-Term Care; 2012. Available at: http://www.health.gov.on.ca/en/public/publications/pubhealth/init_report/reportcontents.html. Accessed March 30, 2014.
16. Public Health Agency of Canada. Canadian Perinatal Health Report, 2008 Edition. Ottawa: PHAC; 2008.
17. Antoniou T, Zagorski B, Loutfy MR, Strike C, Glazier RH. Validation of case-finding algorithms derived from administrative data for identifying adults living with human immunodeficiency virus infection. PLoS One 2011;6:e21748.
18. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care 2002;25:512–6.
19. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1:e18–26.
20. Weiner JP. The Johns Hopkins ACG® Case-Mix System Version 6.0 Release Notes. Baltimore, MD: The Johns Hopkins University Bloomberg School of Public Health, Health Services Research & Development Center; 2003.
21. Matheson FI, Dunn JR, Smith KLW, Moineddin R, Glazier RH. Development of the Canadian Marginalization Index: a new tool for the study of inequality. Can J Public Health 2012;103(Suppl 2):S12–16.
22. Alexander GR, Kotelchuck M. Quantifying the adequacy of prenatal care: a comparison of indices. Public Health Rep 1996;111:408–18.
23. Ray JG, Urquia ML, Berger H, Vermeulen MJ. Maternal and neonatal separation and mortality associated with concurrent admissions to intensive care units. CMAJ 2012;184:E956–62.
24. Urquia ML, Ying I, Glazier RH, Berger H, De Souza LR, Ray JG. Serious preeclampsia among different immigrant groups. J Obstet Gynaecol Can 2012;34:348–52.
25. Vigod SN, Kurdyak PA, Dennis CL, Gruneir A, Newman A, Seeman MV, et al. Maternal and newborn outcomes among women with schizophrenia: a retrospective population-based cohort study. BJOG 2014;121(5):566–74. doi:10.111/1471–0528.12567.
26. Ray JG, Vermeulen MJ, Schull MJ, Singh G, Shah R, Redelmeier DA. Results of the Recent Immigrant Pregnancy and Perinatal Long-Term Evaluation Study (RIPPLES). CMAJ 2007:176:1419–26.
27. Ray JG, Sgro M, Mamdani MM, Glazier RH, Bocking A, Hilliard R, et al. Birth weight curves tailored to maternal world region. J Obstet Gynaecol Can 2012;34:159–71.
28. Pan W. Akaike's information criterion in generalized estimating equations. Biometrics 2001;57:120–5.
29. Lorenzi P, Spicher VM, Laubereau B, Hirschel B, Kind C, Rubin C, et al. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. Swiss HIV Cohort Study, the Swiss Collaborative HIV and Pregnancy Study, and the Swiss Neonatal HIV Study. AIDS 1998;12:F241–7.
30. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS 2007;21:1019–26.
31. Salihu HM, Stanley KM, August EM, Weldeselasse H, Mbah AK, Whiteman VE. The association between HIV/AIDS during pregnancy and fetal growth parameters in Florida: a population-based study. Curr HIV Res 2012;10:539–45.
32. Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1 infected women. HIV Med 2008;9:6–13.
33. Antoniou T, Zagorski B, Macdonald E, Bayoumi AM, Raboud J, Brophy J, et al. Trends in live birth rates and adverse neonatal outcomes among HIV-positive women in Ontario, Canada, 2002–2009: a descriptive population-based study. Int J STD AIDS 2014;25(13):960–6.
34. Boerleider AW, Wiegers TA, Mannien J, Francke AL, Devillé WLJM. Factors affecting the use of prenatal care by non-Western women in industrialized Western countries: a systematic review. BMC Pregnancy Childbirth 2013;13:81.
35. Heaman M, Bayrampour H, Kingston D, Blondel B, Gissler M, Roth C, et al. Migrant women's utilization of prenatal care: a systematic review. Matern Child Health J 2013;17:816–36.
36. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med 2002;346:1863–70.

37. Szyld EG, Warley EM, Freimanis L, Gonin R, Cahn PE, Calvet GA, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. AIDS 2006;20:2345–53.

38. Papp E, Mohammadi H, Loutfy MR, Yudin MH, Murphy KE, Walmsley SL, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. J Infect Dis 2015;211:10–8.

39. Fiore S, Newell ML, Trabattoni D, Thorne C, Gray L, Savasi V, et al. Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women. J Reprod Immunol 2006;70:143–50.

40. Fiore S, Ferrazzi E, Newell ML, Trabattoni D, Clerici M. Protease inhibitor-associated increased risk of preterm delivery is an immunological complication of therapy. J Infect Dis 2007;195:914–6.

41. Patel K, Shapiro DE, Brogly SB, Livingston EG, Stek AM, Bardequez AD, et al. Antenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretrovirals during pregnancy. J Infect Dis 2010;201:1034–44.

42. Papp E, Serghides L. Angiogenesis and adverse pregnancy outcomes in women with HIV: the AAPH study (abstract O-012). Presented at the 3rd International Workshop on HIV & Women; January 14–15, 2013; Toronto, Canada.

43. Canadian Institute for Health Information. Too early, too small: a profile of small babies across Canada. Ottawa: CIHI; 2009.

44. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000:284:843–9.

45. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol 2007;165:849–57.

46. Barker DJ, Osmond C, Golding J, Kuh D, Wadsorth ME. Growth in utero, blood pressure in childhood and adult lie, and mortality from cardiovascular disease. BMJ 1989;298:564–7.