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Risk of adverse maternal outcomes among pregnancies with gestational diabetes mellitus in Ontario, Canada, 2012–2020: a retrospective cohort study

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Abstract

Background The rate of gestational diabetes mellitus (GDM) has increased over the past decades, but it's unclear whether associations with maternal outcomes have changed. We aimed to describe rates of adverse maternal outcomes following deliveries with and without GDM over time and assess risks in these outcomes for GDM by delivery period.

Methods This population-based retrospective cohort study was conducted using provincial birth registry linked with health administrative databases in Ontario, Canada. All singleton hospital deliveries between April 1, 2012 and March 31, 2020 were included. We assessed the trends of adverse maternal outcomes among GDM and non-GDM pregnancies and used modified Poisson regression to estimate associations between GDM and adverse maternal outcomes, using crude and adjusted relative risk (aRR) and risk difference (aRD) with 95% confidence intervals (CIs). Outcome measures included labour induction, caesarean section (CS), assisted vaginal delivery, gestational hypertension/preeclampsia, and maternal morbidity or mortality.

Results Among 1 044 258 deliveries, 82 896 (7.9%) had GDM. The age-adjusted rate of GDM increased from 6.2 (95% CI 6.1–6.4) to 10.2 (95% CI 10.0-10.4) per 100 deliveries from fiscal year 2012/13 to 2019/20. Overall, GDM were at a higher risk (aRR [95% CI]) of induction (1.61 [1.59, 1.62]), CS (1.08 [1.06, 1.09]) and gestational hypertension/preeclampsia (1.35 [1.32, 1.38]). The risk of gestational hypertension/preeclampsia for GDM, compared to no GDM, attenuated from an aRR of 1.45 (1.41, 1.49) in 2012/13-2015/16 to an aRR of 1.29 (1.25, 1.32) in 2016/17-2019/20. The strength of the association between GDM and induction (1.62 [1.60, 1.64] vs. 1.60 [1.59, 1.62]), CS (1.10 [1.08, 1,12] vs. 1.07 [1.05, 1.08]), assisted vaginal delivery (0.96 [0.92, 1.00] vs. 0.94 [0.90, 0.98]), and maternal morbidity and mortality (0.93 [0.78, 1.08] vs. 1.09 [0.97, 1.20]) remained stable over time.

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Conclusions In this large population-based study of singleton hospital deliveries in Ontario, Canada, GDM was associated with higher risks of certain maternal adverse outcomes; however, these risks did not increase despite the increasing rate of GDM over the 8-year period, except for postpartum hemorrhage with interventions. Future large prospective studies should prioritize investigation into the risks of maternal outcomes across different glycemic diagnostic thresholds to inform cost-effective health care resource allocation for GDM pregnancies.

Keywords Gestational diabetes mellitus (GDM), Adverse maternal outcomes, Trend, Canada

Background

As a common obstetric complication, gestational diabetes mellitus (GDM) is characterized as a state of hyperglycemia typically occurring in the second-half of pregnancy [1]. The prevalence of GDM has significantly increased over the last 20 years, affecting approximately 5.0-11.8% of pregnancies in the US and Canada [2]. In addition to increased risk of perinatal morbidity and mortality [3, 4], GDM is also associated with an increased risk of adverse long-term cardiometabolic outcomes for the mothers and their offspring [3, 5]. Timely diagnosis and appropriate treatments of GDM have been shown to improve maternal outcomes [6].

The screening and diagnosis criteria for GDM have varied over the years and no consensus has been reached internationally. Given the linear and continuous relationship between maternal glucose level and pregnancy outcomes demonstrated in the multicenter, five-year Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [7], the International Association of Diabetes and Pregnancy Study Groups (IADPSG) defined a lower diagnostic threshold based on an odds ratio (OR) of 1.75 and adopted a single abnormal glycemic value for GDM diagnosis [8]. In Canada, Diabetes Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) historically had different recommendations for the screening and diagnosis of GDM; however, with guideline updates in 2013 to Diabetes Canada and in 2016 to the SOGC, both now align in recommending a two-step test as the preferred approach and a one-step test as an alternative for diagnosing GDM [9, 10]. However, compared with the two-step test, the one-step approach has led to increased identification of milder GDM cases, creating a more heterogeneous GDM population that may influence the risk of associated maternal adverse outcomes [11]. A growing number of studies have reported an increase in rates of GDM over time, which is partly due to the changes in screening strategies and diagnosis criteria and partly due to increases in advanced maternal age at delivery, obesity, and South-Asian race [12–17].

Beyond the changes in screening strategies and diagnosis criteria, the obstetric care for GDM has concurrently evolved over recent years, with wide implementation of guideline-based, institutionally standardized management protocols, enhanced antenatal monitoring, and earlier obstetric and delivery interventions at or near term pregnancy to mitigate adverse outcomes related to poor glycemic control and fetal overgrowth [18–20]. However, the impact of the increase in GDM on adverse maternal outcomes remains unclear. Only a limited studies have investigated the impact of the increasing rate of GDM on adverse maternal outcomes, and they have yielded inconsistent results [21–25]. One earlier Canadian population-based study observed an increase in adverse maternal outcomes except for caesarean delivery over time for GDM pregnancies during 2004 and 2015 [23]. A recent study with over 2 million deliveries in Spain only found an increase in induction among GDM pregnancies from 2009 to 2015 [24]. Some other studies found no significant changes or reduction in the risks of adverse maternal outcomes over time along with the increase in GDM [21, 22, 25].

To fill this knowledge gap, this study aimed to characterize trends in adverse maternal outcomes following deliveries with and without GDM and assess whether risks of these maternal outcomes associated with GDM differed by delivery period in Ontario, Canada between 2012 and 2020. We hypothesized that the recent increase in GDM, especially with inclusion of milder hyperglycemia using the modified Canadian national guidelines in the latter delivery period, would not increase the risks in adverse maternal outcomes following GDM.

Materials and methods

Study design and population

We conducted a retrospective, population-based cohort study of all in-hospital singleton births in Ontario, Canada, between April 2012 and March 31, 2020. To minimize potential data entry error, we excluded records with missing or indefinite infant sex, missing birth weight or gestational age, and those with implausible gestational age and birth weight combinations identified using an algorithm based on a sex-specific Canadian reference standard [26, 27]. Considering that universal screening of GDM in Ontario occurs at 24–28 weeks of gestation and GDM is typically diagnosed before this window, we further excluded those records with gestational age at delivery ≤ 28 weeks. Finally, records with maternal ages < 12 or > 50 years, or with pre-existing diabetes were excluded.

The cohort was assembled from the Better Outcomes Registry & Network (BORN) Ontario which is a validated, large birth registry including detailed information on antenatal, labour and delivery, intrapartum, postpartum, and newborn health for all births at ≥ 20 weeks of gestation or birth weight ≥ 500 g in Ontario [28–30]. Maternal-child data were collected in near real-time from over 250 hospitals and other health organizations through perinatal records, clinical forms, or patient interviews upon admission to hospital for labour and delivery [28, 31]. Birth registry records were further linked with the maternal and obstetrical hospitalization abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) at BORN Ontario to supplement additional exposure, covariates, and maternal outcomes (Table S1).

Screening and diagnosis of GDM

During the study period, notwithstanding the risk factors-based selective screening recommended by the SOGC up until 2016, universal GDM screening at 24–28 weeks has been generally practiced in Ontario based on the national guideline recommendations from Diabetes Canada from 2003 onwards [18].

With regards to diagnostic criteria for GDM, the 2008 Diabetes Canada guidelines recommended screening using a 50-g glucose challenge test (GCT) followed by a 75-g oral glucose tolerance test (OGTT) among those with an abnormal glucose value (≥ 7.8 mmol/L). GDM diagnosis required the GCT value of ≥ 10.3 mol/L or the presence of 2 or more abnormal OGTT values (fasting: ≥5.3 mmol/L; 1-hour: ≥10.6 mmol; 2-hour: ≥8.9 mmol/L). One single abnormal OGTT value was diagnostic of impaired glucose tolerance [32]. In April 2013, the new Diabetes Canada national guidelines were released to adopt two different approaches to identify GDM [9]. The sequential two-step approach was similar to the previous guidelines aside from the increases in the diagnostic value in GCT to ≥ 11.1 mmol/L, the 2-hour OGTT diagnostic value to 9.0 mmol/L and use of a single abnormal value for diagnosis. The one-step approach employing a single abnormal glucose value in a 75-g OGTT with lower diagnostic values (fasting: ≥5.1 mmol/L; 1-hour: ≥10.0 mmol; 2-hour: ≥8.5 mmol/L) from the 2010 IADPSG guidelines was additionally endorsed as an alternative. In 2016, the SOGC aligned with the 2013 Diabetes Canada guidelines and issued the same recommendations [10]. The details of the Canadian guidelines for screening and diagnosis of GDM are summarized in Table S2.

In the current study, we identified GDM from the birth registry, which routinely captures clinical information on diabetes and pregnancy by the variables of "Diabetes and Pregnancy" and "Pregnancy complications". We also searched the linked hospitalization records in the CIHI-DAD to supplement GDM ascertainment if the records included the International Classification, Tenth version Canadian adaption (ICD-10-CA) diagnosis code O24.8 on the maternal record or P70.0 on the linked infant birth record [23]. Presence of GDM in either database is indicative of GDM. The details to identify GDM are included in Table S3.

Outcomes

Adverse maternal outcomes included process-related outcomes (i.e., labour induction, caesarean section (CS), and assisted vaginal delivery) and other maternal outcomes (i.e., gestational hypertension/preeclampsia, and maternal morbidity or mortality). All caesarean deliveries were included, regardless of indication. Gestational hypertension/preeclampsia was defined following the 2022 SOGC clinical practice guideline and included new-onset hypertension developing at ≥ 20 weeks' gestation [33]. Maternal morbidity or mortality was a composite outcome defined as any of the following events in the immediate peripartum period: maternal death prior to discharge, obstetric embolism, obstetric shock, postpartum hemorrhage with hysterectomy or other procedures to control bleeding, sepsis, thromboembolism or uterine rupture during labour [23].

Maternal outcomes were ascertained if identified in the BORN birth registry or in the CIHI-DAD by using ICD-10-CA diagnosis codes and the Canadian Classification of Interventions (CCI) procedure codes. The process to identify each maternal outcome is included in Table S3.

Statistical analysis

We described all baseline characteristics between pregnancies with GDM and no GDM using means and standard deviations (SDs) for continuous variables and frequency and percentages for categorical variables. Standardized differences were used to compare the distributions of covariates between groups, with an absolute value of ≥ 0.10 indicative of an important difference. Annual age-adjusted rates of GDM per 100 deliveries with 95% confidence intervals (CIs) were calculated by direct standardization using the distribution of maternal age over the study period as a reference. We also computed the rates of each outcome per 100 deliveries, or per 1000 deliveries for rare outcomes, for deliveries with and without GDM between 2012 and 2020, and assessed the temporal change in rates using the Cochrane Armitage tests.

Considering that the national guidelines for GDM screening and diagnostic criteria differed between Diabetes Canada and the SOGC until 2016 [18], we additionally stratified fiscal year of delivery into two 4-year time periods – 2012/13-2015/16 and 2016/17-2019/20 to facilitate the comparison of associations between GDM and

outcomes by delivery periods. We estimated the statistical significance of interaction between time periods of delivery and GDM and used modified Poisson regression models with robust error variance to produce crude and adjusted risk ratios (aRRs) and risk differences (aRDs) with 95% CIs for each outcome, contrasting diabetic with normoglycemic pregnancies. Covariates adjusted in the multivariable regression models were selected a priori based on previous literature and a directed acyclic graph (DAG) (Figure S1): maternal sociodemographic information (age at delivery [< 25,25–34, ≥ 35 years], area-level income quintiles [1, 2, 3, 4, and 5], area-level education quintiles [1, 2, 3, 4, and 5], and race [Asian, and non-Asian]), prenatal or obstetric characteristics (nulliparity [yes or no], pre-pregnancy body mass index (BMI) [< 18.5, 18.5–24.9, 25.0-29.9, and ≥ 30.0 kg/m^2], conception type [fertility treatments, and spontaneous conception], pre-existing medical or obstetric conditions [yes or no], receipt of online or in-person prenatal education [yes or no], and antenatal health care practitioner type [none, midwife, family physician, or obstetrician]), and smoking during pregnancy (yes or no). We did not adjusted for gestational age at delivery considering it might be on the causal pathway between GDM and maternal outcomes, and adjustment might subsequently lead to collider bias [34]. For extremely rare outcomes, we only adjusted for maternal age and nulliparity to facilitate convergence.

The missingness of individual covariates varied from 0% to 12.3%. With the assumption that data was missing at random, we used multiple imputation with a fully conditional specification approach to impute missing values (Table S4). We generated five multiple imputed datasets and combined results across imputed datasets using Robin's rules [35]. For maternal race with missingness (34.4% of the cohort), we kept these observations as a separate missing category.

In sensitivity analyses, we reran our model using complete-case analyses to evaluate the impact of the multiple imputation model. We restricted to first deliveries to account for multiple deliveries to the same pregnant individuals over time given the high recurrence rate of GDM and other obstetric complications which may reflect different underlying physiopathology among these women [36], and potential diagnostic errors related to carry-over or miscoding from prior pregnancies. Lastly, we compared the results by excluding GDM pregnancies with medical treatments as GDM cases without medical treatments might be milder and have better glucose levels, which is an important factor for adverse maternal outcomes.

All data analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC, USA). A 2-sided p value < 0.05 indicated statistical significance.

This study was reviewed and approved by the Research Ethics Boards from the Ottawa Health Science Network and University of Ottawa. No individual patient consent was required as this study involved a secondary use of databases in housed at BORN Ontario. Under the Personal Health Information Protection Act (PHIPA), 2004 A, BORN Ontario prescribed registry can collect and use personal health information without consent to facilitate and improve health care. All data management and analyses were performed within the secure environment at BORN Ontario, aligning with all security and privacy protocols and policies. We followed the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines for reporting [37] (Table S5).

Results

Characteristics of the study population

A total of 1 070 542 pregnancies resulted in a singleton hospital delivery between April 2012 and March 2020 in Ontario, Canada. The final cohort included 1 044 258 pregnancies, and 82 896 received a diagnosis of GDM (Figure S2). The baseline characteristics of deliveries with and without GDM over the study period are presented in Table 1. Compared with normoglycemic pregnancies, pregnant individuals with GDM were more likely to be older, of Asian race, have a higher BMI before pregnancy, conceive following fertility treatments, have medical or obstetrical conditions, and have antenatal care by family physicians or obstetricians, and were less likely to be nulliparous and smoke during pregnancy.

Trends of GDM and associated maternal outcomes

The age-adjusted rate of GDM increased by 63.6% between fiscal years 2012/13 and 2019/20, from 6.2 (95% CI 6.1–6.4) to 10.2 (95% CI 10.0-10.4) per 100 deliveries (Fig. 1). Overall, rates of all adverse maternal outcomes were higher in individuals with GDM relative to no GDM over the study period, except for assisted vaginal delivery (Fig. 2). The rate of induction increased over time in all pregnancies—among GDM pregnancies, it increased from 35.8 (95% CI 34.7 to 36.9) to 46.2 (95% CI 45.3 to 47.0) per 100 deliveries; among pregnancies without GDM, it increased from 22.3 (95% CI 22.0 to 22.5) to 29.2 (95% CI 28.9 to 29.4) per 100 deliveries. Caesarean deliveries and gestational hypertension/preeclampsia increased among non-GDM pregnancies but remained stable among GDM pregnancies. Maternal morbidity and mortality increased over time among both pregnancies with and without GDM, reaching similar levels by the end of study.

Table 1 Maternal and neonatal characteristics of all singleton hospital deliveries in Ontario, Canada, between fiscal years 2012/13 and 2019/20

Characteristics	GDM		Non-GDM		Standardized differences
	No.	(%)	No.	(%)	
Maternal age at delivery, years					
< 25	3 930	(4.7)	128 309	(13.4)	**-0.30**
25–34	47 327	(57.1)	619 143	(64.4)	**-0.15**
≥ 35	31 639	(38.2)	213 906	(22.3)	**0.35**
Missing	0	(0)	< 6 (S)	-	**1.11**
Mean (SD)	32.9	(4.9)	30.5	(5.2)	**0.48**
Neighborhood family income quintile					
Quintile 1 (lowest)	21 303	(25.7)	210 673	(21.9)	0.09
Quintile 2	17 264	(20.8)	192 555	(20.0)	0.02
Quintile 3	17 211	(20.8)	195 465	(20.3)	0.01
Quintile 4	15 056	(18.2)	189 190	(19.7)	-0.04
Quintile 5 (highest)	10 546	(12.7)	153 307	(15.9)	-0.09
Missing	1 516	(1.8)	20 172	(2.1)	-0.02
Neighbourhood education level quintile [a]					
Quintile 1 (lowest)	10 830	(13.1)	151 520	(15.8)	-0.08
Quintile 2	13 547	(16.4)	172 906	(18.0)	-0.04
Quintile 3	17 961	(21.7)	193 944	(20.2)	0.04
Quintile 4	20 554	(24.8)	211 252	(22.0)	0.07
Quintile 5 (highest)	13 976	(16.9)	165 838	(17.3)	-0.01
Missing	6 028	(7.3)	65 902	(6.9)	0.02
Nulliparity					
Yes	31 598	(38.1)	416 611	(43.4)	**-0.11**
No	50 392	(60.8)	534 947	(55.6)	**0.10**
Missing	906	(1.1)	9 804	(1.0)	0.007
Race					
Non-Asian	31 823	(38.4)	466 654	(48.5)	**-0.21**
Asian	27 675	(33.4)	159 320	(16.6)	**0.40**
Missing	23 398	(28.2)	335 388	(34.9)	**-0.14**
Pre-pregnancy BMI, kg/m^2 [b]					
< 18.5	2 284	(2.8)	52 254	(5.4)	**-0.14**
18.5–24.9	25 210	(30.4)	445 264	(46.3)	**-0.33**
25.0-29.9	20 893	(25.2)	202 872	(21.1)	**0.10**
≥ 30.0	24 349	(29.4)	143 227	(14.9)	**0.35**
Missing	10 160	(12.3)	117 745	(12.2)	0.0003
Mean (SD)	28.2	(7.1)	25.1	6.0	**0.47**
Conception type [c]					
Fertility treatments	4 470	(5.4)	29 354	(3.1)	**0.12**
Spontaneous conception	73 656	(88.9)	885 930	(92.2)	**-0.11**
Missing	4 770	(5.8)	46 078	(4.8)	0.04
Maternal smoking [d]					
No	73 110	(88.2)	827 781	(86.1)	0.06
Yes	5 504	(6.6)	89 166	(9.3)	**-0.10**
Missing	4 282	(5.2)	44 415	(4.6)	0.03
Pre-existing medical or obstetrical conditions [e]					
No	54 261	(65.5)	710 322	(73.9)	**-0.18**
Yes	25 669	(31.0)	220 616	(22.9)	**0.18**
Missing	2 966	(3.6)	30 424	(3.2)	0.02
Prenatal education					
No	56 757	(68.5)	630 750	(65.6)	0.06
Yes	16 138	(19.5)	223 879	(23.3)	-0.09
Missing	10 001	(12.1)	106 733	(11.1)	0.03

Table 1 (continued)

Characteristics	GDM		Non-GDM		Standardized differences
	No.	(%)	No.	(%)	
Antenatal health care provider [f]					
None	147	(0.2)	4 129	(0.4)	-0.05
Midwife	7 121	(8.6)	138 096	(14.4)	**0.18**
Non-midwife professionals	71 897	(86.7)	783 640	(81.5)	**0.14**
Missing	3 731	(4.5)	35 497	(3.7)	0.04
Fiscal year of birth					
2012/13	7 992	(9.6)	123 832	(12.9)	**-0.10**
2013/14	7 951	(9.6)	122 626	(12.8)	**-0.10**
2014/15	8 996	(10.9)	121 176	(12.6)	-0.05
2015/16	9 426	(11.4)	120 577	(12.5)	-0.04
2016/17	10 878	(13.1)	119 727	(12.5)	0.02
2017/18	11 804	(14.2)	118 849	(12.4)	0.06
2018/19	12 255	(14.8)	118 017	(12.3)	0.07
2019/20	13 594	(16.4)	116 558	(12.1)	**0.12**

BMI body mass index, *ART* assisted reproductive technologies

Standardized differences with an absolute value of ≥ 0.10 indicate an important difference between GDM and non-GDM pregnancies are in bold

Counts included in Table 1 are based on data before imputation. Column percentages are presented. Numbers are suppressed (S) for small cell sizes (n < 6)

[a] Percentage of college and university degrees among adults 25–64 years old

[b] Pre-pregnancy body mass index (BMI) (kg/m^2) was calculated as weight (kg) prior to pregnancy or at first trimester divided by self-reported height (m^2)

[c] Conception type was based on use of fertility technologies. Fertility technologies including assisted reproductive technologies (e.g. IVF, IVF-ICSI and surrogacy) and non-assisted reproductive treatments (e.g. hormonal treatments and insemination)

[d] A self-reported variable, which was based on smoking status at first prenatal visit

[e] Maternal pre-existing medical or obstetric conditions included any of pre-existing hypertension, autoimmune, cardiac, endocrine conditions, previous stillbirth and previous caesarean deliveries

[f] If a woman had a midwife in addition to other health care providers, she was counted into the midwife group and we assumed midwife would have provided most of the antenatal care. Non-midwife professionals including obstetrician only, family physician only, family physician and obstetrician or nurses

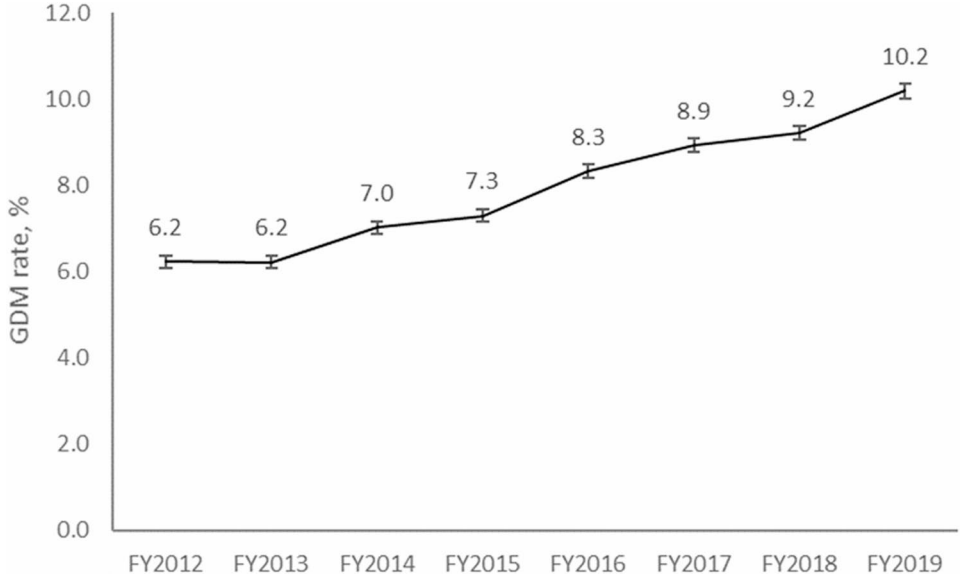

Fig. 1 Age-standardized rate of GDM by fiscal year of delivery in Ontario, Canada

Associations between GDM and maternal outcomes

The RRs and RDs of maternal outcomes in pregnancies with and without GDM across the entire study period were shown in Table S7. After adjusting for maternal age at delivery, neighbourhood income and education level, nulliparity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and year of delivery, GDM was positively associated with induction (aRR 1.61, 95% CI [1.59, 1.62]), CS (aRR

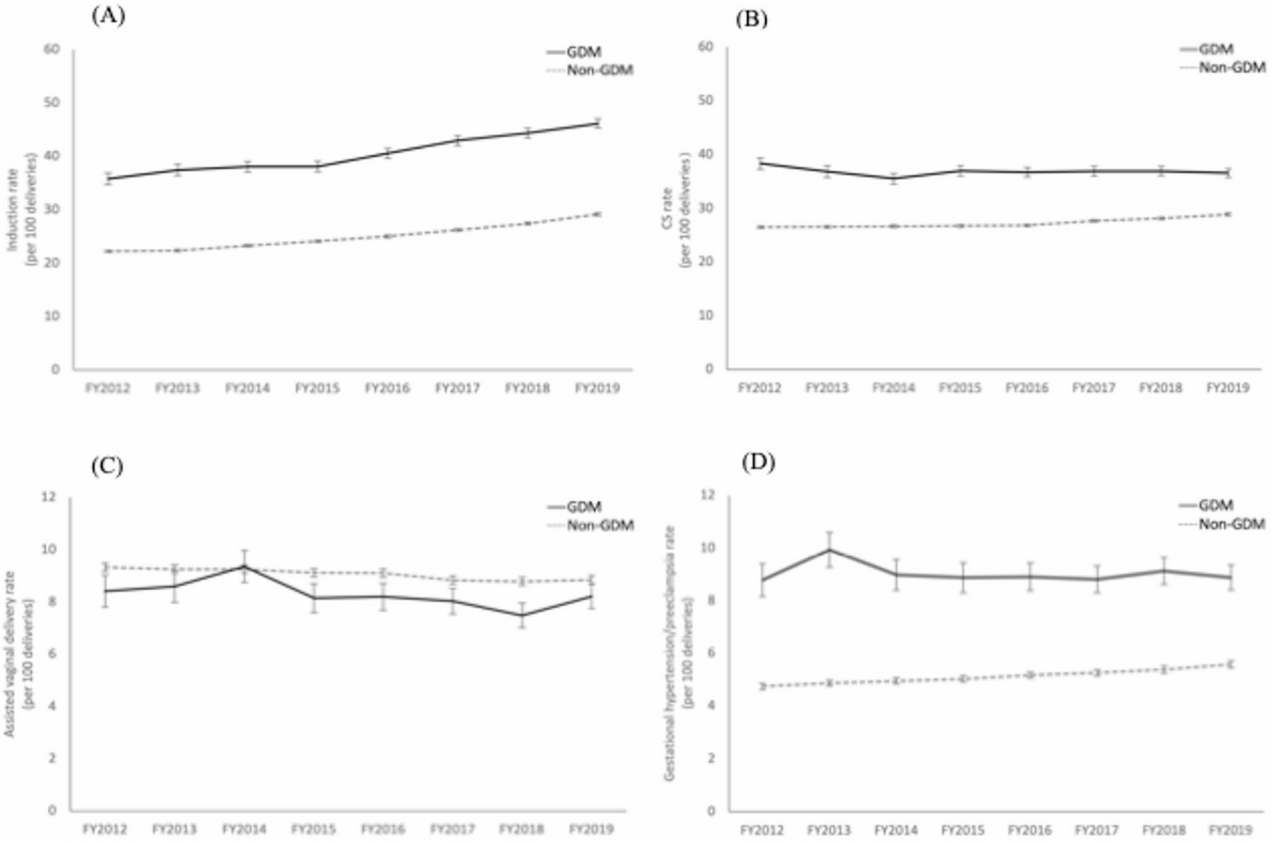

Fig. 2 Rates of adverse outcomes (**A**) Induction; (**B**) CS; (**C**) Assisted vaginal delivery; (**D**) Gestational hypertension/preeclampsia; (**E**) Maternal morbidity and mortality; (**F**) Obstetric embolism; (**G**) Sepsis; (**H**) Thromboembolism; (**I**) Uterine rupture; (**J**) Postpartum hemorrhage with hysterectomy or other procedures to control bleeding in deliveries with and without GDM in Ontario, Canada, between fiscal years 2012/13-2019/20 [a, b, c]. [a] Rate per 100 (1000) gestational diabetic (solid line) and non-gestational diabetic deliveries (dash line); [b] Rates of obstetric shock and maternal death following deliveries with and without GDM were not included due to few cases over the study period; [c] Data for temporal trends in maternal outcomes among deliveries with and without GDM are presented in Table S6

1.08, 95% CI [1.06, 1.09]) and gestational hypertension/preeclampsia (aRR 1.35, 95% CI [1.32, 1.38]), but not with assisted vaginal delivery (aRR 0.95, 95% CI [0.92, 0.98] and maternal morbidity/mortality composite (aRR 1.02, 95% CI [0.93,1.12]).

The comparisons of the associations between GDM and maternal outcomes in early and latter periods of delivery, 2012/13-2015/16 and 2016/17-2019/20, are shown in Fig. 3 and Table S8-S9. With adjustment for maternal age at delivery, income, education level, nulliparity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education and antenatal health care providers, the aRR of induction for GDM compared to no GDM tended to stay stable across delivery periods (1.62, 95% CI [1.60, 1.64] vs. 1.60, 95% CI [1.59, 1.62]). The small significantly inverse relationship of GDM and assisted vaginal delivery was similar in both periods (aRR 0.96, 95% CI [0.92, 1.00] vs. 0.94, 95% CI [0.90, 0.98]). For CS, despite the multiplicative interaction term from the model was statistically significant (P for interaction < 0.001), no qualitative difference in the magnitude of the aRR was observed between the two time periods (1.10, 95% CI [1.08, 1,12] vs. 1.07, 95% CI [1.05, 1.08]). Notably, the risk of gestational hypertension/preeclampsia for GDM, compared to pregnancies without GDM, attenuated from an aRR of 1.45 (95% CI 1.41, 1.49) in 2012/13-2015/16 to 1.29 (95% CI 1.25, 1.32) in 2016/17-2019/20. For composite maternal morbidity and mortality, the aRR for GDM had a non-significant increase from 0.93 (95% CI 0.78, 1.08) in 2012/13-2015/16 to 1.09 (95% CI 0.97, 1.20) in 2016/17-2019/20. With exception of postpartum hemorrhage with interventions, which showed a higher risk in latter period than early period (aRR 0.96, 95% CI [0.75, 1.16] vs. 1.32, 95% CI [1.18, 1.47]), there was no statically significant change observed in the associations of GDM with other component outcomes of maternal morbidity between the two time periods of delivery.

Sensitivity analyses

Complete case analysis had generally comparable findings of in the risks of adverse maternal outcomes across

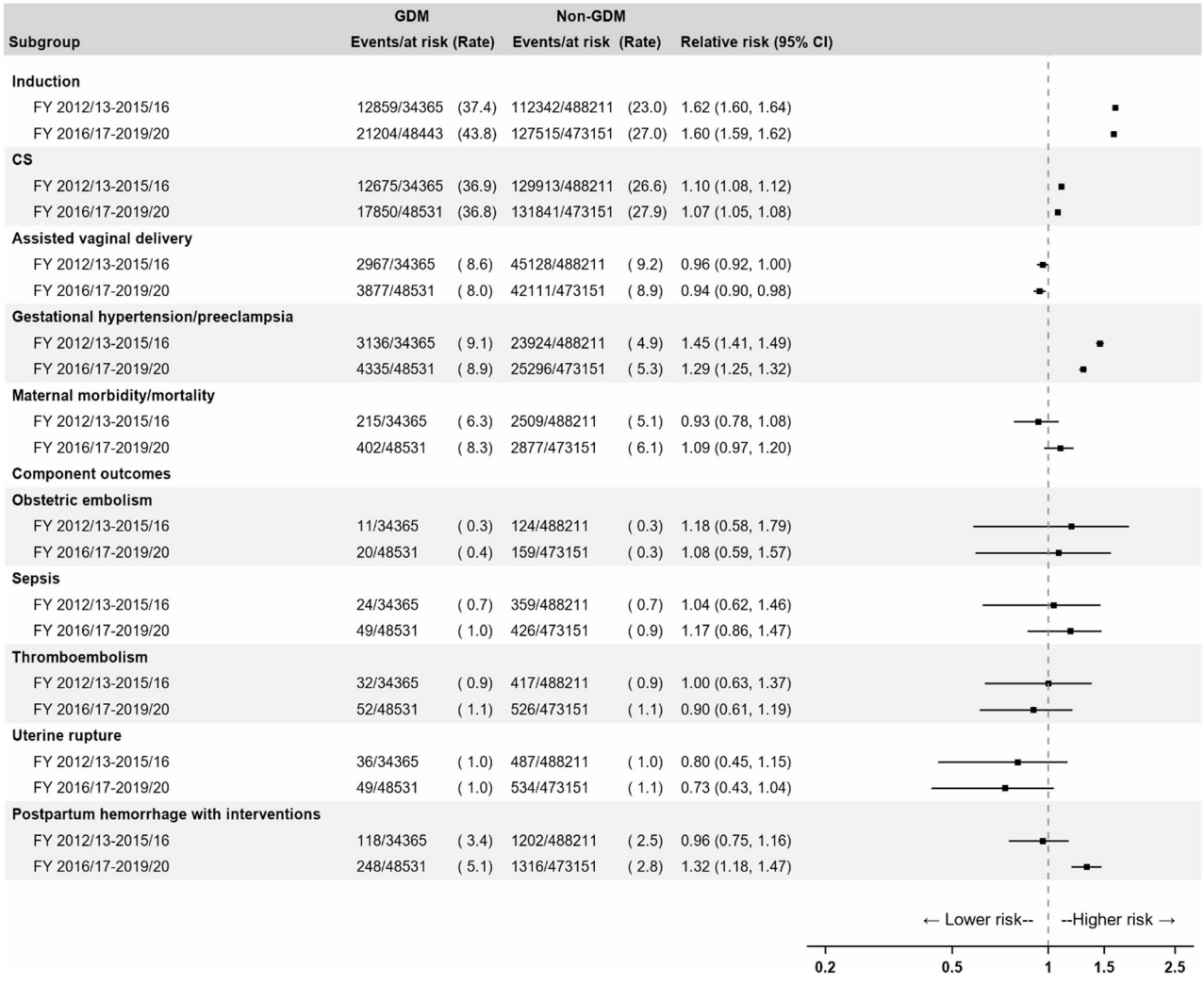

Fig. 3 Association of GDM and maternal outcomes among singleton deliveries in Ontario, Canada, by time periods of delivery ($N = 1\ 044\ 258$) [a, b]. [a] Rates for maternal morbidity and mortality and its component outcomes were expressed as per 1000 deliveries, all other outcomes were expressed as per 100 deliveries; [b] Relative risk comparing pregnancies with GDM vs. no GDM was generated by multivariable regression models, with adjustment for maternal age at delivery, income, education level, nulliparity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education and antenatal health care providers

different time periods of delivery, as did limiting to first deliveries (Table S10 – S11). Exclusion of deliveries with medical treatment for GDM did not substantially change the results. The associations with maternal outcomes were less strong for mild GDM without medical treatments, but the changes in the risks across time periods of delivery were similar to our main results (Table S12).

Discussion

Main findings

This population-based study showed that the age-standardized GDM rates among hospital deliveries increased over the 8 years in Ontario, Canada. Compared to normoglycemic pregnancies, GDM had an increased risk of induction, caesarean deliveries, and gestational hypertension/preeclampsia. Except for postpartum hemorrhage with interventions, the risk of gestational hypertension/preeclampsia for GDM, compared to normoglycemic pregnancies, decreased over time, while induction, CS, assisted vaginal delivery, and severe maternal outcomes remained stable.

Interpretation

The current analysis, which focused on adverse maternal outcomes, builds upon an earlier study using Ontario provincial registry between 2012 and 2020 that the rates of GDM increased progressively among singleton hospital deliveries and GDM without medical treatments had a more pronounced increase over time relative to those requiring medical treatments [17]. However, only a limited number of studies have assessed the changes in the risk of adverse maternal outcomes over time along with

the increasing GDM, and the effect of the recent increase in GDM, especially related to the changes in diagnostic criteria, on outcomes is unclear [38]. Our finding of a significantly higher risk of induction, CS, gestational hypertension or preeclampsia for GDM compared to normoglycemic pregnancies aligns with previous studies [3, 7]. Although the strength of the association between GDM and induction remained stable over time, the increasing rates of induction among GDM pregnancies in our study are supported by recent evidence showing broader utilization of obstetrical interventions for GDM management in clinical practices [7, 23, 24, 39]. Despite having not reached international consensus on the optimal timing of delivery for pregnancies with GDM, clinical guidelines have been widely recommending labour induction to GDM pregnancies at or near term to improve pregnancy outcomes [40, 41]. Consistent with several previous studies [21–24], we found that, despite the increase in the rate of GDM, the risk of CS for GDM compared to non-GDM pregnancies remained stable over time. This likely reflects the stricter screening and diagnosis criteria of GDM and utilization of intensive medical management and interventions including lifestyle modifications, increased use of insulin and metformin as main antihyperglycemic pharmacotherapy, and wide use of induction [6, 18, 42, 43]. It is possible that inclusion of mild degree of hyperglycemia together with medical advances in achieving better glucose control in a short period and early term delivery by induction may have reduced the risk of fetal overgrowth and therefore with no increase in caesarean deliveries [43–45].

Similar to the study by Gortazar in Spain from 2006 to 2015 [21], the reductions in risks of gestational hypertension/preeclampsia for GDM over time in our study might also be attributed to the early diagnosis of GDM and subsequently early treatments of GDM even in a mild state [45]. Although diagnostic values for GDM are variable and thresholds for treatments are inconsistent, several studies have suggested untreated mild hyperglycemia are at a higher risk of poor outcomes compared to normoglycemic pregnancies and improving glycemic values of mild GDM reduces the risk of certain maternal and neonatal outcomes [46–48]. However, one Swedish study using a nationwide birth cohort reported contradictory results, showing the risk of gestational hypertension or preeclampsia for GDM increased from 1991 to 2003 [22]. These discrepancies could be related to the different definitions of pregnancy related hypertension and low sensitivity of the screening strategies for GDM used in Sweden [49].

In contrast to previous results that no changes in severe maternal outcomes over time [24], we found that the risk of postpartum hemorrhage with hysterectomy or other procedures to control bleeding increased significantly over time for pregnancies with GDM compared to those without GDM. This is likely related to changes in obstetric practice patterns over time, particularly more proactive labour and delivery interventions as part of GDM management for concerns about glycemic control or fetal overgrowth. Increased labour induction may lead to greater oxytocin exposure and higher susceptibility to uterine atony-related postpartum hemorrhage [50, 51]. Although overall rate of CS in GDM pregnancies in our study remained stable over time, the indications for CS may have shifted towards GDM cases with suspected fetal macrosomia or non-reassuring fetal status, which may prolong labour and complicate surgical conditions to further increase the risk of severe postpartum hemorrhage [52, 53]. Changes in prevention and management strategies for postpartum hemorrhage in clinical settings, including early identification and active interventions, might also explain this observation [54].

Strengths and limitations

Our study has several strengths. First, the availability of the concurrent comprehensive perinatal data in the diverse obstetric population of the largest province in Canada allowed us to study rare maternal outcomes. BORN Ontario data has been recently validated and demonstrated with high comparable quality to other perinatal databases [29, 30]. Furthermore, we were able to control for several key covariates including maternal pre-pregnancy BMI and prenatal health care, which were important contributors to the outcomes of pregnancy but were not addressed in some of the previous studies [21, 23, 39].

However, interpretation of our findings warrants consideration of several limitations. First, in BORN and other health administrative data, it is likely to have non-differential misclassification of GDM or maternal outcomes due to physician misdiagnoses or imperfect ascertainment, which would generally bias the estimates towards the null in cohort studies. Considering that several maternal outcomes can recur and may be diagnosed differently in subsequent pregnancies, we conducted a sensitivity analysis restricting the cohort to pregnant individuals who had a first delivery during the study period. The results in this more homogeneous subpopulation were similar to the main analysis, supporting the robustness of our findings. Second, information of applied diagnostic guideline or specific OGTT values was not available in the current study, which limited us to precisely compare the impact of different specific diagnostic criteria on changes in outcomes over time. Third, limited available data constrained us to assess the long-term maternal impact of the increasing GDM rate. The observed impact on severe maternal outcomes was likely underestimated as it was limited to the severe complications

occurring during the immediate perinatal periods in the current study. Fourth, given the nature of retrospective observational study, we were unable to address residual confounding from unmeasured and unknown confounders, such as glycemic control, antihyperglycemic medication adherence or reluctance to start medication, and lifestyle behavioral factors, while assessing the changes in the adverse outcomes relating to increasing GDM. Non-adherence to treatment and suboptimal health behaviours might have biased the results away from the null, potentially overestimating the observed associations between GDM and maternal adverse outcomes. Fifth, due to the lack of data to determine the population-level rate of GDM screening test in Ontario, we were unable to restrict our study population to those who underwent GDM screening. Considering that pregnant individuals who did not receive a GDM screening test might differ from those who did, selection bias might have been introduced and distort the observed associations between GDM and maternal adverse outcomes during the study period. Lastly, considering the nature of public-funded health care system and specific GDM screening methods and diagnosis practices in Ontario, the generalizability of our findings to other populations or settings might be limited. In particular, countries or jurisdictions with private health care settings, variations in access to prenatal care, alternative screening strategies, or different diagnostic thresholds may not have the same patterns of detection or management of GDM. Therefore, caution is warranted in the interpretation of our study results.

Research implications

The associations of GDM and adverse maternal outcomes in our study over time has important clinical and public health implications. Our findings suggest that despite the increased GDM rate, the risk of adverse maternal outcomes associated with GDM remained stable or decreased over time. Complementary to the current medical and labour management for GDM pregnancies in clinical practice, future large prospective studies with rigorous adjustment for important covariates and evaluation of maternal outcomes both in the immediate peripartum period and over the longer term are warranted to fully characterize the spectrum of GDM-related risks. Integrating probabilistic misclassification sensitivity analyses into such studies could further quantify the impact of potential diagnosis or data-capture related errors on these associations. In addition, research should prioritize investigating the risks of maternal outcomes across different glycemic diagnostic thresholds to further identify clinically sufficient GDM cases and inform cost-effective health care resource allocation for GDM pregnancies.

Conclusions

In this large population-based study of singleton hospital deliveries in Ontario, Canada, GDM was associated with higher risks of certain adverse maternal outcomes; however, these risks did not increase despite the increasing rate of GDM over the 8-year period, except for postpartum hemorrhage with interventions. Compared to normoglycemic pregnancies, the risk of gestational hypertension/preeclampsia for GDM decreased over time, while induction, CS, assisted vaginal delivery and several severe maternal outcomes remained stable. Future large prospective studies should prioritize investigation into the risks of maternal outcomes across different glycemic diagnostic thresholds to further improve the quality of obstetrical care and inform cost-effective health care resource allocation for GDM pregnancies.

Abbreviations

GDM	Gestational diabetes mellitus
aRR	Adjusted relative risk
aRD	Adjusted risk difference
CIs	Confidence intervals
CS	Caesarean section
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
IADPSG	International Association of Diabetes and Pregnancy Study Groups
OR	Odds ratio
SOGC	Society of Obstetricians and Gynaecologists of Canada
OGTT	Oral glucose tolerance test
BORN	Better Outcomes Registry & Network
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
GCT	Glucose challenge test
ICD-10-CA	International Classification of Diseases Canada, Tenth version
CCI	Canadian Classification of Interventions
SD	Standard deviations
DAG	Directed acyclic graph
BMI	Body mass index
PHIPA	Personal Health Information Protection Act
RECORD	REporting of studies Conducted using Observational Routinelycollected health Data

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

R.L., M.C.W. and S.W.W. conceived the study and designed the study. R.L. analyzed the data and drafted the manuscript. R.L., M.C.W., S.W.W., D.B.F., D.J.C. and M.T. were involved in interpretation of results. M.C.W., S.W.W., D.B.F., D.J.C., and M.T. critically revised the manuscript and contributed to the final version. All authors read and approved the final manuscript.

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Data availability

The datasets used and analysed during the current study are held securely by BORN Ontario and are not publicly available given the data privacy and legal data sharing agreements (DSA). Analytic codes might be available from the corresponding authors on a reasonable request.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Research Ethics Boards from the Ottawa Health Science Network and University of Ottawa. No individual patient consent was required as this study involved a secondary use of databases in housed at BORN Ontario. Under the Personal Health Information Protection Act (PHIPA), 2004 A, BORN Ontario prescribed registry can collect and use personal health information without consent to facilitate and improve health care. All data management and analyses were performed within the secure environment at BORN Ontario, aligning with all security and privacy protocols and policies. However, the interpretation and conclusions contained herein are sorely those of the authors, and do not necessarily reflect those of BORN Ontario.

Consent for publication

Not applicable.

Competing interests

During the conduct of this work, D.B.F. was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute; she continues to hold academic appointments at both institutions, but is now employed by Pfizer and works on unrelated research. All other authors have no potential competing interests to declare.

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