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Research

Maternal and neonatal outcomes in pregnancies with type 2 diabetes in First Nation and other Manitoban people: a population-based study

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Abstract

Background: First Nation people living in Canada experience a high prevalence of type 2 diabetes in pregnancy. In this study, we aimed to describe maternal and neonatal outcomes in First Nation and all other females with type 2 diabetes living in Manitoba, Canada.

Methods: This was a population-level retrospective cohort study using linked administrative data from Manitoba (2012–2017). We compared First Nation females with type 2 diabetes with all other Manitoban females with type 2 diabetes, using relative risks (RRs) and 95% confidence intervals (CIs).

Results: A total of 2181 females with type 2 diabetes were included, and 1218 (55.8%) were First Nation. First Nation females with type 2 diabetes were significantly more likely to experience stillbirth (RR 2.14, 95% CI 1.11–4.13) and perinatal death (RR 2.39, 95% CI 1.37–4.17) than all other Manitoban females with type 2 diabetes. Offspring of First Nation females with type 2 diabetes had a higher risk of most neonatal complications than offspring of all other Manitoban females with type 2 diabetes, including a higher risk of congenital malformations (RR 1.97, 95% CI 1.30–2.99), but First Nation people did not have a higher risk of most maternal complications.

Interpretation: First Nation pregnant individuals living with type 2 diabetes experienced a higher risk for adverse pregnancy outcomes than all other Manitoban females with type 2 diabetes. Additional studies are needed to identify both high-risk and protective factors for pregnancy complications in First Nation people living with type 2 diabetes in pregnancy.

The prevalence of type 2 diabetes in pregnancy has risen substantially, with an estimated 90% relative increase in the number of pregnancies complicated by type 2 diabetes over the last 15 years.[1–4] Pregnancies complicated by type 2 diabetes are associated with a higher risk of maternal and neonatal complications.[3,5,6] For the neonate, these include being large for gestational age, hypoglycemia, neonatal intensive care unit (NICU) admission, congenital malformations and stillbirth, with little improvement in outcomes over the last 15 years.[1,2,7]

Globally, hyperglycemia disproportionally affects Indigenous people.[8] First Nation people are more than twice as likely to have type 2 diabetes in pregnancy than others living in Canada.[9] Previous cohorts examining diabetes in pregnancy in Indigenous populations have demonstrated a higher risk of adverse pregnancy outcomes.[10,11] For First Nation females living in Canada with pre-existing diabetes, these include an increased risk of macrosomia, preterm delivery and neonatal hypoglycemia compared with other individuals with diabetes.[12,13] There is a paucity of data examining pregnancy outcomes specific to type 2 diabetes in First Nation people living in Canada and their offspring.

Given the increasing prevalence of obesity and type 2 diabetes, and the younger age at diagnosis of type 2 diabetes, as well as increasing maternal age, contemporary population-level studies are needed to evaluate whether disparities in pregnancy outcomes complicated by type 2 diabetes continue to exist between First Nation people and others living in Canada.[14,15] Therefore, this study reports on pregnancy outcomes among First Nation and all other females with type 2 diabetes living in Manitoba, Canada, from 2012 to 2017.

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Methods

We performed a population-level retrospective cohort study using administrative data from fiscal years 2011/12 to 2016/17 in Manitoba. Manitoba is an ethnically diverse province with a population of about 1.3 million.[16] Registered First Nation people represent about 10% of the province's adult population.[17] Since Manitoba has provincially funded physician and hospital visits, health records are inclusive of virtually the entire population. To ensure that this study included the perspective of First Nation people and communities, all study aspects from inception to manuscript preparation were conducted in partnership with researchers at the Manitoba Centre for Health Policy and the First Nations Health and Social Secretariat of Manitoba.[17]

Data sources

The Population Health Research Repository at the Manitoba Centre for Health Policy contains deidentified data from multiple administrative and clinical sources, linked on a per-project basis by a scrambled personal health identification number. Multiple databases were used in the study, including the Manitoba Health Insurance Registry (http://mchp-appserv.cpe.umanitoba.ca/dataDescriptions.php?ds=Insurance), laboratory data (Shared Health Diagnostic Services), physician billing data (Medical Claims/Medical Services database), hospital discharge abstracts (Hospital abstracts database), drug dispensation data (Drug Program Information Network) and the Diabetes Education Resource for Children and Adolescents (Appendix 1, available at www.cmajopen.ca/content/10/4/E930/suppl/DC1). The First Nations Research File (http://mchp-appserv.cpe.umanitoba.ca/dataDescriptions.php?ds=MBFirstNationsResearchFile) was used to identify registered First Nation individuals. The Manitoba First Nations Research File includes First Nation people living in Manitoba who are registered as "Status Indians" under the *Indian Act*. These databases have been extensively used for research studies and are well validated.[18,19] This current study is part of a larger report examining the impact of type 2 diabetes on all populations in Manitoba.[17]

Identification of the cohorts

Individuals with pre-existing type 2 diabetes or type 2 diabetes diagnosed in early pregnancy were identified using an administrative data definition that built upon a previously validated definition of all types of diabetes in order to isolate type 2 diabetes (Appendix 2, Appendix Figure 1, available at www.cmajopen.ca/content/10/4/E930/suppl/DC1).[17,20–23] To avoid misclassification of gestational diabetes as type 2 diabetes, individuals with billing codes within 120 days of delivery and 90 days after delivery were not included when capturing *International Statistical Classification of Diseases and Related Health Problems* codes.[24] For the analysis of stillbirth and perinatal death, events were captured for all pregnancies for individuals with type 2 diabetes aged 14–40 years. For the remainder of the outcomes, analyses were restricted to individuals aged 14–40 years with type 2 diabetes who had at least 1 live birth during the study period after their diagnosis of diabetes. These individuals with type 2 diabetes were then matched 1:3 on maternal age (± 2 yr), ethnicity (First Nation v. all other Manitobans), primiparity and region of residence (using regional health authorities) to mother–baby pairs without evidence of any diabetes in pregnancy. For individuals with more than 1 birth during the study period, 1 birth was randomly chosen for matching. Mother–baby dyads were limited to single liveborn infants only; pregnancies of twins or higher order were excluded.

Key definitions and outcome measures

Maternal outcomes included mode of delivery (operative vaginal delivery and cesarean delivery), induction of labour, and maternal morbidity and mortality.[25] Neonatal outcomes included gestational age, birth weight, NICU admission, neonatal readmission, congenital malformations and birth trauma.[17] Preterm delivery and early preterm delivery were defined as delivery before 37- and 34-weeks' gestation, respectively. Large for gestational age was defined as greater than the 90th percentile, and small for gestational age was defined as less than the 10th percentile of their sex and gestational-age specific birth weight.[26] Stillbirth was defined as a birth after 20 weeks' gestation without signs of life, and perinatal death was defined as having either a stillbirth or an infant who died within 6 days of birth. The percentages of stillbirth and perinatal death were calculated using total live births and stillbirths as the denominator. Details of outcome definitions are summarized in Appendix 1.[17]

Statistical analysis

Data extraction and analysis was performed at the Manitoba Centre for Health Policy. Analyses were stratified by type 2 diabetes and by First Nation status. For stillbirth and perinatal death, relative risks (RRs) were calculated based on epidemiologic tables. A modified Poisson method was used to evaluate the association between the exposure and all other outcomes. Models included type 2 diabetes versus no diabetes and First Nation versus all other Manitobans, and the interaction term between type 2 diabetes and First Nation status. The association of type 2 diabetes with each of the maternal and neonatal outcomes was analyzed and reported as RRs and 95% confidence intervals (CIs). A p value of less than 0.05 was considered significant. The data analyses were generated using SAS software, version 9.4 or Stata, version 16.1.

Ethics approval

Ethics approval was obtained from the University of Manitoba Health Research Ethics Board (HS19030; H2015:397).

Results

A flow diagram of included mother–baby pairs is detailed in Figure 1. A total of 2283 live births occurred in individuals with type 2 diabetes during the study period. Of these births, 2181 were in people aged 14–40 years (1218 First Nation people [55.8%] and 963 [44.2%] other Manitobans), with no births recorded under age 14 years (Appendix 3, available at www.cmajopen.ca/content/10/4/E930/suppl/DC1). After choosing 1 random birth per person and matching with controls, a total

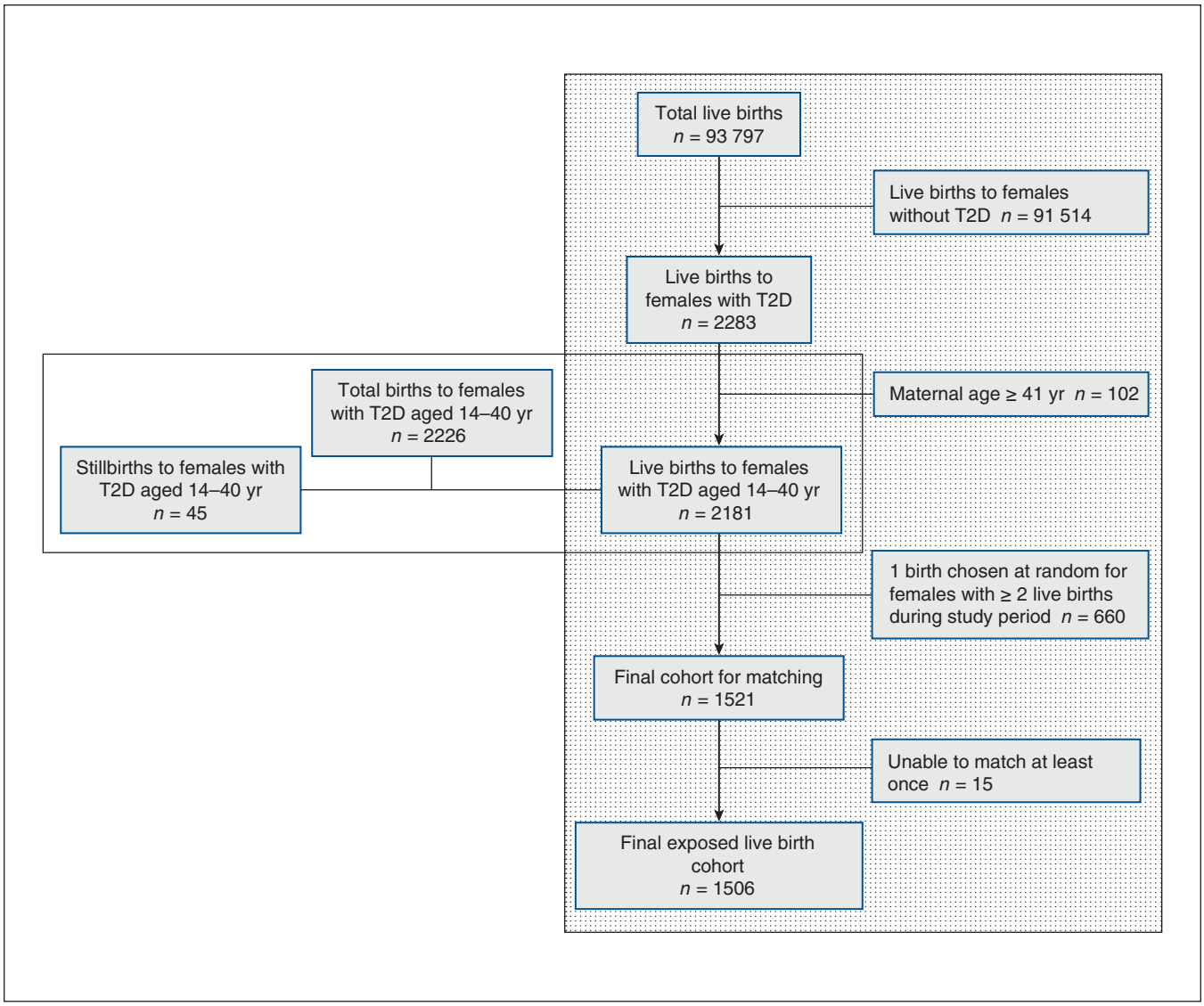

Figure 1: Study flow diagram of included mother–baby pairs in the study. The dotted box indicates the matched cohort. Note: T2D = type 2 diabetes.

of 1506 live births born to people with type 2 diabetes were included (816 [54.2%] First Nation and 690 [45.8%] other Manitoban people).

Stillbirth and perinatal death during the study period

First Nation people with type 2 diabetes were more likely to experience a stillbirth than other Manitobans with type 2 diabetes (2.6% [*n* = 33/1251] v. 1.2% [*n* = 12/975], respectively; RR 2.14, 95% CI 1.11–4.13; *p* = 0.02). First Nation people with type 2 diabetes were also more likely to experience a perinatal death than other Manitobans with type 2 diabetes (3.9% [*n* = 49] v. 1.6% [*n* = 16], respectively; RR 2.39, 95% CI 1.37–4.17; *p* = 0.002).

Maternal and neonatal outcomes in pregnancies with and without type 2 diabetes

Maternal baseline characteristics of the matched cohorts are reported by First Nation versus other Manitoban people with and without diabetes in Table 1.[27] Maternal and neonatal outcomes stratified by First Nation status compared with matched controls are summarized in Appendix 4 (available at www.cmajopen.ca/content/10/4/E930/suppl/DC1), and the RRs of these outcomes are reported in Table 2. In both First Nation and other Manitoban people, type 2 diabetes was associated with an increased risk of cesarean delivery and induction of labour, but there was no significant difference in vaginal delivery, or maternal mortality or morbidity (Table 2).

In both First Nation and all other Manitoban offspring, risk of preterm delivery, early preterm delivery, large-for-gestational-age infant, birth trauma, admission to NICU and congenital malformations was higher with type 2 diabetes than with diabetes-free matches. There was a lower risk of infants being small for gestational age among First Nation people with type 2 diabetes compared with matched controls (RR 0.41, 95% CI 0.28–0.60), but this association was not observed in other Manitobans (Table 2).

Table 1: Maternal characteristics of matched cohorts of individuals with and without type 2 diabetes in First Nation and all other Manitoban females

Characteristic	No. (%)*			
	First Nation with type 2 diabetes *n* = 816	First Nation without type 2 diabetes *n* = 2233	All others with type 2 diabetes *n* = 690	All others without type 2 diabetes *n* = 2068
Median age, yr (IQR)	29 (25–34)	28 (24–33)	32 (29–36)	32 (29–35)
Mean age, yr ± SD	29.1 ± 5.8	28.4 ± 5.8	31.9 ± 4.8	31.8 ± 4.7
Urban†	113 (13.8)	339 (15.2)	513 (74.3)	1544 (74.7)
Parity				
0	151 (18.5)	416 (18.6)	225 (32.6)	673 (32.5)
1	153 (18.7)	390 (17.5)	242 (35.1)	801 (38.7)
2	147 (18.0)	359 (16.1)	125 (18.1)	372 (18.0)
≥ 3	365 (44.7)	1068 (47.8)	98 (14.2)	222 (10.7)
Socioeconomic Factor Index group‡				
High (less than –1)	§	17 (0.8)	29 (4.2)	269 (13.0)
Middle (–1 to 0)	59–64§ (7.2–7.8)	158 (17.1)	322 (46.7)	1044 (50.5)
Low (0 to +1)	135 (16.5)	396 (17.7)	224 (32.5)	620 (30.0)
Very low (+1 plus)	618 (75.7)	1659 (74.3)	112 (16.2)	132 (6.4)

Note: IQR = interquartile range, SD = standard deviation.
*Unless stated otherwise.
†Defined as a home address in 1 of the 2 major urban centres in Manitoba with a population > 50 000 people.
‡Defined using the Socioeconomic Factor Index Version 2, which is calculated at the geographic level and assigned based on included individuals' postal code[27]; *n* = 10 missing.
§Data suppressed owing to small numbers in group.

Table 2: Maternal and neonatal outcomes in First Nation and other pregnancies in people with diabetes compared with those without diabetes*

Variable	Relative risk (95% CI)		*p* value for interaction
	First Nation with type 2 diabetes v. diabetes-free matches	Other Manitobans with type 2 diabetes v. diabetes-free matches	
Maternal outcomes			
Cesarean delivery	**2.34 (2.07–2.65)**	**1.77 (1.58–1.97)**	**< 0.001**
Operative vaginal delivery	1.40 (1.00–1.95)	0.90 (0.66–1.23)	0.6
Induction	**1.97 (1.80–2.16)**	**2.09 (1.86–2.35)**	0.4
Mortality or morbidity	0.83 (0.36–1.93)	1.18 (0.59–2.35)	0.5
Neonatal outcomes			
Preterm delivery	**3.99 (3.37–4.73)**	**4.19 (3.38–5.20)**	0.3
Early preterm delivery	**2.68 (1.85–3.90)**	**1.94 (1.14–3.29)**	0.7
Large for gestational age	**2.90 (2.58–3.27)**	**2.42 (2.03–2.88)**	0.09
Small for gestational age	**0.41 (0.28–0.60)**	0.85 (0.63–1.15)	0.003
Birth trauma	**6.25 (2.58–15.15)**	**5.24 (2.21–12.45)**	0.8
NICU admission	**3.93 (3.32–4.65)**	**3.42 (2.82–4.15)**	0.3
Neonatal readmission	**1.60 (1.12–2.29)**	0.88 (0.53–1.49)	0.07
Congenital malformation	**3.61 (2.55–5.12)**	**2.72 (1.67–4.43)**	0.4

Note: CI = confidence interval, NICU = neonatal intensive care unit.
*Boldface font indicates statistical significance.

Maternal and neonatal outcomes in First Nation and other Manitoban people with type 2 diabetes

In pregnant individuals with type 2 diabetes, the RR of cesarean delivery, operative vaginal delivery, and maternal mortality or morbidity did not differ between First Nation females and all other Manitoban females (Table 3). However, First Nation pregnant individuals with type 2 diabetes were more likely to have induction of labour than other Manitobans with type 2 diabetes in pregnancy (Table 3).

Offspring of First Nation females with type 2 diabetes had a higher risk of preterm and early preterm delivery, NICU admission and neonatal readmission to hospital than offspring of all other Manitoban females with type 2 diabetes (Table 3). In addition, offspring of First Nation females with type 2 diabetes were more likely to be large-for-gestational-age neonates and less likely to be small-for-gestational-age neonates than offspring of all other Manitoban females with type 2 diabetes (Table 3). There was an almost twofold increased risk of congenital malformations in pregnancies among First Nation females with type 2 diabetes compared with all other Manitoban females with type 2 diabetes (RR 1.97, 95% CI 1.30–2.99).

Interpretation

Although type 2 diabetes is known to increase the risk of congenital anomaly, stillbirth and perinatal mortality, these risks were greater by twofold for First Nation people compared with all other Manitobans with type 2 diabetes. Additionally, most adverse neonatal outcomes were more common among First Nation females compared with other Manitoban females. Both First Nation and other Manitoban pregnant individuals with type 2 diabetes continue to have a higher risk of adverse pregnancy outcomes, although the magnitude of risk seems disproportionate by ethnicity.

Table 3: Maternal and neonatal outcomes in First Nation people with type 2 diabetes compared with other Manitoban people with type 2 diabetes*

Variable	Relative risk (95% CI)
Maternal outcomes	
Cesarean delivery	0.89 (0.79–1.00)
Operative vaginal delivery	0.86 (0.59–1.27)
Induction	**1.22 (1.10–1.35)**
Mortality or morbidity	0.54 (0.21–1.38)
Neonatal outcomes	
Preterm delivery	**1.31 (1.11–1.54)**
Early preterm delivery	**1.99 (1.23–3.26)**
Large for gestational age	**1.79 (1.55–2.07)**
Small for gestational age	**0.46 (0.30–0.73)**
Birth trauma	0.97 (0.48–1.97)
NICU admission	**1.23 (1.05–1.44)**
Neonatal readmission	**2.11 (1.24–3.62)**
Congenital malformation	**1.97 (1.30–2.99)**

Note: CI = confidence interval, NICU = neonatal intensive care unit.
*Boldface font indicates statistical significance.

Overall, Indigenous people living in Canada experience a higher rate of stillbirth and neonatal death than non-Indigenous people, regardless of a diabetes diagnosis.[28] Before our study, there were limited data available examining these severe adverse outcomes specifically among First Nation females with type 2 diabetes compared with other populations. Our study is consistent with another large Canadian cohort study in Quebec that found that First Nation females with pre-existing diabetes experienced perinatal death to a greater extent than non-Indigenous populations, though the authors did not perform a direct statistical comparison between those populations.[29] Our cohort included only females with type 2 diabetes, whereas the Quebec cohort did not differentiate by type of pre-existing diabetes.[29,30] More recent data from the United Kingdom showed that although people with type 2 diabetes are more likely to reach glycemic control targets throughout pregnancy than people with type 1 diabetes, severe adverse neonatal outcomes are as common or more common.[5,31] We postulate that the higher risk of stillbirth and perinatal death among First Nation pregnant individuals is likely multifactorial and may include factors such as access to care, differences in socioeconomic status, higher rates of obesity or above-target glycemic control, and systemic racism within our health care system. Additional research is required to identify modifiable risk factors in this population.

In our cohort, type 2 diabetes was associated with a higher risk of large-for-gestational-age neonates in both First Nation and other Manitoban females. First Nation females in our study were more likely to have a large-for-gestational-age neonate and less likely to have a small-for-gestational-age neonate than other Manitoban females. Our findings are consistent with results of an earlier Alberta-based cohort study that compared birth weight in First Nation and non–First Nation females, regardless of diabetes status.[32] In this study, infants of First Nation females were significantly more likely to have a high birth weight and very high birth weight. Unlike the Alberta cohort, our cohort used size for gestational age parameters and was restricted to females with type 2 diabetes, which is a well-recognized risk factor for fetal overgrowth. Additionally, definitions of macrosomia using an absolute birth weight instead of a percentile corrected for gestational age underestimate the identification of large-for-gestational-age infants.[11,33,34] Large-for-gestational-age size is associated with an increased risk of other adverse pregnancy outcomes such as neonatal hypoglycemia and stillbirth.[3,31,35] Both diabetes in pregnancy and fetal macrosomia are also independent predictors of cesarean delivery, which is consistent with our study finding that type 2 diabetes increased risk of cesarean delivery. To mitigate the risk of stillbirth, pregnancies complicated by diabetes with suboptimal glycemic control and fetal macrosomia are often delivered earlier in the late preterm or early term period; although this practice pattern attempts to prevent stillbirth, it can translate into postnatal sequelae for the newborn. Additional research is needed to

identify modifiable risk factors for large-for-gestational-age neonates such as above-target glycemic control, metformin use, maternal weight and excess gestational weight gain in First Nation and all other people with type 2 diabetes in pregnancy, and to improve optimal timing and mode of delivery.

Our study benefits from several important strengths. It is a large population-based cohort allowing for examination of less frequent outcomes such as stillbirth and perinatal death. It also benefits from its specific definition for type 2 diabetes, allowing us to make robust conclusions regarding adverse pregnancy outcomes in pregnancies with type 2 diabetes. The use of the more robust definitions of fetal growth abnormalities using percentile cut-offs is also a study strength.

Limitations

Our study also had limitations. We had incomplete data for hemoglobin A_{1c} measurements so were unable to examine the role of glycemic control in these adverse outcomes. Although we matched our type 2 diabetes and non–type 2 diabetes cohorts for important factors such as maternal age, we were unable to adjust for potential confounders not captured by our data, such as maternal obesity, smoking status or medication use. Lastly, our study did not examine or address the complex causes for the differences in pregnancy outcomes in First Nation people and all other Manitobans with type 2 diabetes.

Conclusion

First Nation lives continue to be affected by the legacy of colonization which has had and is continuing to have a profound and intergenerational effect on First Nation health. Our large population-based cohort study showed that First Nation people living with type 2 diabetes experienced a higher risk for adverse pregnancy outcomes than other Manitobans with type 2 diabetes. As maternal age, obesity and early-onset type 2 diabetes increase, we may expect to see a rise in type 2 diabetes in pregnancy. Thus, without improvements in care and policy changes, the higher rates in adverse pregnancy outcomes in First Nation people with type 2 diabetes in pregnancy will persist. Additional studies are urgently needed to identify both high-risk and protective factors for adverse outcomes in First Nation people with type 2 diabetes in pregnancy as well as to understand the way systemic racism in health care delivery and access contributes to these outcomes.

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