

Gestational diabetes mellitus: An exploration of temporal trends in maternal and neonatal outcomes in Ontario and a systematic review of benefits of induction

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Preface

This is a manuscripts-based thesis. This thesis consists of four studies, with each study presented as a chapter. Chapters 4 and 7 have been published, Chapter 6 is under revision, and Chapter 5 is under peer review. The status of each study is as follows.

Manuscript 1 (Chapter 4): Temporal Trends in Gestational Diabetes Mellitus and Associated Risk Factors in Ontario, Canada, 2012 to 2020: A Population-Based Cohort Study. It was published in the *Journal of Obstetrics and Gynaecology Canada* in August 2024, and is cited as: Luo R, Fell DB, Corsi DJ, Taljaard M, Wen SW, Walker MC. Temporal Trends in Gestational Diabetes Mellitus and Associated Risk Factors in Ontario, Canada, 2012 to 2020: A Population-Based Cohort Study. *Journal of Obstetrics and Gynaecology Canada*. 2024 Aug;46(8):102573.

Manuscript 2 (Chapter 5): Risk of Adverse Maternal Outcomes Among Pregnancies With Gestational Diabetes Mellitus in Ontario, Canada, 2012-2020: a Retrospective Cohort Study. It was submitted to *BMC Pregnancy and Childbirth*.

Manuscript 3 (Chapter 6): Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020. It was submitted to *BMC Pregnancy and Childbirth* and is under revision.

Manuscript 4 (Chapter 7): Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with gestational diabetes mellitus at term pregnancy: a systematic review and meta-analysis. It was published in *BMC Pregnancy and Childbirth* in July 2023, and is cited as: Luo R, Wen W, Corsi DJ, Fell DB, Taljaard M, Wen SW, Walker MC. Comparison of adverse maternal and perinatal outcomes between induction

and expectant management among women with gestational diabetes mellitus at term pregnancy:
a systematic review and meta-analysis. *BMC Pregnancy and Childbirth*. 2023 Jul 12;23(1):509

Statement of Originality

I, Rong Luo, confirm that this thesis is an original work by myself. I conducted the research, performed the analyses, interpreted the results, and drafted manuscripts. The co-Authors of the manuscripts provided methodological advice, contributed to the interpretations of study results, and critically revised the manuscripts.

Contribution of Authors

Manuscript 1 (Chapter 4): I conceived the idea for this study and developed the original protocol, which evolved over time with consultations with Dr. Walker, Dr. Fell and Dr. Wen. I conducted the analyses, interpreted all the results and drafted the manuscript. Dr. Fell provided invaluable methodological suggestions to improve the analyses and interpretation. Dr. Corsi and Dr. Taljaard provided instrumental advice to improve the interpretation of study results. All authors critically reviewed the manuscript for intellectual content.

Manuscript 2 (Chapter 5): I developed the original protocol for this study, with methodological inputs from Dr. Walker, Dr. Fell, and Dr. Wen. Dr. Walker, Dr. Fell, Dr. Wen, Dr. Corsi and Dr. Taljaard all provided methodological advice and contributed to the interpretation of the study results. All authors provided editorial and critical review on the manuscript.

Manuscript 3 (Chapter 6): I led the study design and developed the original protocol for this study, with methodological inputs from Dr. Walker, Dr. Fell, and Dr. Wen. Dr. Fell and Dr. Corsi provided suggestions for the refinements to the analysis and results interpretation. Dr. Taljaard provided invaluable methodological advice to improve interpretation of the study results. All authors edited and reviewed the manuscript.

Manuscript 4 (Chapter 7): I conceived and designed this systematic review and meta-analysis, and developed the search strategy in consultation with a medical library from the Ottawa Hospital. Wendy Wen, a researcher from the University of Ottawa, was the second reviewer for the screening and data extraction process. I performed all data analyses, interpreted study results, and drafted the manuscript. Dr. Walker and Dr. Wen were involved in designing and developing the study protocol, providing methodological advice, interpreting the results, and revising the

manuscript. Dr. Corsi, Dr. Fell, and Dr. Taljaard contributed to the interpretation of study results and revised the manuscript. All authors critically reviewed the manuscript for intellectual content.

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Abstract

Background

Gestational diabetes mellitus (GDM) is a common pregnancy complication that has increased substantially worldwide over the past decades. However, there are few data on recent trends in GDM and the associated impact on adverse pregnancy outcomes in the Canadian population. Induction of labour is recommended to improve perinatal outcomes for GDM pregnancies reaching term gestation, however, epidemiological studies have yielded inconsistent results. The three primary objectives of this thesis were to (1) describe recent trends in GDM and their associations with common risk factors; (2) assess temporal trends in the rates of GDM-associated adverse maternal and neonatal outcomes and compare risks of these outcomes by delivery period; (3) assess the impact of induction of labour at term gestation on adverse outcomes among pregnancies with GDM.

Methods

A population-based retrospective cohort study of all pregnant individuals who had a singleton hospital birth (live birth and stillbirth) between April 1, 2012 and March 31, 2020 in Ontario, Canada, was used to address thesis objectives (1) and (2). Decomposition and multivariable regression analyses with generalized estimation equations were used to evaluate temporal trends and associations with changing trends in GDM. A systematic review and meta-analysis of experimental and observational comparative studies was undertaken to address thesis objective (3).

Results

Objective (1)

Among 1 044 258 pregnant individuals, the annual rate of GDM increased significantly between 2012/13 and 2019/20, from 6.1 to 10.4 per 100 deliveries, in Ontario, Canada (adjusted relative risk:1.53, 95% CI [1.50, 1.56]). The increase was greater in those who did not receive pharmaceutical treatments than those who received pharmaceutical treatments, especially in more recent years. Twenty seven percent of the temporal increase in GDM can be attributed to the distributional changes of three risk factors: the increasing prevalence of advanced maternal age at delivery, pre-pregnancy obesity, and Asian race/ethnicity.

Objective (2)

Among adverse maternal outcomes, despite temporally increasing rates of induction in both GDM and non-GDM pregnancies, the magnitude of the association between GDM and induction was similar between 2012/13-2015/16 and 2016/17-2019/20 (1.62, 95% CI [1.60, 1.64] vs 1.60, 95% CI [1.59, 1.62]). The adjusted relative risk of pregnancy-induced hypertension for GDM compared to non-GDM attenuated from 1.45 (95% CI 1.41, 1.49) in 2012/13-2015/16 to 1.29 (95% CI 2.25, 2.32) in 2016/17-2019/20. The association between GDM and CS (1.10, 95% CI [1.08, 1.12] vs 1.07, 95% CI [1.05, 1.08]), and assisted vaginal delivery (0.96, 95% CI [0.92, 1.00] vs 0.94, 95% CI [0.90, 0.98]) remained similar between the two time periods. For overall maternal morbidity and mortality, the adjusted relative risk was close to 1 and not statistically significant in either time period (0.93, 95% CI [0.78, 1.08] vs 1.09, 95% CI [0.97, 1.20]).

Among adverse neonatal outcomes, although the rate of overall severe neonatal morbidity and mortality (SNM) increased over time among both pregnancies with and without GDM, the positive association between GDM and SNM was stable between the time periods (1.50, 95% CI

[1.48, 1.52] vs 1.54, 95% CI [1.52, 1.56]). The magnitude of the association of GDM with LGA and macrosomia was lower in 2016/17-2019/20 than 2012/13-2015/16 (1.42, 95% CI [1.39, 1.45] vs 1.31, 95% CI [1.28, 1.34] for LGA; 0.98, 95% CI [0.95, 1.02] vs 0.86, 95% CI [0.83, 0.90] for macrosomia). There were no significant changes in the associations of GDM with other neonatal outcomes.

Objective (3)

The systematic review identified 11 experimental and observational comparative studies. Random-effects meta-analysis demonstrated that compared to expectant management, induction at term gestation was associated with a lower pooled odds of macrosomia (randomized controlled trials: 0.49, 95% CI [0.30, 0.81]; $I^2=0\%$; observational studies: 0.64, 95% CI [0.54, 0.77]; $I^2=0\%$); and severe perineal lacerations (observational studies: 0.59, 95% CI [0.39, 0.88]; $I^2=0\%$) among GDM pregnancies. There were no significant differences in odds of CS or other adverse perinatal outcomes between the two groups.

Conclusion

There has been a substantial increase in the GDM rates in Ontario from 2012/13 to 2019/20, with twenty seven percent of this increase attributed to the higher prevalence of advanced maternal age at delivery, pre-pregnancy obesity, and Asian ethnicity. On the other hand, despite the increasing rate of GDM, no significant increase in the risk of GDM-associated adverse maternal and neonatal outcomes was observed, except for postpartum hemorrhage with interventions. For pregnant individuals with GDM, induction at term gestation could lower the risk of macrosomia and severe perineal lacerations compared to expectant management. Future well-designed

clinical trials with large sample sizes are needed for better screening, diagnosis, and management of GDM.

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List of Acronyms and Abbreviations

GDM	Gestational diabetes mellitus
T2DM	Type 2 diabetes mellitus
CS	Caesarean section
IOL	Induction of labour
BORN	Better Outcomes Registry & Network
CIHI-DAD	Canadian Institute for Health Information-Discharge Abstract Database
TNF- α	Tumor necrosis factor alpha
IL-6	Interleukin-6
IL-1 β	Interleukin-1 β
IRS	Insulin receptor substrate
PI3K	Phosphatidylinositol 3-kinase
GLUT4	Glucose transporter type 4
ROS	Reactive oxygen species
GSIS	Glucose-stimulated insulin secretion
IDF	International Diabetes Federation
DM	Diabetes mellitus
PCOS	Polycystic ovarian syndrome
ADA	American Diabetes Association
SOGC	Society of Obstetricians and Gynaecologists of Canada
FIGO	International Federation of Gynaecology and Obstetrics
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ADIPS	Australasian Diabetes in Pregnancy Society
OGTT	Oral glucose tolerance test

GCT	Glucose challenge test
NDDG	National Diabetes Data Group
CC	Carpenter and Coustan
WHO	World Health Organization
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
PPV	Positive predictive value
IGT	Impaired glucose tolerance
NICU	Neonatal intensive care unit
SGA	Small-for-gestational-age
SMBG	Self-monitored blood glucose
CGMS	Continuous glucose monitoring system
RCT	Randomized controlled trials
IOM	Institute of Medicine
GI	Glycemic index
PGE2	Prostaglandins E2
EFW	Estimated fetal weight
ACOG	American College of Obstetricians and Gynaecologists
QCG	Queensland Clinical Guidelines
BIS	BORN Information system
PCCF+	Postal Code Conversion File Plus
ICD-10-CA	Canadian version of International Classification of Diseases, 10 th revision
CCI	Canadian Classification of Health Interventions
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval

OR	Odds ratio
OHSN-REB	Ottawa Health Science Network Research Ethics Board
RR	Risk ratio/relative risk
BMI	Body mass index
DAG	Directed acyclic graph
RD	Risk difference
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
SNM	Severe neonatal morbidity and mortality
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
MeSH	Medical Subject Headings
ICTRP	International Clinical Trials Registry Platform
PICOS	Population-Intervention-Comparators-Outcomes-Study
ICU	Intensive care unit
NOS	Newcastle-Ottawa Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GDT	Guideline Development Tool
CTG	Fetal cardiotocography
UA	Umbilical artery

Chapter 1. Introduction

1.1 Background

Characterized as glucose intolerance of variable severity with onset or first diagnosis during the second or third trimester of pregnancy, excluding pre-existing overt diabetes,¹ gestational diabetes mellitus (GDM) as one of the most common pregnancy complications continues to be a growing public health and clinical concern. GDM has been related to short- and long-term adverse outcomes for both mothers and their offspring. Pregnant individuals with GDM are at higher risks of pre-eclampsia or hypertensive disorders during pregnancy, preterm delivery, caesarean section (CS), and increased risks of progression to type 2 diabetes mellitus (T2DM) or cardiovascular diseases in later life,^{2,3} compared to those with normoglycemic pregnancies. Neonates exposed to intrauterine hyperglycemia are at an elevated risk of perinatal death, macrosomia, shoulder dystocia and other birth injuries, and various cardio-metabolic disorders, including obesity and diabetes, in childhood and early adulthood.²⁻⁵

Although there is a lack of global consensus on screening and diagnostic criteria, GDM has increased substantially over the past decades in Canada and worldwide, and is expected to continuously rise.⁶⁻⁹ Reasons for such increases in GDM rates have not been fully understood. Epidemiological studies have suggested that shifts in the screening and diagnostic criteria over time, particularly with the uptake of the one-step International Association of Diabetes and Pregnancy Study Groups (IADPSG) screening and diagnosis approach, may have influenced these trends.^{10,11} Others have postulated changes in population demographic composition and lifestyle factors, such as an increasing proportion of delayed maternal age at delivery, maternal overweight or obesity, Asian ethnicity, physical inactivity and poor diet quality is also contribute to the increase.¹²⁻¹⁶ Despite the increases in GDM rates, it is unclear whether and to what extent

this increase impacts the associated adverse outcomes.¹⁷ Only a limited number of studies have evaluated whether the increased GDM rate impacted on GDM-associated severe maternal and neonatal outcomes, and the results have been inconclusive.^{6,7,15,18–21}

The appropriate medical and obstetric management, including treatments, mode and timing of delivery, is an important factor for the outcomes of pregnancies with GDM.²² Although inconsistency exists in national and international clinical guidelines, induction of labour (IOL) has been recommended for GDM pregnancies reaching term gestation to prevent intrauterine fetal death and other maternal and neonatal complications related to fetal overgrowth.^{23–27}

Epidemiological studies on the association between induction at term gestation and adverse maternal and neonatal outcomes among GDM pregnancies have yielded inconsistent results.^{27–36}

To the best of our knowledge, there have been significant changes in the demographics within the Canadian population over the years; however, contemporary estimates of the GDM rates in Canada are lacking. Ontario, the most populous Canadian province with a high level of ethnic/racial diversity, provides a unique opportunity to assess secular trends in GDM, determinants, and impacts on associated adverse maternal and neonatal outcomes in Canada. Additionally, few systematic reviews have compared adverse perinatal outcomes between induction and expectant management in pregnancies with GDM reaching term gestation.

1.2 Thesis Objectives and Research Questions

The overall goal of this doctoral thesis was to fill the abovementioned knowledge gap and generate evidence to guide clinical practice and public health for pregnant individuals with GDM, and to inform the direction of future studies. I hypothesized that GDM rates have increased in recent years in Ontario, Canada and that the increase in GDM would not increase

the risk of the adverse outcomes associated with GDM at the population level. Moreover, I hypothesized that, for pregnant individuals with GDM, induction at term gestation would not increase the risk of adverse maternal and perinatal outcomes compared to expectant management. The specific objectives and research questions included were:

Objective 1: To assess the temporal trends in GDM rates and associated risk factors in Ontario from 2012 to 2020 (Chapter 4);

Research questions:

1. Did the distribution of GDM-associated risk factors change over time in Ontario, Canada?
2. What are the recent temporal trends in GDM rates in Ontario, Canada?
3. Which risk factors are associated with the temporal increase of GDM in Ontario, Canada?

Objective 2: To assess whether the increases in the rate of GDM were associated with increases in the risk of adverse maternal and neonatal outcomes over time in Ontario, Canada (Chapters 5-6)

Research questions:

1. What are the trends in the rates of adverse maternal and neonatal outcomes among pregnant individuals with and without GDM between 2012 and 2020 in Ontario, Canada?
2. Does the increased rate of GDM change the risk of GDM-associated adverse maternal and neonatal outcomes at population level?

Objective 3: To summarize the existing evidence using a systematic review on the effect of induction at term among pregnant individuals with GDM (Chapter 7)

Research questions:

1. What are the benefits and risks of adverse maternal and perinatal outcomes for induction at term gestation compared to expectant management among pregnant individuals with GDM?
2. What are the potential sources of heterogeneity across studies on the association between induction at term gestation compared to expectant management among GDM pregnancies?

1.3 Organization of the Thesis

This doctoral thesis contains four studies that have been formatted as manuscripts for publication, each addressing the specific objective. The rationale, methods, and results of the four studies are presented in Chapters 4, 5, 6 and 7, respectively. The overall thesis is structured as follows:

- Chapter 1 outlines the overall rationale, objectives, and organizational structure of the thesis.
- Chapter 2 provides an overview of the current literature on definition, pathophysiology, etiology, epidemiology, and management for pregnancies with GDM.
- Chapter 3 describes the process and formation of the study population for Chapters 4 - 6, based on the Better Outcomes Registry & Network (BORN) Ontario, a large, validated birth registry capturing all hospital births (>99% of all births) across the Canadian province of

Ontario, with comprehensive information collected from the periconceptional to the postpartum period. The inclusion and exclusion criteria of the study population, data analysis, and ethics approval for Chapters 4-6 are also presented.

- Chapter 4 is a manuscript entitled “Temporal trends in gestational diabetes mellitus and associated risk factors in Ontario, Canada, 2012 to 2020: a population-based cohort study”. This manuscript has been published by the *Journal of Obstetrics and Gynaecology Canada* in August 2024. There have been important changes in the demographics of the Canadian population over the years. However, the recent temporal trends in GDM and how changes in associated risk factors have contributed to such increase in GDM over the past decade have not been well documented in Ontario, which has a large and diverse obstetric population. Using a retrospective, population-based birth cohort from the provincial birth registry, the BORN Ontario, linked with the Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD), the purpose of this study was to examine the temporal trends in GDM rates and associated risk factors in Ontario, Canada, and estimate the temporal increase attributable to changes in maternal characteristics by decomposition analysis.
- Chapter 5 is a manuscript entitled “Risk of Adverse Maternal Outcomes Among Pregnancies With Gestational Diabetes Mellitus in Ontario, Canada, 2012-2020: a Retrospective Cohort Study”. This manuscript was submitted to BMC pregnancy and childbirth; it is currently under review. Using data from the BORN Ontario linked with the CIHI-DAD maternal and neonatal records, the purpose of this study was to assess the temporal changes in rates of adverse maternal outcomes following deliveries with and without GDM. Given the changes over time in national guidelines in recommendations for screening and diagnosis criteria for

GDM, and the Canada-wide adoption of the 2-step test and the 1-step test based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria in 2016,¹⁰ we further divided the study period into 2012/13-2015/16 and 2016/17-2019/20. We evaluated whether the risk of adverse maternal outcomes associated with GDM changed by delivery periods in Ontario, Canada between 2012 and 2020.

- Chapter 6 is a manuscript entitled “Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020”. This manuscript was submitted to BMC pregnancy and childbirth; it is currently under revision. Using data from the BORN linked with the delivery hospitalization records from the CIHI-DAD, the purpose of this study was to assess the temporal changes in rates of adverse neonatal outcomes following deliveries with and without GDM, and investigate whether the risk of adverse neonatal outcomes associated with GDM changed by delivery periods before and after the nationwide adoption of two different screening and diagnostic approaches for GDM in Ontario, Canada between 2012 and 2020.
- Chapter 7 is a manuscript entitled “Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with GDM at term pregnancy, a systematic review”. This manuscript has been published by *BMC Pregnancy and Childbirth* in July 2023. The goal of this systematic review and meta-analysis was to summarize available evidence from the literature on benefits and risks of induction at term gestation among pregnant individuals complicated with GDM. Given the between-study heterogeneity has limited the interpretability of previous results, our study also aimed to explore the potential sources of heterogeneity underlying the inconsistent findings, which included clinical heterogeneity, methodological heterogeneity and statistical heterogeneity.

- Chapter 8 summarizes the key findings from different chapters and discusses the interpretations and implications.

Chapter 2. Literature Review

2.1 Definition and Pathophysiology

As one of the prevalent endocrinopathies in pregnancy, GDM was first described in the 1950s.³⁷ The definition of GDM as a state of hyperglycemia with onset or first recognition during pregnancy is widely accepted, although the optimal screening procedure and diagnostic criteria are an ongoing debate issue.¹ GDM typically occurs in the second or third trimester of pregnancy, and resolves in the immediate postpartum period. The pathophysiology of GDM has been attributed to maternal pancreatic decompensation for the pathophysiological increase in insulin resistance in pregnancy.³⁸ Although the exact mechanisms underlying GDM remain unclear, metabolic stress, adipokines, and placental signaling are potentially the key pathways related to increased insulin resistance and β -cells maladaptation during pregnancy (**Figure 2.1**).^{38–40} These include the diabetogenic placental hormones (such as human placenta lactogen, human growth hormone, growth hormone, prolactin, and estrogens and gestagens), increased release of pro-inflammatory cytokines (such as tumor necrosis factor alpha (TNF- α), Interleukin-6 (IL-6) and Interleukin-1 β (IL-1 β)), reduced adiponectin, hyperleptinemia and leptin resistance, impaired insulin signaling by alternation of downstream regulators (such as insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K) and glucose transporter type 4 (GLUT4)), abnormal transportation of glucose, and overproduction of reactive oxygen species (ROS), impaired proliferation and expansion, and apoptosis of β -cells.^{38–40} Collectively, these pathways disrupt insulin levels and dysregulate the maternal glucose homeostasis during pregnancy.

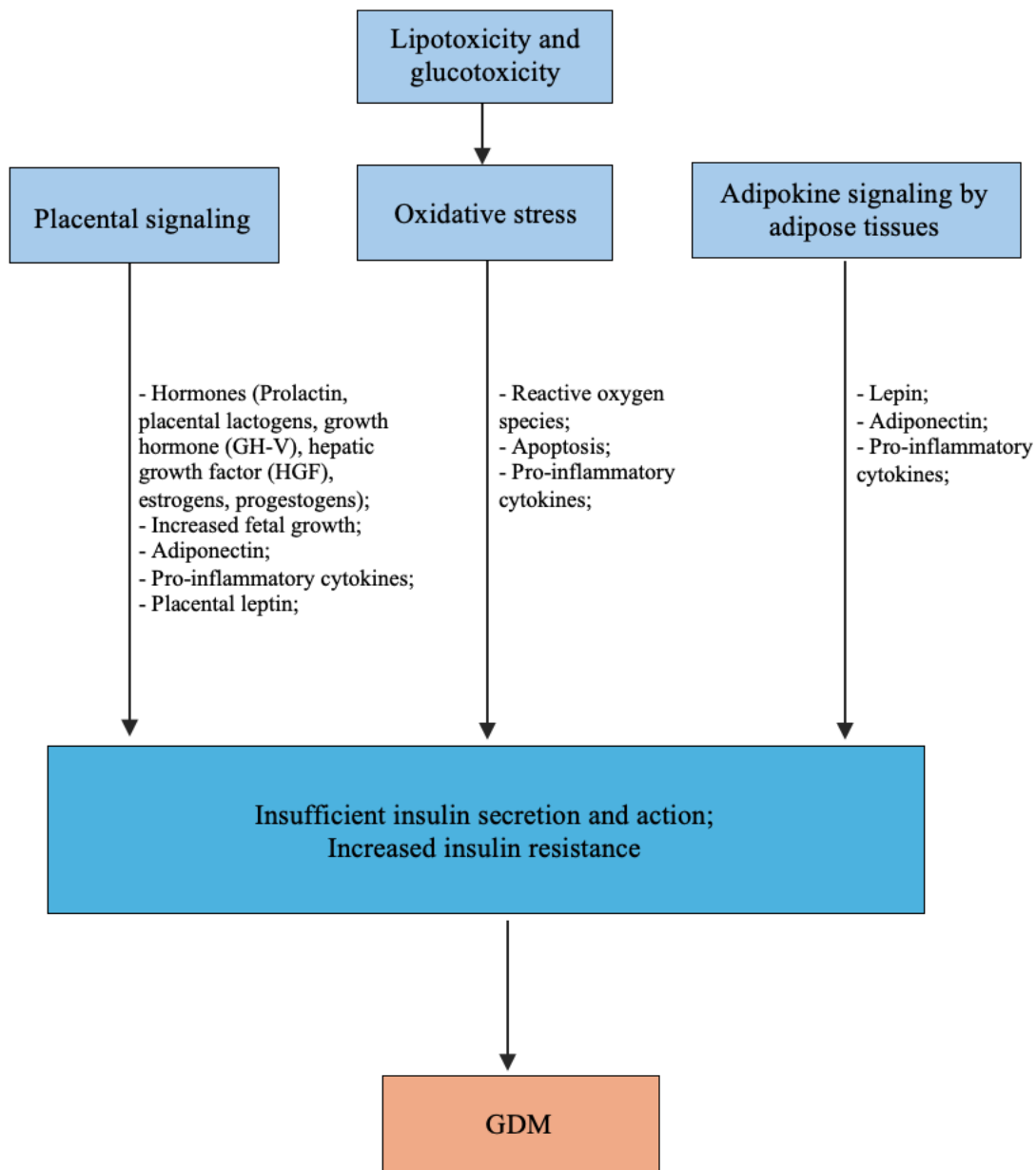


Figure 2.1 Simplified potential pathophysiological mechanisms in the development of GDM

Normally, pregnancy is a complex endocrine-metabolic process requiring a series of physiological hormonal and metabolic adaptations to meet the increasing nutritional needs of the growing fetus.^{39,41} Insulin sensitivity, one of the important metabolic adaptations for glucose

regulation, changes across the course of gestation. In the early stage of pregnancy, insulin sensitivity increases to support uptake of glucose into adipose stores for future energy demands, whereas in mid- and late-pregnancy, insulin sensitivity decreases to one-third of that in non-pregnant state and hepatic gluconeogenesis increases.^{40,42} A transient state of insulin resistance usually starts at the second trimester and increases by a surge of local and placental hormones including leptin, adiponectin, estrogen, progesterone, cortisol, placental lactogen, and placental growth hormone in later gestation.⁴⁰ Insulin resistance causes increases in maternal blood glucose and free fatty acids, resulting in more glucose available for transportation across the placenta to fuel the growth and development of the fetus.⁴³ However, maternal glucose delivery across the placenta to the fetus depends on the gradient of glucose between mother and the fetus.⁴⁴ With progressive insulin resistance and continuing hepatic glucose production and output, a healthy pregnancy can adapt with compensatory increases in insulin secretion through hypertrophy and hyperplasia of pancreatic β -cells and increased glucose-stimulated insulin secretion (GSIS) to maintain glucose homeostasis.^{40,45} Conversely, if maternal pancreatic β -cells had a decompensatory response due to the insufficient insulin secretion or delayed action in pregnancy, it elevates blood glucose level and leads to GDM.³⁸

2.2 Prevalence

Depending on the population profiles, screening methods and diagnostic criteria being applied, the prevalence of GDM varies worldwide, ranging from 5% - 14%.^{46–50} In 2021, the International Diabetes Federation (IDF) estimated approximately one in every six live births (21.1 million) were born to hyperglycemic pregnancies globally, of which 80.3% were complicated by GDM.⁵¹ A recent meta-analysis showed that the highest prevalence of GDM was in the Middle East and North Africa, with a standardized pooled estimate of 27.6% (26.9%-28.4%), whereas the lowest

was in North America and the Caribbean, with a standardized pooled estimate of 7.1% (7.0-7.2%).⁹ In Canada, approximately 7 - 16% of all pregnancies are affected by GDM based on the applied screening and diagnostic criteria.¹⁰ Nationally, the geographical distribution of GDM varies in Canada, with the highest overall prevalence of 10.4% in British Columbia and the lowest prevalence of 3.1% in Nunavut.⁵²

In parallel with the obesity and pre-diabetes epidemics, the prevalence of GDM has been increasing substantially over the recent decades worldwide and across Canada.^{11,52} In British Columbia, the annual prevalence of GDM increased from 7.2% in 2005 to 14.7% in 2019, while in Alberta, its annual prevalence increased from 3.9% to 9.2% over the same period.^{8,53} The increasing prevalence of GDM among hospital deliveries in Ontario has also been reported, almost doubling from 4.4% in 2005-2009 to 8.2% in 2015-2019.⁵² GDM is a significant public health and clinical challenge, given its related substantial direct and indirect health expenditures.^{54,55}

2.3 Etiology and Risk Factors

Although the etiology of GDM has not been fully established, it has been generally considered that GDM is a multifactorial gestational complication, and various genetic, biological, environmental and lifestyle factors contribute to its onset.⁵⁶ A limited number of epidemiological studies have investigated the risk factors for GDM, most of which were limited to the confounding factors.⁵⁷ Besides, variations in screening and diagnosis criteria for GDM and measurements for risk factors complicate the comparisons of the findings between studies. Despite these concerns, maternal overweight or obesity, a family history of diabetes mellitus (DM), race/ethnicity, advanced maternal age, previous delivery of macrosomic neonates, and

history of GDM have been consistently identified as major risk factors.⁵⁸ A meta-analysis of 20 cohort studies from North America, Europe, and Australia reported that pregnant women with overweight, obesity and severe obesity were associated with a 2-fold, 4-fold, and 9-fold higher risk of GDM compared to those women who had normal weight.⁵⁹ Pregnant individuals of racial/ethnic minority groups in western countries, especially Hispanics, Africans, and Asians or South Asians, have a higher risk of GDM compared Caucasians.^{24,58,60} Moreover, indigenous populations from Australia, Canada, New Zealand and the USA are at a higher risk of GDM compared to the non-indigenous counterparts.⁶¹ The risk of GDM is suggested to increase linearly with maternal age, and pregnant individuals aged ≥ 40 years have the risk of developing GDM as high as 5 times compared to those aged < 20 years.⁶² Family history of any diabetes, especially T2DM in first-degree relatives, may impose a 2-4 times increased risk of developing GDM during pregnancy.^{42,63} Obstetric histories are also crucial factors for subsequent GDM. The previous delivery of a macrosomic neonate may increase the risk of GDM by up to 20%, while a history of GDM increases the risk by 30-84% in a subsequent pregnancy.^{64,65} Others reported maternal medical or obstetric conditions such as polycystic ovarian syndrome (PCOS), corticosteroid use, hypothyroidism, having a previous stillbirth, may also increase the risk of GDM.^{58,66} Although lower socioeconomical status and parity have been suggested relating to GDM, their findings are inconclusive due to the heterogeneity in the study populations and methodologies.⁴⁰⁻⁴³

Genetic factors have been recently implicated in the etiology for GDM and several candidate genes are identified.⁵⁶ Although genome-wide association studies to date are very limited, the genetic risk of GDM might be predisposed by the shared genetic basis between GDM and T2DM

as well as gene variants predominantly for GDM mechanisms relating to islet cells, central glucose hemostasis, steroidogenesis and placental expression.⁷⁰

Emerging data in the past decade also indicate some dietary and lifestyle factors before and during pregnancy associated with the risk of GDM. Observational studies suggest dietary patterns of high intake of saturated fat, lower consumption of dietary fiber with high glycemic load are associated with glucose intolerance and subsequent increasing GDM risk.^{71–73} Although evidence of the effect of physical activity on pregnant individuals are limited, it's biologically plausible that physical activity affects glucose homeostasis by increasing insulin sensitivity and secretion and potentially reduce GDM risk.⁷⁴ The results from a meta-analysis of twelve observational studies suggest higher levels of physical activity before pregnancy or in early pregnancy have a protective effect on GDM, despite the limitations of heterogeneous types of physical activity, intensity and duration.⁷⁵

2.4 Screening and Diagnostic Criteria

GDM has been recognized since the 1950s, yet the approaches of screening and the criteria for diagnosis remain subjects of controversy to date, including timing of screening, testing methods, and optimum glycemic diagnosis cut-offs for GDM.⁷⁶

Some guidelines, including the American Diabetes Association (ADA), Diabetes Canada, and the Society of Obstetricians and Gynaecologists of Canada (SOGC), the International Federation of Gynaecology and Obstetrics (FIGO), the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and the Australasian Diabetes in Pregnancy Society (ADIPS) recommend universal screening between 24 and 28 weeks of gestation,^{1,77–81} whereas, the majority of European societies advocate screening should be targeted at women at high risk of

GDM by the risk-factor-based selective screening,^{25,82} and early screening should be encouraged.⁸³ Although there is no clear consensus on the list of risk factors to be used for selective screening, pregnant individuals with age ≥ 35 years, pre-pregnancy BMI ≥ 30 kg/m², previous GDM, a family history of diabetes, high risk ethnicity (Asian, South Asian, African, Hispanic and Aboriginal), or previous macrosomic infant are typically considered as a high risk of developing GDM.^{23,76} No conclusive evidence supports the beneficial effects of early screening and treatment of GDM on pregnancy outcomes.⁷⁶ Notably, recent studies have suggested that a significant number of women (5% - 45%) without risk factors might be missed by selective screening and remain untreated, but the pregnancy outcomes of missed GDM cases were conflicting.⁷⁶ There is no sufficient high-quality evidence on the optimal screening strategies (universal or selective) to improve pregnancy outcomes given only a single trial to date compared the two methods.⁸⁴

Major regional and international variations in the screening methods and diagnostic thresholds also exist, which center around a one-step approach and a two-step approach (Figure 2.2). The two-step approach using an oral glucose tolerance test (OGTT) for GDM diagnosis was initially developed based on predicting the risk of maternal T2DM within 8 years postpartum by O'Sullivan in 1964, and it has been widely practiced in most countries for more than two decades.^{85,86} The two-step approach is consisting of an initial screening with non-fasting 50g oral glucose challenge test (GCT) between 24 and 28 weeks of gestation followed by a diagnostic test by OGTT if there is any abnormal GCT value. The diagnostic test could be a 100g, 3-hour or a 75g, 2-hour OGTT with different criteria such as the National Diabetes Data Group (NDDG) criteria, the Carpenter and Coustan (CC) criteria and the 1999 World Health Organization (WHO) criteria.⁸⁷⁻⁸⁹ Given the findings from the 2008 Hyperglycemia and Adverse Pregnancy

Outcome (HAPO) Study, which demonstrated a continuous, graded, linear relationship between glycemic values and adverse pregnancy outcomes (primary outcomes: LGA, primary CS, neonatal hypoglycemia, and hyperinsulinemia; secondary outcomes: preterm delivery, shoulder dystocia or birth injury, NICU, hyperbilirubinemia, and preeclampsia), the IADPSG proposed a universal, one-step 75g OGTT screening and diagnostic test for GDM.² The IADPSG defined diagnostic thresholds (fasting plasma glucose: 5.1mmol/l; 1-h plasma glucose: 10.0 mmol/l; 2-h plasma glucose: 8.5 mmol/l) based on the 1.75-fold increased odds for adverse neonatal outcomes (cord blood C-peptide, neonatal body fat and large-for-gestational-age neonate) compared to those blood glycemic levels at or below the mean based on the HAPO study,⁸⁰ with one or more glucose values exceeding the cut-off values indicative of GDM. Although the IADPSG criteria remains controversial in terms of test positive predictive value (PPV), merely focusing on neonatal outcomes, and cost effectiveness, it has been endorsed and recommended by several organizations including the WHO, FIGO, ADA, and ADIPS to screen and diagnose GDM.^{1,76,77,81,90}

In Canada, the historical national guidelines on GDM screening and diagnosis between the two largest obstetric and diabetology organizations, Diabetes Canada and the SOGC, have disparities over the years, and the lack of uniformity across recommendations allows various screening approaches and different ascertainment of GDM.¹⁰ As a result of the continuum of risk demonstrated by the 2008 HAPO study and the 2010 IADPSG guideline, Diabetes Canada and the SOGC modified each guideline (in 2013 and 2016, respectively) and both recommended universal screening and diagnosis by the one-step IADPSG approach and the modified two-step 75g OGTT approach with recalculated diagnostic cut-offs (based on an odds ratio of 2.0 from the HAPO study). This ultimately allowed the classification of varying degrees of hyperglycemia as

GDM among all pregnant individuals at 24-28 weeks of gestation.^{78,79} The main modifications in the updated guidelines included adoption of the one-step test by using a 2-h 75g OGTT with lower diagnostic thresholds, elevated diagnostic thresholds following a 50 g GCT for an immediate diagnosis from ≥ 10.3 mmol/L to ≥ 11.1 mmol/L, similar diagnostic cut-off value of 2-h post glucose from 8.9 mmol/L to 9.0 mmol/L in the two-step OGTT testing, and use of a single abnormal value for diagnosis instead of two among the 3 values. Previously, only one abnormal value in the two-step approach was diagnosed as impaired glucose tolerance (IGT) of pregnancy not GDM per se.⁹¹ Although the recommendations were only reached by consensus given the evidence was not sufficient and mostly were from observational studies, collectively, the sensitivity of these new diagnostic criteria for GDM was increased.¹⁰ The details for the changes in the Canadian national guidelines over time by Diabetes Canada and the SOGC are summarized in Table 2.1.

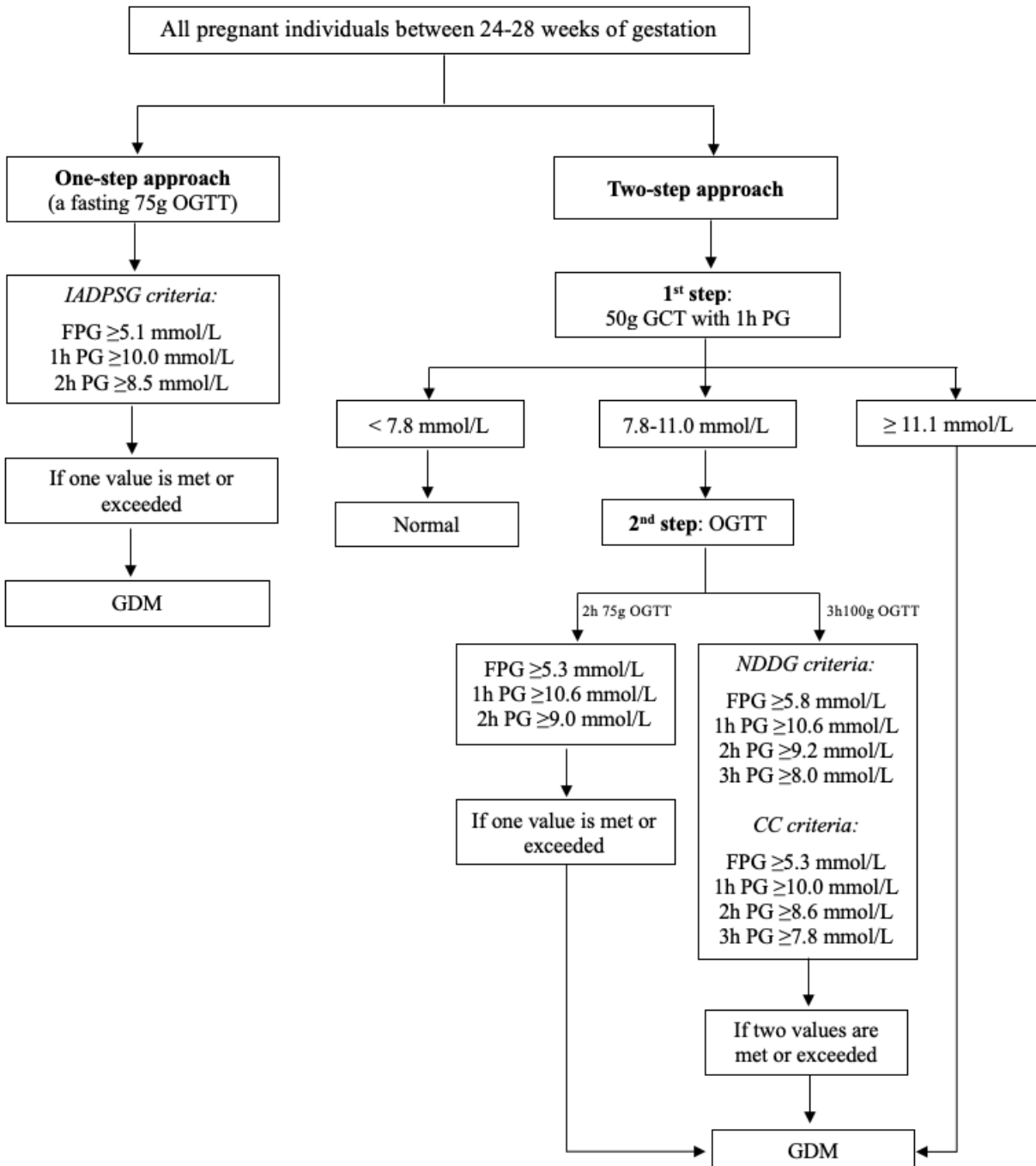


Figure 2.2 Screening and diagnosis approaches for GDM

Table 2.1 Canadian guidelines for screening and diagnosis of GDM

Year, Organization	Screen method	Screening Test	No. of abnormal diagnostic values	FPG (mmol/l)	1h PG (mmol/l)	2h PG (mmol/l)	3h PG (mmol/l)	A1c	RPG (mmol/l)
Diabetes Canada									
2008 ⁹¹	Universal	2-step 2-h 75g OGTT ^s	2	5.3	10.6	8.9	-	-	-
2013 ⁷⁹	Universal	2-step 2-h 75g OGTT ^{\$\$}	1	5.3	10.6	9.0			
		1-step 2-h 75g OGTT	1	5.1	10.0	8.5	-	-	-
2018 ⁹²	Universal	2-step 2-h 75g OGTT ^{\$\$}	1	5.3	10.6	9.0	-	-	-
		1-step 2-h 75g OGTT	1	5.1	10.0	8.5	-	-	-
SOGC									
2002 ⁹³	Selective	2-step 2-h 75g OGTT ^s	2	5.3	10.0	8.6	-	-	-
		2-step 3-h 100g OGTT [*]	2	5.3/5.8	10.0/10.6	8.6/9.2	7.8/8.0	-	-
2016 ⁷⁸	Universal	2-step 2-h 75g OGTT ^{\$\$}	1	5.3	10.6	9.0	-	-	-
		1 step 2-h 75g OGTT	1	5.1	10.0	8.5	-	-	-
2019 ⁵⁸	Universal	2-step 2-h 75g OGTT ^{\$\$}	1	5.3	10.6	9.0	-	-	-
		1 step 2-h 75g OGTT	1	5.1	10.0	8.5	-	-	-
2020 ^{# 94}	Universal	2-step 2-h 75g OGTT ^{\$\$}	1	5.3	10.6	9.0	-	-	-
		Alternative	1	-	-	-		>5.7%	>11.1

Note: OGTT=Oral Glucose Tolerance Test; FPG, fasting plasma glucose; PG, plasma glucose; RPG, non-fasting, random plasma glucose;

[§] If the 1 hour post-glucose plasma glucose in 50g GCT is between 7.8-10.2 mmol/l, subsequent 75g OGTT test will be followed; if the 1 hour post-glucose plasma glucose ≥ 10.3 (mmol/l) in a 50g GCT, it indicates GDM diagnosis without a subsequent 75g OGTT; a single abnormal value in OGTT test indicated impaired glucose tolerance;

^{\$\$} If the 1 hour post-glucose plasma glucose in 50g GCT is between 7.8-11.0 mmol/l, subsequent 75g OGTT test will be followed; if the 1 hour post-glucose plasma glucose ≥ 11.1 (mmol/l) in a 50g GCT, it indicates GDM diagnosis without a subsequent 75g OGTT;

* Diagnostic cut-off values based on the CC and NDDG criteria;

Diabetes Canada and the SOGC shared the same clinical guidelines.

2.5 Adverse Maternal and Neonatal Outcomes

GDM carries significant risks for short- and long-term adverse outcomes on the mother, fetus, and neonates, which are primarily related to hyperglycemia and co-existing metabolic environments.⁵⁸ Pregnant individuals with GDM are at increased risks of adverse pregnancy outcomes including gestational hypertensive disorders, preeclampsia, obstetric interventions of induction and CS, and perineal tears at short term.^{2,95,96} Although GDM typically resolves to normoglycemia after delivery, it's associated with an increased risk for recurrent GDM, pre-diabetes or T2DM at subsequent pregnancies.⁶⁴ Pregnancies with GDM impose a 10-fold higher risk of progression to T2DM and a 2-fold higher risk of cardiovascular events than normoglycemic pregnancies, and the incidence of T2DM appears to be the highest over the subsequent five years.^{96,97}

Compared to infants born to normoglycemic individuals during pregnancy, those born to pregnant individuals with GDM are at a higher risk of preterm birth, hypoglycemia, jaundice, hyperinsulinemia, respiratory disease, low Apgar score at one-minute, admission to neonatal intensive care unit (NICU) and long-term metabolic complications including childhood and early-adult onset of T2DM and obesity.^{4,24,95} Exposure to the hyperglycemic intrauterine environment might also increase the risk of perinatal mortality.^{5,98}

Hyperglycemia has been related to the increased risk of excessive fetal growth. Infants born to mothers with GDM have an approximately 3 times risk of macrosomia and 2 times of LGA, respectively, compared to infants born to normoglycemic mothers.^{99,100} Anthropometric studies have found macrosomia in GDM pregnancies has a unique growth pattern by central deposition of subcutaneous fat in the abdominal and interscapular areas, which is different from

macrosomia contributed by other predisposing factors (e.g. maternal obesity).^{101,102} This pattern of disproportionate overgrowth among macrosomic infants of diabetic pregnancies therefore has been suggested to contribute to the higher risk of severe neonatal morbidity including adverse respiratory diseases, hypoglycemia, shoulder dystocia, clavicular fracture, and brachial plexus injury.^{2,99,103,104}

However, less is known regarding the impact of recent increases in GDM on these adverse outcomes. Limited studies have evaluated whether the increasing rate of GDM impacts adverse maternal and neonatal outcomes and yielded inconsistent findings.^{6,7,15,18–20} One large population-based study in Ontario, Canada found no significant increase in risks of severe perinatal outcomes for GDM pregnancies from 1996 to 2010, although GDM rates doubled over the study period.⁷ Conversely, the Canadian nationwide population-based study observed increasing maternal and neonatal outcomes except for perinatal mortality and CS over time following pregnancies with GDM between 2004 and 2015.⁶ An earlier study using data from the Swedish Medical Birth Register observed an increase in GDM between the period 1991-2003, but found the risk of obstetrical or neonatal outcomes associated with GDM were stable.¹⁹ Similarly, Hilden et al. assessed the trends in pregnancy outcomes for GDM pregnancies in Sweden using a nationwide cohort over the period of 1998 and 2012, and found no significant changes in perinatal mortality and prematurity but declining trend in LGA and birth trauma among GDM pregnancies.¹⁸ In Spain, Gortazar et al. assessed the trends in prevalence of GDM and perinatal outcomes in a population-based cohort of singleton births in Catalonia between 2006 and 2015.²⁰ They found that, despite the increasing rate of GDM, there were no changes in CS and small-for-gestational-age (SGA) neonates, but a reduced risk of preeclampsia, preterm birth, macrosomia and LGA for GDM across time periods.²⁰ Similarly, another Spanish

nationwide study of over 2 million hospital deliveries did not find temporal changes in CS or severe maternal morbidity from 2009 to 2015 in pregnancies with and without GDM.²¹ However, the rate of fetal overgrowth and induction increased more significantly among GDM pregnancies compared to normoglycemic pregnancies.²¹ A large US study by Lavery and colleagues examined the impact of trends in GDM over 125 million pregnancies between 1979 and 2010, and reported that the increased prevalence of GDM was associated with a 184% decline in the rate of LGA/macrosomia and 0.75% increase in the rate of stillbirths for 2008-10 compared with 1979-1981.¹⁵ One Danish study by Ovesen et al. used a small hospital-based cohort of 1910 GDM pregnancies between 2004 and 2016 and only observed a reduction in elective CS and birth weight for neonates along with the concurrent increase in GDM.¹⁰⁵ The inconsistencies across these findings were largely due to different study populations, heterogeneous screening and diagnostic methods, and different outcome measures in diverse settings.

2.6 Glucose Monitoring and Treatments

Once diagnosed, pregnant individuals with GDM are treated to lower blood glucose levels to reduce the risks of adverse maternal and neonatal outcomes.^{106,107} Maternal glucose monitoring is needed to guide proper treatments and reduce the risk of associated adverse pregnancy outcomes. However, there are ongoing debates regarding optimal glycemic targets and monitoring methods for GDM. The mean fasting blood glucose and postprandial blood glucose values by frequent self-monitored blood glucose (SMBG) have been recommended to guide GDM treatments and optimize pregnancy outcomes. Although the use of a continuous glucose monitoring system (CGMS) for monitoring blood glucose might improve glycemic control and effectively identify undetected hyperglycemia and further benefit from treatment, little evidence is available regarding its cost-effectiveness.^{92,108,109}

Treatment of pregnancies with GDM generally starts with the nonpharmacologic therapeutic approaches by dietary and lifestyle behaviors to control glycemic values, including management of gestational weight gain, nutritional intervention, and physical exercise. A recent systematic review of randomized controlled trials (RCTs) found that GDM pregnancies with lifestyle interventions had a lower risk of having LGA, macrosomia, postnatal depression, and postpartum weight retention.¹¹⁰ However, the impact of lifestyle interventions on long-term outcomes are less reported. The Institute of Medicine (IOM) revised the guidelines in 2009 for weight gain during pregnancy with additional consideration of weight status prior to pregnancy, yet little is known for appropriate gestational weight gain for pregnant individuals with GDM.¹¹¹ Findings from two recent retrospective cohort studies suggest compared to normal weight gain, excessive weight gain according to the IOM criteria might increase the risk of preeclampsia, CS, macrosomia and LGA.^{112,113} Nutritional therapy through various diets patterns to modify dietary intake are usually taken a first-line strategy to manage GDM. Current evidence, although limited, a low-glycemic index (GI) diet might benefit GDM pregnancies.¹¹⁴ One recent systematic review and meta-analysis of 9 RCTs comparing different types of dietary interventions among 884 GDM pregnancies shows diet with a low-GI reduced future insulin use and birth weight compared to total energy-restricted diet or low-carbohydrate diet, without increasing small for gestational-age neonates and macrosomia.¹¹⁵ More recent RCTs also suggest low-GI diets are associated with reduced postprandial glycemic values among hyperglycemic pregnancies.^{116,117} Additionally, physical activity programs have been suggested as an important intervention in the management of GDM. One earlier review found improvement of glycemic control and reduction of insulin use by physical activity among GDM pregnancies, yet limitations by small sample

size, heterogeneous study population, and the compliance related to physical activity-based interventions were concerning.¹¹⁸

For GDM pregnancies unable to achieve glycemic targets through lifestyle interventions, pharmacological antihyperglycemic treatments are considered. As a current standard pharmacological treatment to achieve tight glycemic targets for GDM patients in North America, insulin administered by multiple daily injections is recommended to improve maternal and fetal outcomes.¹¹⁹ A growing body of evidence also suggests that insulin analogues (short- or rapid-, intermediate- and long-acting) is a relatively safe and effective alternative to insulin to achieve tight glycemic control in pregnancy.^{23,120} Oral antidiabetic agents such as metformin (biguanide) and glyburide (second-generation sulfonylurea) have been increasingly used as alternatives for GDM women given the lower costs, easier administration, and greater acceptability.^{23,121} However, there is no sufficient evidence to conclude the best oral antihyperglycemic therapy for women with GDM given the limited and inconsistent findings.^{122,123} Data from recent reviews comparing treatments for women with GDM found that insulin might be associated with an increase in hypertensive disorders and maternal weight gain in pregnancy when compared to metformin.^{119,124,125} Additionally, given that metformin easily crosses the placenta, studies have shown metformin exposure in infants is associated with a shorter gestational age and a higher risk of spontaneous preterm births.¹²⁵ However, results from follow-up studies demonstrated that infants of pregnant individuals using metformin for GDM had similar body composition and linguistic and neurological development at early toddlerhood, but a higher adiponectin concentration and lower leptin/adiponectin-ratio in boys at age of 9 years compared to infants of mothers treated by insulin.^{126–129} For glyburide, evidence suggests it was associated with an

increase in birth weight, macrosomia, and neonatal hypoglycemia compared to insulin or metformin, therefore it is not suggested as a first or second line treatment for GDM.¹²⁵

2.7 Labour and Delivery

The goal of labour and delivery for pregnant individuals with GDM, especially for those with good glycemic control, has been suggested to optimize maternal and neonatal outcomes while minimizing iatrogenic interventions.²⁴ Yet, GDM pregnancies that do not undergo spontaneous vaginal delivery may have either induction or CS to improve birth outcomes.^{130,131} For labour induction, the methods normally depend on maternal cervical status and vary by institutional protocols. The process of induction generally starts with cervical ripening by prostaglandins E2 (PGE2) or misoprostol, followed by mechanical methods using specific balloon devices including catheter if pharmacological options failed to initiate labour.^{132,133} According to the urgency or timing of CS, it can be classified into elective and emergency CS procedures, where emergency CS is undertaken before or during labour due to the immediate risks for the pregnant individual or the fetus and elective CS is typically planned in advance before labour onset, without a strict medical indication to have early birth of the infant.^{134,135}

Labour and delivery management for pregnant individuals with GDM near or reaching term gestation has consistently been a challenge. Apart from glycemic control status and history of obstetric complications in previous pregnancies, fetal overgrowth is an important factor in considering the timing and mode of delivery given higher fetal weight is in the common pathway of maternal and fetal risk factors for adverse pregnancy outcomes for these pregnancies.^{136,137} To date, most debates upon labour and delivery of GDM pregnancies arise around delivery at early term (<39 weeks) or full term ($\geq$ 39 weeks).¹³⁸ Earlier delivery may potentially decrease the risk

of stillbirth, excessive fetal weight, and associated complications, but may increase the risk of neonatal respiratory morbidities and mortality related to immaturity, including respiratory distress syndrome and the need for mechanical ventilation, especially in the presence of poor glycemic control.^{139,140} However, most of the existing findings are from retrospective cohort studies and mainly limited by the nature of observational design and the methodological approach of using vaginal delivery with spontaneous labour onset as a comparator.^{141,142} In clinical practice, the real option faced by most clinicians and patients for delivery is induction or expectant management of pregnancy, and the latter involves with close monitoring and waiting for spontaneous labor onset in the absence of maternal or fetal indications for delivery.¹⁴³ Pregnancies with GDM which are managed expectantly at a specific gestational age carry the risk of a subsequent intrauterine death or an interventional delivery by CS or induction for medical indications at a later gestation if spontaneous labour has not occurred by the due date.¹⁴² The use of spontaneous vaginal delivery as comparator on the existing literature consequently limits the causal inference and interpretation of induction effect in GDM pregnancies. Only three RCTs have compared outcomes between labour induction with expectant management in pregnancies complicated with GDM, with inconclusive results due to small sample size, heterogeneous population profiles, inconsistent diagnosis criteria of GDM, and variable inclusion and exclusion criteria.^{28,29,144} The first trial published by Kjos et al in 1993 randomized 200 pregnant individuals with uncomplicated well-controlled diabetic pregnancy to either elective induction or expectant management starting at 38 weeks.²⁹ This study did not find significant differences in CS, shoulder dystocia, neonatal hypoglycemia, or perinatal morality between the two groups, except for a higher risk of LGA in the expectant management group. In another trial by Singh and colleges comparing active induction at 39-40 weeks versus expectant management

till 41 weeks among pregnant individuals with well-controlled GDM, the authors concluded that the trial was underpowered to detect a difference in maternal or neonatal morbidities and mortality.¹⁴⁴ A more recent multi-center trial by Alberico showed no difference in risks of CS, perinatal morbidity or morbidity comparing induction at 38-39 weeks versus expectant management, with exception of a higher risk of neonatal hyperbilirubinemia in the induction group.²⁸ However, this study lacked study power due to the severe recruiting challenges and excluded pregnancies with estimated fetal weight (EFW) >4000g, limiting the applicability of the study results for clinical decision making.

Currently, major variations exist regarding labour and delivery management of GDM pregnancies across national and international clinical guidelines, and most of the guidelines reached by consensus and expert opinions due to the limited and inconsistent evidence (Table 2.2). Both the American College of Obstetricians and Gynaecologists (ACOG) and Queensland Clinical Guidelines (QCG) recommend offering an elective CS for pregnant individuals with GDM with suspected fetal macrosomia (EFW of $\geq 4,500$ g).^{24,145} Most of the guidelines state that pregnant individuals with GDM could be expectantly managed up to 40^{6/7} week, yet, the Canadian guidelines recommend delivery following induction between 38-40 weeks whereas the remaining advocate to deliver at 39 weeks and onwards.^{23–26,58,145}

Table 2.2 Summarization of different guidelines for timing of delivery for women with GDM

Guideline	Country	Recommendation	Quality of evidence
SOGC 2019 ⁵⁸	Canada	Pregnant individuals with GDM should be offered induction between 38-40 weeks of gestation depending on their glycemic control and other co-morbidity factors	There is fair evidence (evidence level B) to recommend the clinical preventive action; evidence from well-designed cohort or case-control studies,

Diabetes Canada 2018 ⁹²	Canada	Pregnant individuals with GDM can be offered induction of labour between 38–40 weeks; earlier or later induction should be considered based on glycemic control and the presence or absence of other comorbidity conditions	Consensus
ACOG 2018 ²⁴	USA	For pregnant individuals with GDM controlled by only diet and exercise (A1GDM), delivery should not be before 39 weeks and expectant management could be up to 40 6/7 weeks; For pregnant individuals with GDM well controlled by medications (A2GDM), delivery is recommended at 39 0/7 to 6/7 weeks;	Consensus and expert opinion
National Institute for Health and Care Excellence (NICE) 2015 ²⁵	UK	Advise pregnant individuals with GDM to deliver no later than 40+6 weeks and offer elective birth (induction or caesarean section) to individuals who have not given birth by this time	Advise
ADIPS 1998 ²⁶	Australia	Delivery before full term is not indicated unless there is evidence of macrosomia, polyhydramnios, poor metabolic control or other obstetric indications	Consensus
QCG 2021 ¹⁴⁵	Australia	If well managed with medical nutrition therapy and no fetal macrosomia or other complications, wait for spontaneous labour; If suspected fetal macrosomia or other complications, consider birth from 38+0-39+0 weeks; In most cases, women with optimal blood glucose levels controlled by pharmacological therapy do not require expedited birth before 39+0 weeks;	Consensus

Chapter 3. Research Settings and Methods

3.1 Study Population

The eligible study population consists of all pregnant individuals who had a singleton live birth or stillbirth (birth weight ≥ 500 grams or gestational age ≥ 20 weeks) in Ontario hospitals from April 1, 2012 to March 31, 2020. Records were excluded if they had undefined infant sex; missing birth weight or gestational age at birth; implausible birth weight/gestational age combinations based on a sex-specific Canadian reference standard to minimize potential data entry error.^{146,147} Given the universal screening for GDM is performed at 24-28 weeks of gestation, pregnant individuals who delivered at < 29 or > 43 weeks were excluded. We also excluded records with maternal age at delivery < 12 or > 50 years, or pre-existing diabetes.

3.2 Data Sources

3.2.1 Better Outcomes & Registry Network (BORN) Ontario

As a prescribed registry under the province's Personal Information Protection Action, the BORN Ontario has been established in 2009 to collect, interpret and report each pregnancy, birth, newborn, and child to improve and facilitate perinatal care across the province of Ontario, Canada.¹⁴⁸ The BORN Information system (BIS) was launched in April 2012 as a robust internet-based data platform to collect comprehensive maternal-newborn data of nearly all births ($>99\%$) with ≥ 500 grams or ≥ 20 weeks of gestation from >250 maternal-neonatal health organizations. With capture of approximately 140,000 births each year, BORN Ontario is the largest provincial perinatal registry, accounting for 40% of all births across Canada.¹⁴⁹ To date, it has captured over 1.5 million maternal-infant records.¹⁵⁰ BORN collects maternal demographics and pregnancy characteristics, fertility and use of any assisted reproductive technologies, prenatal screening, health histories and behaviors, pregnancy complications and interventions,

intrapartum events, labour and delivery details, neonatal intensive care, and newborn screening and follow-up information across various types of clinical encounters.¹⁵¹ All data are routinely collected in near real-time through medical records, clinical forms, and patient interview at the time of each encounter by health-information custodians providing care for the maternal-infant population in Ontario. Healthcare encounter-based data are further linked to create aggregate records for each pregnant individual and infant.¹⁵¹ BORN data are available to requestors at aggregate or record level, and we used record-level data sets for this thesis.

BORN follows a comprehensive framework focusing on timeliness, accuracy (validity), comparability (reliability), usability and relevance to promote data quality in each aspect of data collection, analysis, use and disclosure.¹⁵¹ Recent audits and validation studies show BORN records have good agreement with patient hospital abstract and clinical administrative hospital databases in Ontario.^{148,149,152,153} A chart re-abstraction study of 29 selected data elements (21 categorical and 8 continuous) demonstrated >90% agreement between patient charts and BORN records for over 75% of the audited data elements.¹⁴⁸ Notably, the two categorical variables, diabetes in pregnancy and complications of pregnancy both had a kappa value of 0.79, demonstrating substantial agreement.¹⁴⁸ Similarly, the agreement assessment of key maternal and newborn data elements between BORN and the CIHI-DAD in the fiscal years 2012/13 to 2014/15 found $\geq 90\%$ agreement and substantial to almost perfect agreement for all selected variables such as labour induction, CS, gestational age at birth and infant birth weight.¹⁵² BORN implements improvement programs by ongoing data validation, quality checks and formal training for data collection and entry individuals to assure the data of high quality.³⁰

3.2.2 Other Data Sources

Additional data sources used in this thesis include the DAD from the CIHI, and Postal Code Conversion File Plus (PCCF+) and the 2016 Canadian Census.

CIHI is an organization that provides information on Canada's health system and the health of Canadians.¹⁵⁴ As a major data holding by CIHI, the DAD captures demographic, administrative and clinical information on hospital discharges from acute inpatient hospitals in all Canadian provinces and territories, except Quebec.¹⁵⁵ The BORN Ontario receives CIHI-DAD maternal, newborns (livebirths and stillbirths), and infant (up to 1 year of age) records from all acute admissions to hospitals in Ontario on an annual basis.¹⁵⁵ For clinical data, the DAD uses the Canadian version of International Classification of Diseases, 10th revision (ICD-10-CA) for clinical diagnosis and the Canadian Classification of Health Interventions (CCI) codes for clinical procedures.¹⁵⁵

The 2016 PCCF+ version 7B is a SAS program developed by Statistics Canada and Canada Post that matches 6-digit postal codes with dissemination areas from the 2016 national Census data.¹⁵⁶

3.2.3 Data Linkages

We used deterministic and probabilistic approaches to link CIHI data to the eligible study cohort assembled from the BIS to ascertain and/or supplement GDM diagnosis during pregnancy and adverse neonatal and maternal outcomes. Using maternal postal codes, we further linked the Census data and PCCF+ to obtain maternal median household income quintiles and education quintiles at dissemination-areas level.

3.3 Number of Pregnant Individuals Included During the Study Period

During the period analysed (fiscal years 2012/13 to 2019/20), there were 1 070 542 pregnant individuals who had a singleton hospital delivery in Ontario. 26 284 (2.5%) were excluded because of unclassified infant sex, implausible or missing gestational age or birth weight, gestational age at birth below 29 or greater than 43 weeks, maternal age at delivery below 12 or greater than 50 years, and pre-existing diabetes. A total of 1 044 258 were included in our final analysis (Figure 3.1).

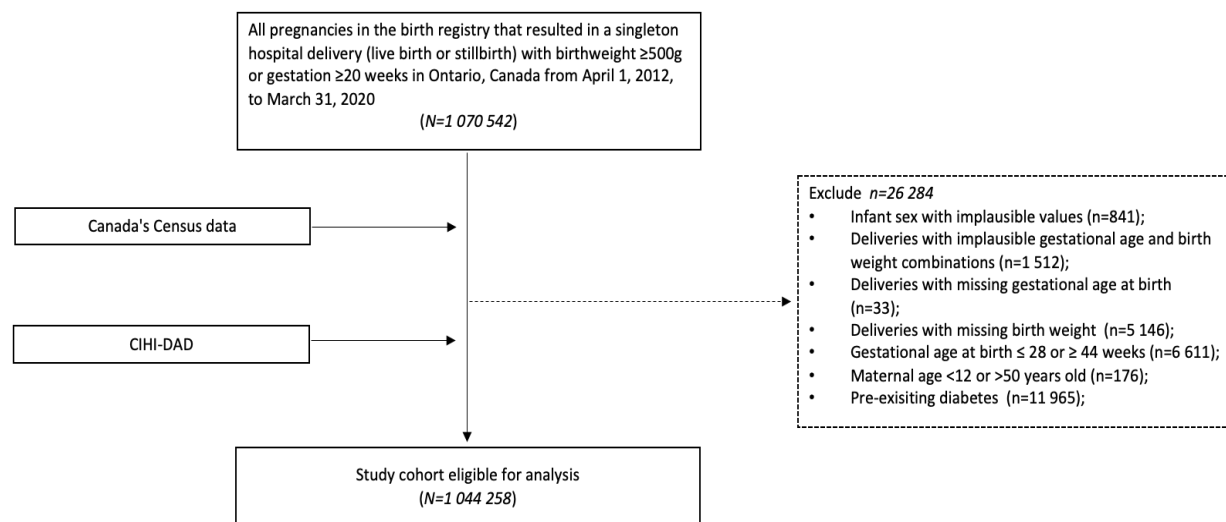


Figure 3.1 Study flow chart for the analytic dataset

3.4 Statistical Analysis

Baseline demographic characteristics were presented for overall study population and by GDM. Continuous variables were summarized using means and standard deviations (SDs) or medians and interquartile ranges (IQRs); categorical variable were summarized using frequency and percentages. Temporal trends in GDM and adverse outcomes were examined in two ways. First, we contrasted the rates between the fiscal years 2019/20 and 2012/13, using absolute and relative differences with corresponding 95% confidence intervals (CIs). Second, we examined the

statistical significance of temporal trends over time using the Cochran-Armitage test for trends in proportions and modified Poisson regression. We further used multivariable modified Poisson regression to generate relative risks and risk differences with 95% confidence intervals for the associations between GDM and adverse outcomes. Details of the statistical analyses are provided in each individual study chapter. All data management and analyses were performed within the secure environment at BORN Ontario, aligning with all security and privacy protocols and policies. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A two-tailed P-value <0.05 was considered statistically significant.

3.4.1 Modified Poisson regression

Modified Poisson regression is specified as a generalized linear model with a Poisson error distribution with a robust error variance to estimate the effect measure directly for a binary outcome in clustered data.¹⁵⁷

A logistic regression model, which is a type of generalized linear model using logit function to link the outcome to a set of independent variables, is commonly used for binary outcomes in public health, however, it's only able to directly estimate odds ratios for outcomes. Under the assumption of the relatively low probability of an outcome (i.e. rare event), odds ratios could be used as an approximation of the relative risks.¹⁵⁸ Nevertheless, when the outcome is common, the use of odds ratios (ORs) as an estimate of relative risks can bias the results away from the null and overestimate the association.

Log-binomial regression, which is a generalized linear model with a binomial error distribution and log link function, provides direct estimates of risk and relative risks for binary outcome data.¹⁵⁹ The model is written as follows:

$$\log(p) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_i X_i \quad (1)$$

Where p is the probability of experiencing the outcome of interest, $X_1, X_2, \dots, X_i$ are the explanatory variables. Considering the values of probability lie between zero and one, the left side of equation 1 using the log link function maps the probability of the outcome onto the negative scales. This creates boundaries of the parameter space for the regression coefficients and might have failed convergence when fitting the generalized linear models by maximizing the log-likelihood function.¹⁵⁷

The modified Poisson regression approach has been widely used as a useful alternative to log-binomial regression to resolve convergence issues and yield comparatively similar point estimates and standard errors for a binary outcome in independent or clustered data.^{157,160,161}

Modified Poisson regression applies a maximum quasi-likelihood function to fit binary data.¹⁶¹ It shares the same form of equation 1 but with a Poisson error distribution, and uses the classic sandwich estimator under a generalized estimating equations framework to correct the error misspecification and obtain robust variance estimates.¹⁵⁷ Previous studies showed the coefficient estimates from the modified Poisson regression is consistent with the estimates from the log-binomial regression, and the covariance matrix of the Poisson regression fit is a consistent estimate of the covariance matrix using the maximum likelihood estimate from the log-binomial regression.¹⁶²

The robust Poisson regression model with a log link function was used to estimate relative risks. Relative risks associated with a one unit-change in the main independent variable are computed by exponentiation of coefficients from the model. Similarly, a model with the identity link function was used to estimate risk difference. The coefficient from the regression model was

used to estimate the risk difference associated with a one-unit change in the main independent variable.

To account for repeated deliveries to the same pregnant individuals during the study period from 2012 to 2020, we employed generalized estimating equations with an exchangeable working correlation matrix to correct the standard errors and obtain a robust variance estimator.¹⁶⁰ Based on published recommendations,^{157,162} we used the PROC GENMOD procedure with the REPEATED statement in SAS 9.4 to perform the modified Poisson regressions included in the thesis.

3.4.2 Kitagawa standardization and decomposition analysis

As a fundamental descriptive method, the Kitagawa standardization and decomposition analysis is useful to evaluate and quantify components of the difference of the rates of outcome between two populations over time, geography or demographic groups.¹⁶³ This method was first proposed by Kitagawa in the 1950s in the social science and has been emergingly applied to answer important questions in perinatal epidemiology.^{163–168} Essentially, this method conceptualizes the difference between two different observed rates in a population at two separate time point as two additive components – change in rates of outcome attributable to the changes in the distribution of the predictor of interest and changes in predictor-specific rates of the outcome.^{163,167} The Kitagawa decomposition formula can be written as:

$$L_2 - L_1 = \sum_{i=1}^n ((P_{2i} - P_{1i}) * \frac{(R_{2i} + R_{1i})}{2}) + \sum_{i=1}^n ((R_{2i} - R_{1i}) * \frac{(P_{2i} + P_{1i})}{2}) \quad (2)$$

Where L_1 and L_2 in the left side of equation (2) denote the rate of an outcome at each time point; P_{1i} and P_{2i} refer to the proportions of population in the i^{th} category of the predictor at each time

point; R_{1i} and R_{2i} refer to the rate of an outcome in the i^{th} category of the predictor at each time point. The first part of the equation represents the extent to which rates would have changed if the distribution of predictor of interest changed as observed but predictor-specific rates of the outcome had remained constant (e.g. relative contribution of the distributional changes in predictor); the latter part the equation represents the extent to which rates would have changed if predictor-specific rates of the outcome changed as observed but the distribution of predictor remained unchanged (e.g. relative contribution of the changes in predictor-specific rates). The sum of these two components indicate the total difference in the rate of outcome between the

In our study, we aimed to assess the proportion of the change in the rates of GDM over time attributable to the temporal changes in maternal characteristics - age at delivery, pre-pregnancy BMI and race/ethnicity, using the modified Kitagawa standardization and decomposition method by Yang et al.¹⁶⁷ All singleton deliveries were grouped into a total of 36 stratum according to any combination of age (<25, 25-34, ≥ 35 years), pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥ 30.0 kg/m²) and race/ethnicity (Asian, Non-Asian and missing) categories. Unadjusted rates and standardised rates of GDM were calculated for each stratum of age-BMI-ethnicity for each fiscal year. The standardized rate of GDM used the fiscal year of 2012/2013 as the reference group. The change in standardized rates was the estimated change in GDM rates due to the temporal changes in age-BMI-ethnicity specific rates of GDM if the distributions of age, pre-pregnancy BMI and race/ethnicity remained constant; the difference between crude and standardized rates was the component of the increase in GDM rates attributable to the distributional changes in age, pre-pregnancy BMI and race/ethnicity.

3.5 Ethics Approval

Ethics approval for the thesis Chapters 4, 5, and 6 using data from the BORN Ontario was granted by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (20210400-01H) and the University of Ottawa Research Ethics Board (H-03-21-6792). This thesis was secondary analyses of data from the BORN Ontario, individual patient consent was therefore waived by the OHSN-REB. As a prescribed registry under provincial Personal Health Information Protection Act, 2004A, BORN can collect, use and disclose personal health information without patient consent for the purpose to facilitate and improve perinatal health delivery for maternal-neonatal population in Ontario, Canada.

**Chapter 4. Temporal Trends in Gestational Diabetes Mellitus and Associated Risk
Factors in Ontario, Canada, 2012 to 2020: a Population-Based Cohort Study
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4.1 Title Page

Temporal trends in gestational diabetes mellitus and associated risk factors in Ontario, Canada,
2012 to 2020: a population-based cohort study

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Author's 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.J.C., D.B.F. and M.T. critically revised the manuscript and contributed to the final version. All authors read and approved the final manuscript.

4.2 Abstract

Objective: The prevalence of gestational diabetes mellitus (GDM) has been increasing globally over recent decades; however, underlying reasons for the increase remain unclear. We analyzed trends in GDM rates and evaluated risk factors associated with the observed trends in Ontario, Canada.

Methods: We conducted a retrospective population-based cohort study using the Better Outcomes Registry & Network (BORN) Ontario, linked with the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). All pregnant individuals who had a singleton hospital delivery from April 1, 2012 to March 31, 2020 were included. We calculated rates and 95% confidence intervals (CIs) for GDM by year of delivery and contrasted fiscal year 2019/20 with 2012/13. Temporal trends in GDM were quantified using crude and adjusted risk ratios (RRs) by modified Poisson regression. We further quantified the temporal increase attributable to changes in maternal characteristics by decomposition analysis.

Results: Among 1 044 258 pregnant individuals, 82 896 (7.9%) were diagnosed with GDM over the 8 years. GDM rate rose from 6.1 to 10.4 per 100 deliveries between fiscal years 2012/13 and 2019/20. The risk of GDM in 2019/20 was 1.53 times (95% CI 1.50-1.56) higher compared with 2012/13. 27% of the increase in GDM was due to changes in maternal age, pre-pregnancy BMI, and Asian ethnicity.

Conclusion: The GDM rate has been consistently increasing in Ontario, Canada. The contribution of increasing maternal age, pre-pregnancy obesity, and Asian ethnicity to the recent increase in GDM is notable. Further investigation is required to better understand the contributors to increasing GDM.

Keywords: Trend, gestational diabetes mellitus, risk factors, Canada

Résumé

Objectif: La prévalence du diabète sucré gestationnel (DSG) a augmenté à l'échelle mondiale au cours des dernières décennies, mais les raisons sous-jacentes de cette augmentation ne sont pas claires. Nous avons analysé les tendances des taux de diabète gestationnel et évalué les facteurs de risque associés aux tendances observées en Ontario, au Canada. Nous avons également estimé la fraction attribuable à la population (FAP) du diabète sucré pour chaque facteur de risque au fil du temps.

Méthodes: Nous avons mené une étude de cohorte rétrospective basée sur la population en utilisant le Registre et réseau des bons résultats dès la naissance (BORN) Ontario, lié à la base de données des congés de l'Institut canadien d'information sur la santé (ICIS-DAD). Toutes les femmes enceintes ayant accouché d'un enfant unique à l'hôpital entre le 1er avril 2012 et le 31 mars 2020 ont été incluses dans l'étude. Nous avons calculé les taux et les intervalles de confiance à 95 % du diabète gestationnel par année d'accouchement et nous avons comparé l'année fiscale 2019/20 à 2012/13. Les tendances temporelles du diabète gestationnel ont été quantifiées à l'aide de rapports de risque bruts et ajustés (aRR) par régression de Poisson modifiée. Nous avons également quantifié l'augmentation temporelle attribuable aux changements dans les caractéristiques maternelles par une analyse de décomposition.

Résultats: Parmi 1 044 258 individus enceintes, 82 896 (7,9 %) ont été diagnostiqués avec un DSG au cours des 8 années. Le taux de DSG est passé de 6,1 à 10,4 pour 100 accouchements entre les exercices fiscaux 2012/13 et 2019/20. Le risque de DSG en 2019/20 était 1,53 fois (IC 95 % 1,50-1,56) plus élevé qu'en 2012/13. 27 % de l'augmentation du DSG était due à des changements dans l'âge maternel, l'IMC avant la grossesse et l'origine ethnique asiatique.

Conclusion: Le taux de DSG augmente de manière constante en Ontario, au Canada. La contribution de l'augmentation de l'âge maternel, de l'obésité avant la grossesse et de l'ethnicité asiatique à l'augmentation récente du DSG n'est pas négligeable. Des recherches plus approfondies sont nécessaires pour mieux comprendre les facteurs qui contribuent à l'augmentation du DSG.

4.3 Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset or first detection during pregnancy.¹ It's one of the most common pregnancy complications, affecting approximately 7% of pregnancies in Canada.¹⁶⁹ Although most GDM resolves after delivery, it remains a considerable public health burden given disproportionately higher risks of adverse maternal and neonatal short-term and long-term outcomes.^{170,171}

The prevalence of gestational diabetes mellitus (GDM) has been increasing globally over recent decades and is expected to continuously increase.^{9,12} Several explanations have been proposed for recent increases in GDM rates, including changes in screening approaches and diagnostic criteria for GDM over time in response to the 2008 Hypoglycemia and Adverse Pregnancy Outcome (HAPO) study and the 2010 International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations.^{10,172} In Canada, Diabetes Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) modified guidelines in 2013 and 2016, respectively, and endorsed two different approaches for GDM screening and diagnosis.^{78,79} One population-based study assessed the temporal trends in GDM in British Columbia, Canada from 2005 to 2019 and reported that the observed increase reflected the shift in screening methods over time.⁸ Some have also postulated that changes in maternal socio-demographic and lifestyle factors such as increases in age, body mass index (BMI), physical inactivity and suboptimal nutritional intake have likely contributed to the increased GDM rates.^{12–15,53,173}

To the best of our knowledge, there have been important changes in the demographics of the Canadian population over the years, however, the secular trends in GDM and the extent to which changes in underlying risk factors have contributed to increases in GDM during the past decade have not been well documented in Ontario which has a large and racially diverse obstetric

population. Therefore, we sought to assess temporal trends in GDM rates among singleton hospital deliveries in Ontario, Canada between 2012 and 2020 and estimate the impact of associated risk factors on these trends.

4.4 Materials and Methods

Study Design and Population

We performed a retrospective, population-based cohort study of all singleton hospital births (live births and stillbirths) in Ontario, Canada, between April 1, 2012 and March 31, 2020. We excluded records with missing birth weight, gestational age at birth, and unclassified infant sex, and applied an algorithm to identify records with implausible birth weight and gestational age combinations based on a sex-specific Canadian reference standard.^{146,147} As GDM is universally screened at 24-28 weeks of gestation, we excluded deliveries at ≤ 28 weeks. We also excluded records with maternal age at delivery <12 or >50 years, or with pre-existing diabetes.

The eligible birth cohort was assembled from the Better Outcomes Registry & Network Ontario Information System (BIS), which is a province-wide system routinely collecting comprehensive maternal-neonatal information for all births since 2012.¹⁵¹ The completeness and quality of information collected are upheld based on the multi-dimensional framework. Validity in selected data fields, including diabetes and pregnancy (kappa 0.79, 95% confidence interval [CI] 0.72-0.86), is comparable to other perinatal databases.^{148,151}

To improve outcome ascertainment, we used deterministic and probabilistic techniques to link the study population with maternal and neonatal hospital abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). We also linked to the 2016 Canadian Census through maternal postal codes and the Postal Code Conversion File Plus (PCCF+) version 7B to obtain dissemination area-level socioeconomic data including neighbourhood-level median family income and education quintiles.

Outcome Measure

The primary outcome was the presence of GDM. During the study period, the national screening and diagnosis guidelines for GDM changed: before April 2013, it used a two-step approach, with a 50-g glucose challenge test (GCT) followed by a 2h 75-g oral glucose tolerance test (OGTT) among those with an abnormal 1-hour glucose value; after April 2013, it undertook two approaches following the recommendations of Diabetes Canada.^{79,91} The preferred two-step approach recommended by the 2013 Diabetes Canada guideline closely mirrored the 2008 one, albeit with some differences. These included an increase in the 50-g GCT diagnostic threshold from 10.3 mmol/L to ≥ 11.1 mmol/L, a slight elevation in the 2h 75-g OGTT diagnostic value from 8.9 mmol/L to ≥ 9.0 mmol/L, and the utilization of a single abnormal OGTT value for GDM diagnosis. The one-step approach, as an alternative method, employed a 2h 75-g OGTT with a lower diagnostic cut-off, where any value of fasting plasma glucose ≥ 5.1 mmol/L, 1h post glucose ≥ 10.0 mmol/L or 2h post glucose ≥ 8.5 mmol/L indicated GDM.⁷⁹

GDM cases were primarily identified through the BORN "pregnancy and diabetes" and "complications of pregnancy" variables, to which we then applied an algorithm to identify additional GDM cases in CIHI-DAD datasets using the diagnostic codes (International Classification of Diseases, 10th Revision, Canada [ICD-10-CA]): women with diagnostic codes of O24.8 or infants with P70.0 who did not have additional codes for pre-existing diabetes. Among GDM cases, we additionally used the specific pick-list values of "pregnancy and diabetes" and ICD-10-CA diagnostic code Y42.3 to identify GDM cases using insulin and oral hypoglycemic drugs. The specific variables used for GDM diagnosis and treatments are detailed in Table S1.

Covariates

We examined population characteristics that have been previously associated with GDM, including maternal age at delivery, parity, pre-pregnancy body mass index (BMI), neighbourhood median family income quintiles, neighbourhood education level quintiles, ethnicity, pre-existing medical conditions (any of pre-existing hypertension, autoimmune, heart, renal, pulmonary and endocrine disorders), previous stillbirth, previous caesarean, smoking status at first prenatal visit, conception type, prenatal education and infant sex.^{8,174,175} We presented the causal assumptions between year of delivery (main factor of interest), outcome and covariates in a directed acyclic graph (DAG) (Figure S1).

Statistical Analysis

Rates and 95% confidence intervals (CIs) for GDM were computed for each fiscal year. We described temporal changes in GDM rates across maternal age at delivery, pre-pregnancy BMI, and maternal ethnicity using unadjusted rate differences and 95% CIs, contrasting <25 years of age vs. ≥ 35 , BMI <18.5 kg/m² vs. ≥ 30 , and non-Asian ethnicity vs. Asian.

Temporal trends in GDM were examined in two ways. First, we contrasted the rate of GDM between fiscal year 2019/20 and fiscal year 2012/13, using absolute and relative differences with corresponding 95% CIs. Second, we estimated temporal trends in GDM by unadjusted and adjusted risk ratios (RRs) and 95% CIs using modified Poisson regression models with robust standard errors, which accounted for repeated deliveries to the same women during the study period. The fiscal year of delivery was modelled as an ordinal variable by including indicator variables for each year, with fiscal year 2012/13 as the reference. In the multivariable analyses, the model was adjusted for maternal age at delivery, pre-pregnancy BMI, and maternal ethnicity.

Additional adjustment was made in a separate model for neighbourhood income and education levels, parity, conception type, smoking, pre-existing medical or obstetric conditions, prenatal education and infant sex. Multiple imputation was used to address missing data of covariates included in the multivariable models. We generated five multiply imputed datasets using a fully conditional specification approach (M=5; Details in Table S2).

Lastly, we quantified the temporal changes in GDM rates contributed by changes in maternal age at delivery, ethnicity and pre-pregnancy BMI using the Kitagawa standardization and decomposition approach, which has been applied by previous perinatal research.^{164,167} Briefly, all deliveries were stratified into 36 groups by any combination of maternal age (<25, 25-34, ≥35), ethnicity (Non-Asian, Asian and missing) and pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0). Unadjusted and standardized rates of GDM were calculated for each group in each delivery period, along with fiscal year 2012/13 as the standardized reference year. Under the assumption of no confounding bias in the associations, the difference between standardized rates would be the estimated temporal change in GDM rates if age-ethnicity-BMI distribution remained the same. The difference between crude and standardized rates was the component of temporal increase in GDM rates associated with the changes in these maternal factors.

We conducted prespecified sensitivity analyses to assess the robustness of the main findings. To evaluate the impact of missing data, we restricted our analysis to complete cases only. Moreover, as GDM recurs at a high rate and might have different pathology compared to GDM occurrence for the first time, we compared the results by limiting data to women with first delivery.

We used SAS version 9.4 (SAS Institute, Cary, NC) for all analyses, with statistical significance at a two-tailed $P < 0.05$. This study obtained ethical approvals from Research Ethics Board of

Ottawa Hospital Science Network Research (20210400-01H) and University of Ottawa (H-03-21-6792).

4.5 Results

Of 1 070 542 singleton deliveries in Ontario hospitals between April 1 2012 and March 31 2020, 1 044 258 (97.5%) were included in our final study population. Overall, 82 896 (7.9%) were diagnosed with GDM, of which 63.8% required no medical treatments (Figure 4.1; Table S3). Table 4.1 shows the distributions of maternal characteristics changed significantly over time. The proportion of women with pre-pregnancy obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) increased from 17.3% to 19.7%; the proportion of those with age ≥ 35 years at delivery increased from 21.9% to 25.7%. Asian populations increased from 14.9% to 20.0%. The use of fertility treatments for conception had a relative increase of over 60%, from 2.8% to 4.5%. Maternal smoking, lowest neighbourhood family income quintile, highest neighbourhood education quintile, and no prenatal education decreased over time.

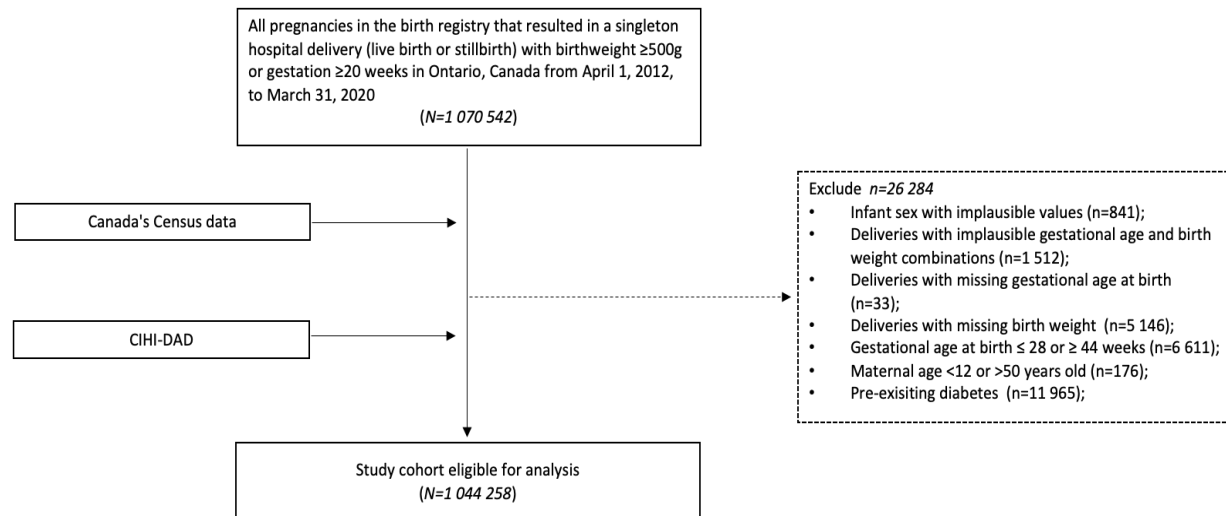


Figure 4.1 Study flow diagram. All deliveries were identified through BORN Ontario

Table 4.1 Gestational diabetes mellitus (GDM) and population characteristics for pregnant women who had singleton hospital deliveries in Ontario, Canada, fiscal years 2012/13- 2019/20 (N=1 044 258)

Characteristics	No. (%) of pregnant individuals ^a				Change in rate from 2012/13 to 2019/20, % (95% CI)	
	2012/13 n=131 824	2014/15 n= 130 172	2016/17 n= 130 605	2019/20 n=130 152	Absolute change ^f	Relative change
GDM						
Diagnosis	7 992 (6.1)	8 996 (6.9)	10 878 (8.3)	13 594 (10.4)	4.4 (4.2 - 4.6)	72.3 (68.8 - 75.7)
Subtypes						
GDM with no medical treatments	5 105 (3.9)	5 695 (4.4)	6 925 (5.3)	8 852 (6.8)	2.9 (2.8 - 3.1)	75.6 (71.2 - 80.1)
GDM with medical treatments	2 887 (2.2)	3 301 (2.5)	3 953 (3.0)	4 742 (3.6)	1.5 (1.3 - 1.6)	66.4 (60.5 - 72.2)
Demographics						
Maternal age at delivery ≥35 years	28 819 (21.9)	29 015 (22.3)	30 465 (23.3)	33 433 (25.7)	3.7 (3.4 - 4.1)	17.0 (15.5 - 18.5)
Lowest neighborhood family income quintile	31 234 (23.7)	29 944 (23.0)	29 154 (22.3)	28 522 (21.9)	-1.8 (-2.1 - -1.5)	-7.5 (-8.9 - -6.2)
Highest neighbourhood education level quintile ^b	24 884 (18.9)	24 145 (18.6)	24 162 (18.5)	23 675 (18.2)	-0.7 (-1.0 - -0.4)	-3.76 (-5.2 - -2.1)
Nulliparity	57 691 (43.8)	57 444 (44.1)	55 507 (42.5)	57 413 (44.1)	0.3 (-0.03 - 0.7)	0.8 (-0.1 - 1.7)
Asian	19 629 (14.9)	23 010 (17.7)	24 153 (18.5)	26 046 (20.0)	5.1 (4.8 - 5.4)	34.4 (32.4 - 36.3)
Pre-pregnancy BMI ≥ 30.0 kg/m ²	22 758 (17.3)	22 846 (17.6)	23 365 (17.9)	25 634 (19.7)	2.7 (2.4 - 3.0)	15.9 (14.2 - 17.6)
Conception by fertility treatments ^c	3 694 (2.8)	3 976 (3.1)	4 504 (3.5)	5 842 (4.5)	1.7 (1.5 - 1.8)	60.2 (55.1 - 65.3)
Maternal smoking ^d	13 984 (10.6)	13 558 (10.4)	12 136 (9.3)	9 712 (7.5)	-3.1 (-3.4 - -2.9)	-29.7 (-31.7 - -27.6)
Pre-existing medical or obstetric conditions ^e	30 609 (23.2)	31 079 (23.9)	31 526 (24.1)	33 544 (25.8)	2.6 (2.2 - 2.9)	11.0 (9.6 - 12.4)
No prenatal education	96 847 (73.5)	96 573 (74.2)	99 265 (76.0)	84 611 (65.0)	-8.5 (-8.8 - -8.1)	-11.5 (-12.0 - -11.0)

Male infant	67 779 (51.4)	66 713 (51.3)	67 081 (51.4)	66 612 (51.2)	-0.2 (-0.6 - 0.1)	-0.5 (-1.2 - 0.3)

Note: GDM=gestational diabetes mellitus; BMI = body mass index.

^a Counts included in Table 1 are based on the 1st imputed dataset. Column percentages are presented for each fiscal year at delivery.

^b Percentage of college and university degrees among adults 25–64 years old.

^c Fertility treatments include assisted reproductive technology and non-assisted reproductive treatments.

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

^e Pre-existing medical or obstetrical conditions were a composite of pre-existing maternal or obstetric health conditions, including any of pre-existing hypertension, autoimmune, cardiac and endocrine conditions, previous stillbirth, and previous caesarean section.

^f Absolute change in rate per 100 deliveries was calculated as the rate in fiscal year 2019/20 minus the rate in fiscal year 2012/13.

Temporal trends in GDM

Between fiscal years 2012/13 and 2019/20, GDM rate increased from 6.1 (95% CI 5.9-6.2) to 10.4 (95% CI 10.3-10.6) per 100 deliveries in Ontario, Canada, with an absolute increase of 4.4% (95% CI 4.2%- 4.6%) (Table 1). GDM requiring no medical treatments had a larger increase over time, from 3.9 (95% CI: 3.8-4.0) to 6.8 (95% CI: 6.7-6.9) per 100 deliveries. GDM increased progressively over time, with a greater proportion of the absolute increase in more recent years (Figure 4.2). Over the study period, large increasing differences in GDM rates were noted between the lowest and highest categories of maternal age at delivery, pre-pregnancy BMI, and ethnicity (Figure S2).

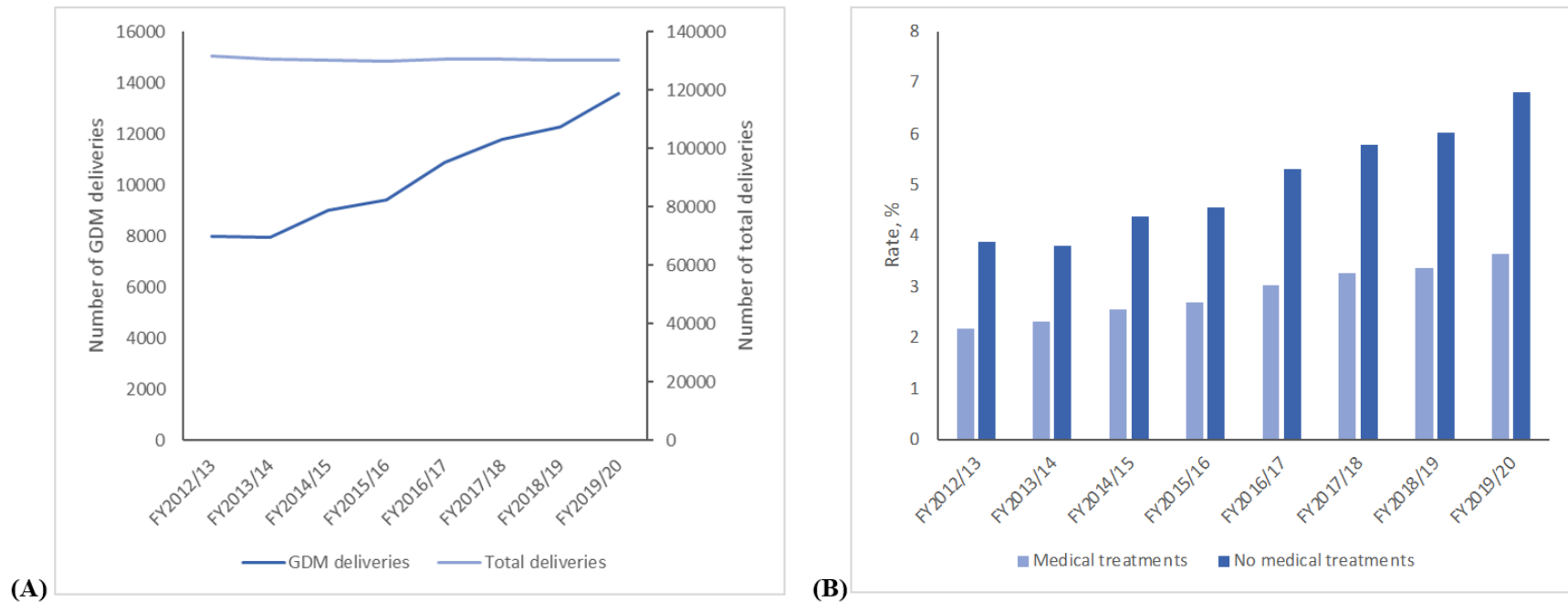


Figure 4.2 Trends in (A) the number of deliveries with GDM diagnosis and (B) the rate of GDM in Ontario, Canada, April 1, 2012 to March 31, 2020^{a,b,c}

^a Rate of GDM was calculated among all deliveries in each fiscal year. Rates of overall GDM and subtypes of GDM increased significantly from fiscal year of 2012 to 2019 (p for trend <0.0001). ^b Data for estimates displayed in plot can be found in Table S3. ^c The overall rate of GDM was 7.9 per 100 deliveries over the 8-year study period, and overall rate of GDM requiring no medical treatments was 5.1 per 100 deliveries.

Table 4.2 shows the results of temporal trend in GDM in regression models. The crude model estimated 1.72 times (95% CI 1.67-1.77) increase in risk of GDM in 2019/20 compared to 2012/13. After adjusting for the changes in maternal age at delivery, ethnicity and pre-pregnancy BMI, the risk of GDM in 2019/20 was attenuated to 1.52 times higher (95% CI 1.49-1.55). Further adjustment for other covariates identified in the DAG had no impact on the increased risk of GDM in 2019/20 compared to 2012/13 (RR 1.53, 95% CI 1.50-1.56).

Table 4.2 Estimated risk of gestational diabetes mellitus (GDM) in Ontario, Canada, fiscal years 2012/13-2019/20

Fiscal year of delivery	RR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
2012/13	Ref	Ref	Ref
2013/14	1.00 (0.97-1.04)	0.98 (0.95, 1.02)	0.98 (0.95, 1.02)
2014/15	1.14 (1.10-1.18)	1.10 (1.07, 1.14)	1.10 (1.07, 1.14)
2015/16	1.20 (1.16, 1.24)	1.14 (1.11, 1.18)	1.14 (1.11, 1.17)
2016/17	1.37 (1.33, 1.42)	1.30 (1.27, 1.33)	1.30 (1.27, 1.33)
2017/18	1.49 (1.45, 1.54)	1.37 (1.34, 1.40)	1.36 (1.33, 1.39)
2018/19	1.55 (1.51, 1.60)	1.40 (1.36, 1.43)	1.39 (1.35, 1.42)
2019/20	1.72 (1.67, 1.77)	1.52 (1.49, 1.55)	1.53 (1.50, 1.56)

Note: CI = confidence interval, RR = relative risk.

^a Crude regression model;

^b Adjusted estimates were pooled risk ratios calculated using imputed datasets (n=5) by fully conditional specification approach. Model was adjusted for maternal age at delivery, maternal ethnicity and pre-pregnancy BMI;

^c Adjusted estimates were pooled risk ratios calculated using imputed datasets (n=5) by fully conditional specification approach. Model was adjusted for maternal age at delivery, neighbourhood income level, neighbourhood education level, ethnicity, parity, pre-pregnancy body mass index (BMI), conception type, smoking, pre-existing medical or obstetric conditions, prenatal education and infant sex.

Results of standardization and decomposition analysis

The standardization and decomposition analysis found that 27.0% of the temporal increase in GDM rates between fiscal years 2012/13 and 2019/20 was attributable to the changes in maternal age at delivery, pre-pregnancy BMI and maternal ethnicity over time (Table 4.3).

Sensitivity analyses

The results in sensitivity analyses were similar to our main findings. The complete case analysis found no apparent changes in point estimates for each year and the magnitude of temporal increase was generally comparable (Table S4). Analysis limited to first deliveries had similar conclusions, although the temporal estimates for GDM were slightly higher (Table S5).

Table 4.3 Temporal trends in gestational diabetes mellitus (GDM) rates in singleton hospital deliveries, Ontario, Canada, fiscal years 2012/13-2019/20: standardisation and decomposition analysis

Fiscal year of delivery	Number of deliveries	Number of GDM	Crude Rates per 100 deliveries	Change from FY 2012/13 ^a		Standardised rate of GDM (per 100 deliveries) ^a	Change from FY 2012/13 ^b		Change associated with maternal factors ^c	
				Per 100 deliveries	% of FY 2012/13 value		Per 100 deliveries	% of FY 2012/13 value	Per 100 deliveries	% of total variation
2012/13	131 824	7 992	6.1	0.0	0.0	6.1	0.0	0.0	-	-
2013/14	130 577	7 951	6.1	0.0	0.4	6.0	-0.1	-1.5	-0.1	-
2014/15	130 172	8 996	6.9	0.8	14.0	6.7	0.6	10.4	-0.2	25.9
2015/16	130 003	9 426	7.3	1.2	19.6	6.9	0.8	13.9	-0.3	29.3
2016/17	130 605	10 878	8.3	2.3	37.4	7.9	1.8	29.8	-0.5	20.3
2017/18	130 653	11 804	9.0	3.0	0.5	8.3	2.2	36.9	-0.7	24.5
2018/19	130 272	12 255	9.4	3.3	55.2	8.5	2.4	39.9	-0.9	27.7
2019/20	130 152	13 594	10.4	4.4	72.3	9.3	3.2	52.8	-1.2	27.0

^a Change of crude rate from fiscal year 2012/13.

^b Change of standardised rate of GDM from fiscal year 2012/13.

^c Standardized for maternal age (<25, 25-34 and ≥35 years), pre-pregnancy body mass index (BMI) (< 18.5, 18.5-24.9, 25.0-29.9, ≥ 30.0) and ethnicity (Asian, non-Asian and missing) based on the fiscal year of 2012/13 distribution.

4.6 Discussion

Main Findings

Our study showed a substantial increase in GDM rate from 6.1 to 10.4 per 100 deliveries in Ontario, Canada, between fiscal years 2012/13 and 2019/20. The absolute increase occurred more progressively in more recent years, particularly in cases of GDM without medical treatments. The risk of GDM in 2019/20 was 1.53 times (95% CI 1.50-1.56) higher compared with 2012/13. Only 27% of the temporal increase in GDM rates was attributed to the changes in the distributions of maternal age at delivery, pre-pregnancy BMI, and maternal ethnicity over time.

Strengths and limitations

One of the key strengths of this study was the use of the recent provincial ethnic diverse perinatal data, the largest prescribed birth registry with rigorous data quality in Canada.¹⁵¹ With the comprehensive data collected across the pregnancy and birth continuum, it allows us to evaluate and compare a wide range of risk factors over time. Having the additional data linkage ensured that all women with GDM diagnosis were well captured during the study period.

Our study had several limitations. First, despite using linked datasets, there might be non-differential misclassification relating to the diagnostic codes of GDM and data entry. The observed temporal trend in GDM therefore may be biased towards the null and underestimated. Second, changes in clinical guidelines for GDM screening and diagnosis in Canada need to be highlighted.¹⁰ Recent evidence from Canada and the US reported changes in screening methods contributed significantly to the observed increase in GDM rates.^{8,15} Unfortunately, given the lack of screening and diagnostic criteria data in our dataset, we were only able to account for 27% of

temporal increase of GDM due to the changing maternal factors and cannot rule out that the changes in screening and diagnostic criteria by the 2013 DC guideline could significantly contribute to the temporal increase. Third, our results might be impacted by residual confounding due to the lack of genetic, environmental, behavioral, and psychological information such as family history of diabetes, exercise and diet patterns, and gestational weight change in early or mid-gestation.¹³ Our models may also be subject to the insufficient adjustments for maternal ethnicity, sociodemographic status at individual-level, and pre-pregnancy BMI, which was obtained based on maternal pre-pregnancy weight by either self-reported or objective measurement in BIS. Thus, the temporal increase for GDM in our study would likely be overestimated, and the contributions of maternal factors might be underestimated. Fourth, as in all epidemiological studies, selection bias might affect our results. Limiting the cohort to gestational age at delivery at 28 weeks and above might miss some GDM cases diagnosed and delivered before 28 weeks of gestation, though the number of these cases were very small. Lastly, the nature of the public-funded health system and the exclusion of deliveries with multiple gestations or deliveries out of hospitals might limit the generalisability of our study findings.

Interpretation

Similar to previous studies conducted in Canada and other countries,^{7,8,15,18,20,53,169,176} our study using more recent provincial birth data showed a significantly temporal rise in GDM rate over the 8-year period, and the magnitude of the temporal increase was attenuated after further adjustment of maternal characteristics. Conversely, one study in the US reported the rates of GDM were stable from 1999 to 2005 across all age and racial groups.¹⁷⁷ Potential explanations

are the different distributions of population characteristics, and only inclusion of laboratory-confirmed GDM resulting in missing cases who were diagnosed in other settings.¹⁷⁷

Increases in rates of GDM are likely explained by multiple etiological factors, and the observed trends might reflect ongoing patterns in risk factors. However, few studies have examined and quantified the impact of changing risk factors on the temporal increase of GDM in recent years in Canada. Previous studies reported that the increases in GDM were paralleled by increasing rates of sociodemographic risk factors.^{13–15,53,173} Similarly, we found proportion of advanced maternal age and Asian ethnicity in Ontario increased consistently over time, which could partly explain the observed upward trend in GDM rates. However, GDM rates increased regardless of age groups and ethnic groups in our study, indicating that other factors beyond maternal age and ethnicity are possibly contributing to the observed increase. Several studies reported pre-pregnancy obesity had no effects on the increase in GDM.^{14,178} However, in this study, the rates of pre-pregnancy obesity based on BMI increased significantly over time, suggesting temporal increases in GDM over the 8-year period might be additionally explained by similar increases in pre-pregnancy BMI. The discrepancies between study results might be due to varying obesity metrics, population composition and environmental changes over time. Our study further demonstrated that 27% of the increase in GDM rate was attributable to changes in the distributions of maternal age, pre-pregnancy BMI and ethnicity over time.

4.7 Conclusion

Our large, retrospective population-based study of singleton hospital deliveries in Ontario, Canada showed a substantial increase in rate of GDM, especially mild GDM, from fiscal years 2012/13 to 2019/20. Over a quarter of the observed temporal increase in GDM rates was due to the changes in the distributions of maternal age at delivery, pre-pregnancy BMI, and maternal

ethnicity. Well-designed studies with additional inclusion of data on screening methods and diagnostic thresholds are warranted to better understand the contributors to the increasing trend in GDM rates.

Conflicts of interest

During the conduct of this work, DBF 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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Additional files for Chapter 4 can be found in Appendix B

Additional file 1:

Table S1. BORN Information system (BIS) and international classification of diseases (tenth revision, Canada) for GDM diagnosis

Additional file 2:

Table S2. Distribution of variables with missing values in original and imputed datasets

Additional file 3:

Table S3. GDM rates by fiscal year of delivery from April 1, 2012 to March 31, 2020 (data for Figure 2)

Additional file 4:

Table S4. Temporal trends in GDM in Ontario, Canada, fiscal years 2012/13-2019/20, in complete-case analysis

Additional file 5:

Table S5. Temporal trends in GDM among women with first pregnancy in Ontario, Canada, fiscal years 2012/13-2019/20

Additional file 6:

Figure S1. Directed Acyclic Graph (DAG) of causal assumptions between year of delivery and GDM.

Additional file 7:

Figure S2. Temporal trends in rates of GDM among all singleton hospital deliveries in Ontario, Canada, April 1, 2012 to March 31, 2020, stratified by maternal age at delivery, (A, B), pre-pregnancy BMI (C,D), and maternal ethnicity (E,F)

**Chapter 5. Risk of Adverse Maternal Outcomes Among Pregnancies With Gestational
Diabetes Mellitus in Ontario, Canada, 2012-2020: a Retrospective Cohort
Study (Manuscript)**

5.1 Title Page

Risk of Adverse Maternal Outcomes Among Pregnancies With Gestational Diabetes Mellitus in Ontario, Canada, 2012-2020: a Retrospective Cohort Study

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5.2 Abstract

Background The rate of gestational diabetes mellitus (GDM) has increased over the past decades, but it remains unclear whether the 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 risks (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). Outcome measures included labour induction, caesarean section (CS), assisted vaginal delivery, pregnancy-induced hypertension, 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 (adjusted RR [95% CI]) of induction (1.61 [1.59, 1.62]), CS (1.08 [1.06, 1.09]) and pregnancy-induced hypertension (1.35 [1.32, 1.38]). The risk of pregnancy-induced hypertension for GDM, compared to no GDM, attenuated from an adjusted RR of 1.45 (1.41, 1.49) in 2012/13-2015/16 to 1.29 (2.25, 2.32) 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]), and assisted vaginal delivery (0.96 [0.92, 1.00] vs 0.94 [0.90, 0.98]) remained stable over time. For maternal morbidity and mortality, although the direction of the association changed over time, the associations with

GDM were not statistically significant in either time period (0.93 [0.78, 1.08] vs 1.09 [0.97, 1.20]).

Conclusions In this large population-based study of singleton hospital deliveries in Ontario, Canada, despite the increased GDM rate, the risk of adverse maternal outcomes associated with GDM remained stable or decreased over the 8-year period. Future large prospective studies should prioritize investigation into the risks of maternal outcomes across different glycemic diagnostic thresholds to inform cost-effective healthcare resource allocation for GDM pregnancies.

Keywords

Gestational diabetes mellitus (GDM), adverse maternal outcomes, trend, Canada

5.3 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.⁵⁰ In addition to increased risk of perinatal morbidity and mortality,^{171,179} GDM is also associated with an increased risk of adverse long-term cardiometabolic outcomes for the mothers and their offspring.^{171,180} Timely diagnosis and appropriate treatments of GDM have been shown to improve maternal outcomes.¹¹⁰

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,² the International Association of Diabetes and Pregnancy Study Groups (IADPSG) defined a lower diagnostic threshold based on an odds ratio (OR) of 1.75 of a composite neonatal outcome (hyperinsulinemia, LGA and neonatal fat >90th percentile) and adopted a single abnormal glycemic value for GDM diagnosis.⁸⁰ 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.^{78,79} 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 diagnostic criteria and partly due to increases in advanced maternal age at delivery, obesity, and Asian race.^{8,13,15,53,181,182}

However, the impact of the increase in GDM on adverse maternal outcomes remains unclear. Limited studies have investigated the impact of increasing GDM on adverse maternal outcomes, and they have yielded inconsistent results.^{6,19–21,105} 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 2015.⁶ A recent study with over 2 million deliveries in Spain only found an increase in induction among GDM pregnancies from 2009 to 2015.²¹ Some other studies found no significant changes or reduction in the risks of adverse maternal outcomes over time along with the increase in GDM rates.

The aim of this study was 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.

5.4 Material 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. We excluded records with maternal ages <12 or >50 years, missing or indefinite infant sex, implausible gestational age or birth weight, women with gestational age at delivery ≤ 28 weeks or with pre-existing diabetes.

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.^{19,20,105,148,151,183} 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.^{151,184} 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.¹⁰

With regards to diagnostic criteria for GDM, the 2008 Diabetes Canada guidelines recommended screening using a 50g glucose challenge test (GCT) followed by a 75g 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 mmol/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.⁹¹ In April 2013, the new Diabetes Canada national guidelines were released to adopt two different approaches to identify GDM.⁷⁹ 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.⁷⁸ 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.⁶ 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., pregnancy-induced hypertension, and maternal morbidity or mortality). Caesarean deliveries included any clinical indications and non-medical indications. Based on Hypertension Canada's 2018 guidelines, pregnancy-induced hypertension included gestational hypertension (≥ 20 weeks' gestation), pre-eclampsia, and eclampsia.¹⁸⁵ Maternal morbidity or mortality was defined as a composite outcome based on the existing literature⁶ and the opinions of the clinicians, including 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.

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 2016,¹⁰ 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/ethnicity [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/m²], 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 healthcare practitioner type [none, midwife, family physician, or obstetrician]), and smoking during pregnancy (yes or no). We did not adjust 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.¹⁸⁶ 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 Rubin's rules.¹⁸⁷ For maternal race/ethnicity 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 and, thus, potential different underlying physiopathology among these women.¹⁸⁸ Lastly, we compared the results by excluding GDM pregnancies with medical treatments as mild GDM cases without medical treatments might have better glycemic control, 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 housed at BORN Ontario. Under the Personal Health Information Protection Act, 2004A, BORN Ontario prescribed registry can collect and use personal health information without consent to facilitate and improve healthcare. 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 (Table S5).¹⁸⁹

5.5 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 5.1. Compared with normoglycemic pregnancies, pregnant individuals with GDM were more likely to be older, of Asian race/ethnicity, 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 (Figure 5.1). 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 (Figure 5.2). 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. CS and pregnancy-induced hypertension 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 5.1 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/Ethnicity					
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 ^{2b}					

	< 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
Antenatal healthcare 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

Note: BMI= body mass index, ART = assisted reproductive technologies.

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.

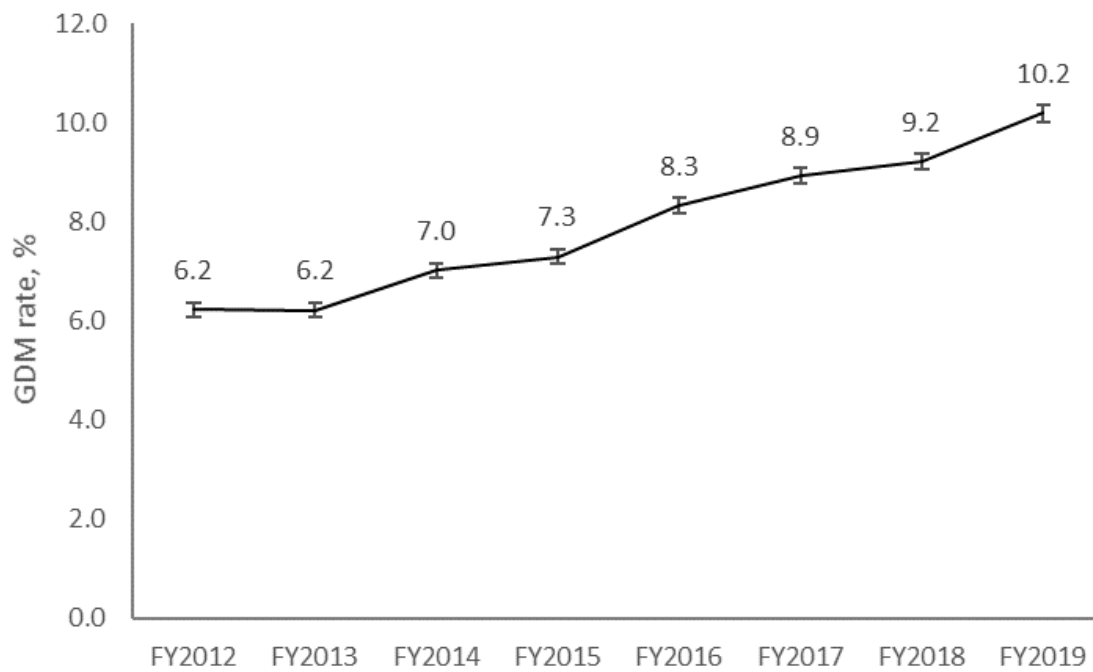
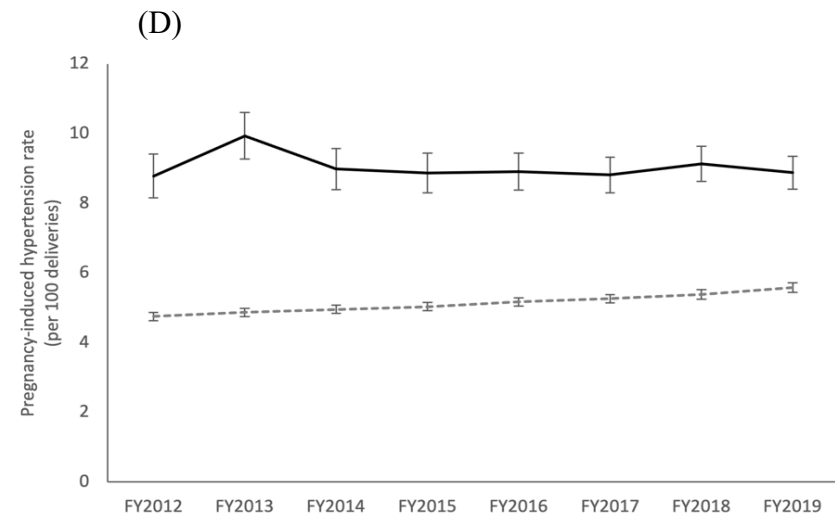
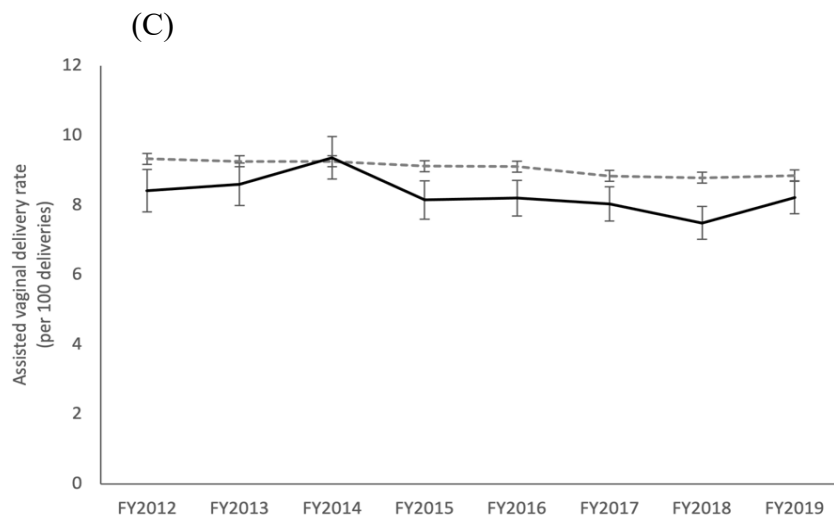
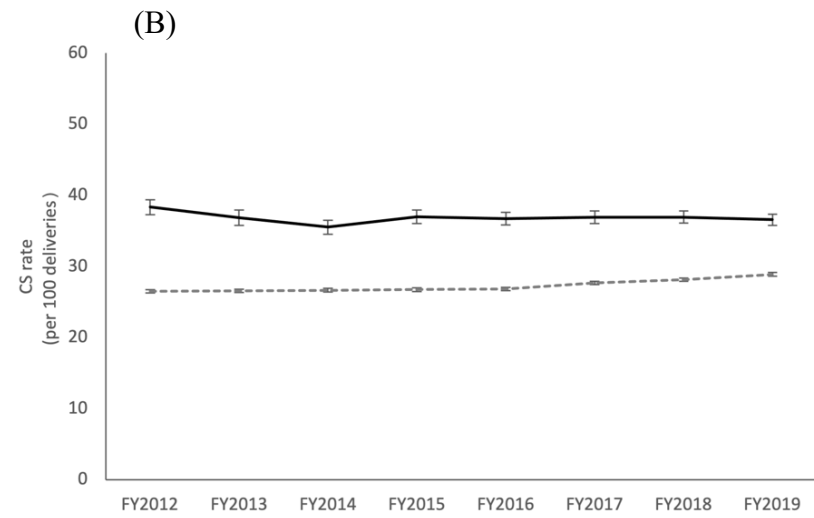
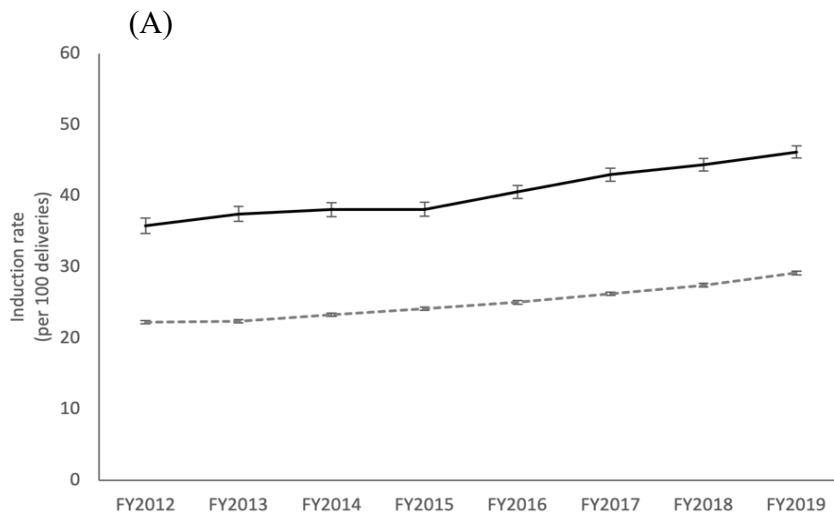
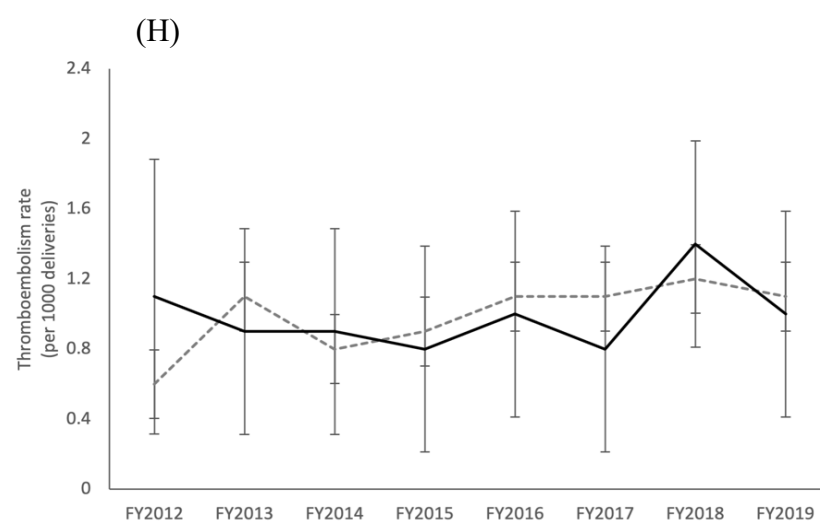
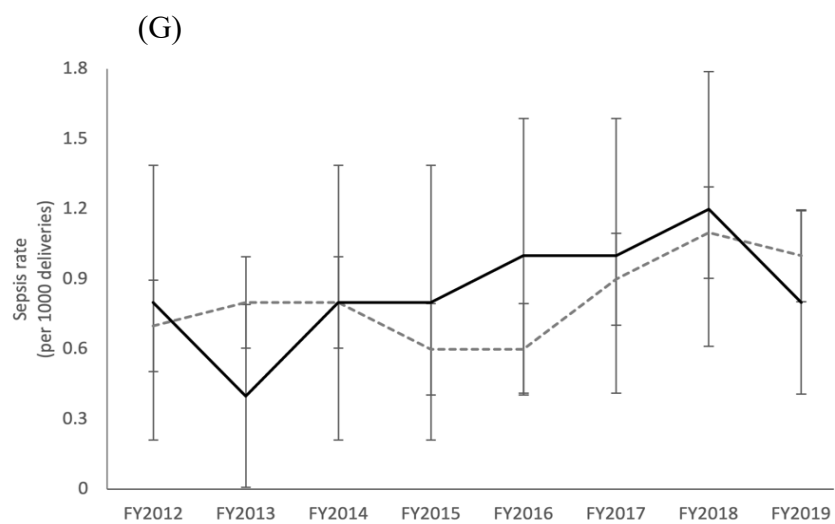
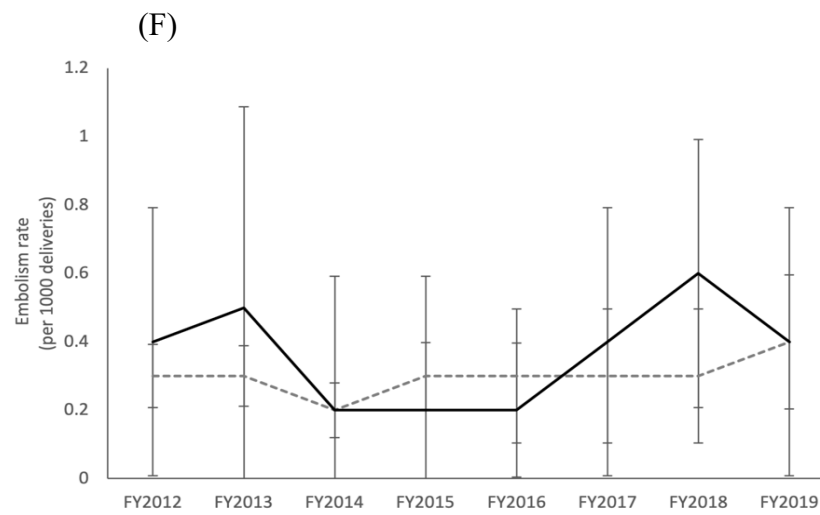
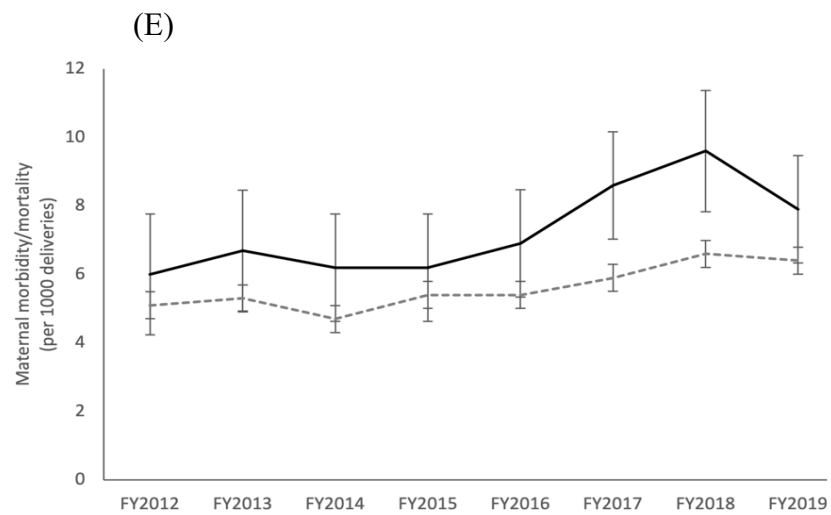


Figure 5.1 Age-standardized rate of GDM by fiscal year of delivery in Ontario, Canada





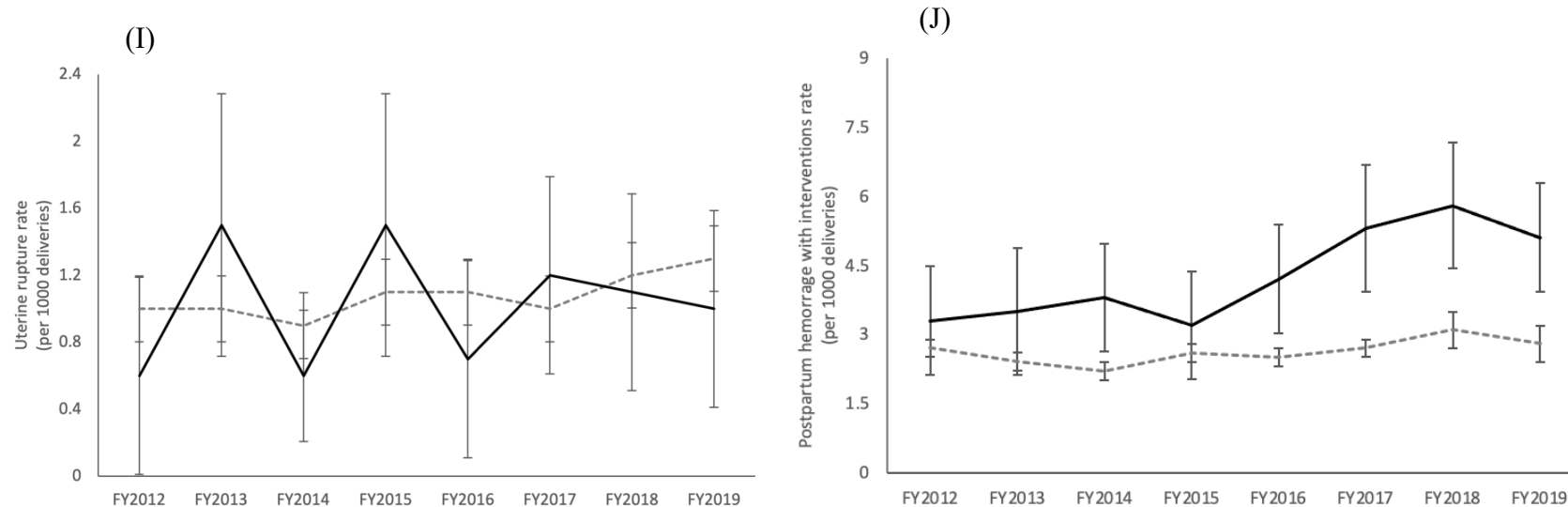


Figure 5.2 Rates of adverse outcomes (A) Induction; (B) CS; (C) Assisted vaginal delivery; (D) Gestational hypertensive disorders; (E) Severe maternal morbidity and mortality; (F) Obstetric embolism; (G) Sepsis; (H) Thromboembolism; (I) Uterine rupture; (J) Postpartum hemorrhage with hysterectomy or 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.

Associations Between GDM and Maternal Outcomes

Table 5.2 shows the RRs and RDs of maternal outcomes in pregnancies with and without GDM across the entire study period. With the exception of assisted vaginal delivery (adjusted RR 0.95, 95% CI [0.92, 0.98] and maternal morbidity/mortality (1.02, 95% CI [0.93,1.12]), GDM was positively associated with induction (1.61, 95% CI [1.59, 1.62]), CS (1.08, 95% CI [1.06, 1.09]) and pregnancy-induced hypertension (1.35, 95% CI [1.32, 1.38]).

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 Figure 5.3 and Table S7-S8. The adjusted RR 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 (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 adjusted RR 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 pregnancy-induced hypertension for GDM, compared to pregnancies without GDM, attenuated from an adjusted RR 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 relative risk was close to 1 and not statistically significant in either time period (0.93, 95% CI [0.78, 1.08] vs 1.09, 95% CI [0.97, 1.20]). With exception of postpartum hemorrhage with interventions to control bleeding, which showed a higher risk in latter period than early period (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.

Table 5.2 Association of GDM and adverse maternal outcomes in Ontario, Canada, fiscal years 2012/13-2019/20

Outcomes	Rate for GDM, % (n=82 896)	Rate for non-GDM, % (n= 961 362)	Crude RR (95% CI)	Adjusted RR (95% CI)^a	Crude RD, % (95% CI)	Adjusted RD, % (95% CI)^a
Induction	41.1	25.0	1.65 (1.63, 1.67)	1.61 (1.59, 1.62)	16.1 (15.8, 16.5)	15.1 (14.8, 15.5)
CS	36.8	27.2	1.35 (1.33, 1.37)	1.08 (1.06, 1.09)	9.60 (9.22, 9.97)	3.43 (3.12, 3.75)
Assisted vaginal delivery	8.3	9.1	0.91 (0.88, 0.94)	0.95 (0.92, 0.98)	-0.82 (-1.02, -0.62)	-0.35 (-0.53, -0.18)
Pregnancy-induced hypertension	9.0	5.1	1.76 (1.71, 1.81)	1.35 (1.32, 1.38)	3.89 (3.68, 4.11)	2.37 (2.17, 2.56)
Maternal morbidity/mortality ^{b,c}	7.4	5.6	1.33 (1.22, 1.45)	1.02 (0.93, 1.12)	1.84 (1.23, 2.45)	0.41 (-0.12, 0.95)
Component outcome ^{c,d}						
Obstetric embolism	0.4	0.3	1.27 (0.87, 1.85)	1.12 (0.74, 1.50)	0.08 (-0.06, 0.22)	0.01 (-0.12, 0.13)
Sepsis	0.9	0.8	1.08 (0.84, 1.38)	1.01 (0.75, 1.26)	0.06 (-0.15, 0.28)	0.01 (-0.19, 0.20)
Thromboembolism	1.0	1.0	1.03 (0.82, 1.30)	0.89 (0.66, 1.13)	0.03 (-0.20, 0.26)	-0.14 (-0.37, 0.09)
Uterine rupture	1.0	1.1	0.97 (0.77, 1.21)	0.76 (0.53, 0.99)	-0.04 (-0.27, 0.20)	-0.24 (-0.45, -0.02)
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	4.4	2.6	1.69 (1.51, 1.89)	1.17 (1.05, 1.29)	1.80 (1.33, 2.26)	1.04 (0.61, 1.47)

Note: CS= Caesarean section, RR=Risk ratio, RD=Risk difference.

^a Adjusted estimates were pooled estimates calculated using imputed datasets (n=5) by fully conditional specification approach. The adjusted estimates were generated by the multivariable Poisson regression model, which included maternal age at delivery, income, education level, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and year of delivery.

^b Maternal morbidity /mortality included maternal mortality or any of obstetric embolism, obstetric shock, sepsis, thromboembolism, uterine rupture and postpartum hemorrhage with hysterectomy or other procedures to control bleeding.

^c Rate and risk difference of maternal morbidity /mortality and each component outcome of maternal morbidity was expressed as per 1000 deliveries.

^d Risk difference of component outcomes was only adjusted for maternal age, parity and year of delivery to enable convergence in the multivariable regression models; Effect estimates of obstetric shock and maternal death were not presented given few numbers of events during the study period.

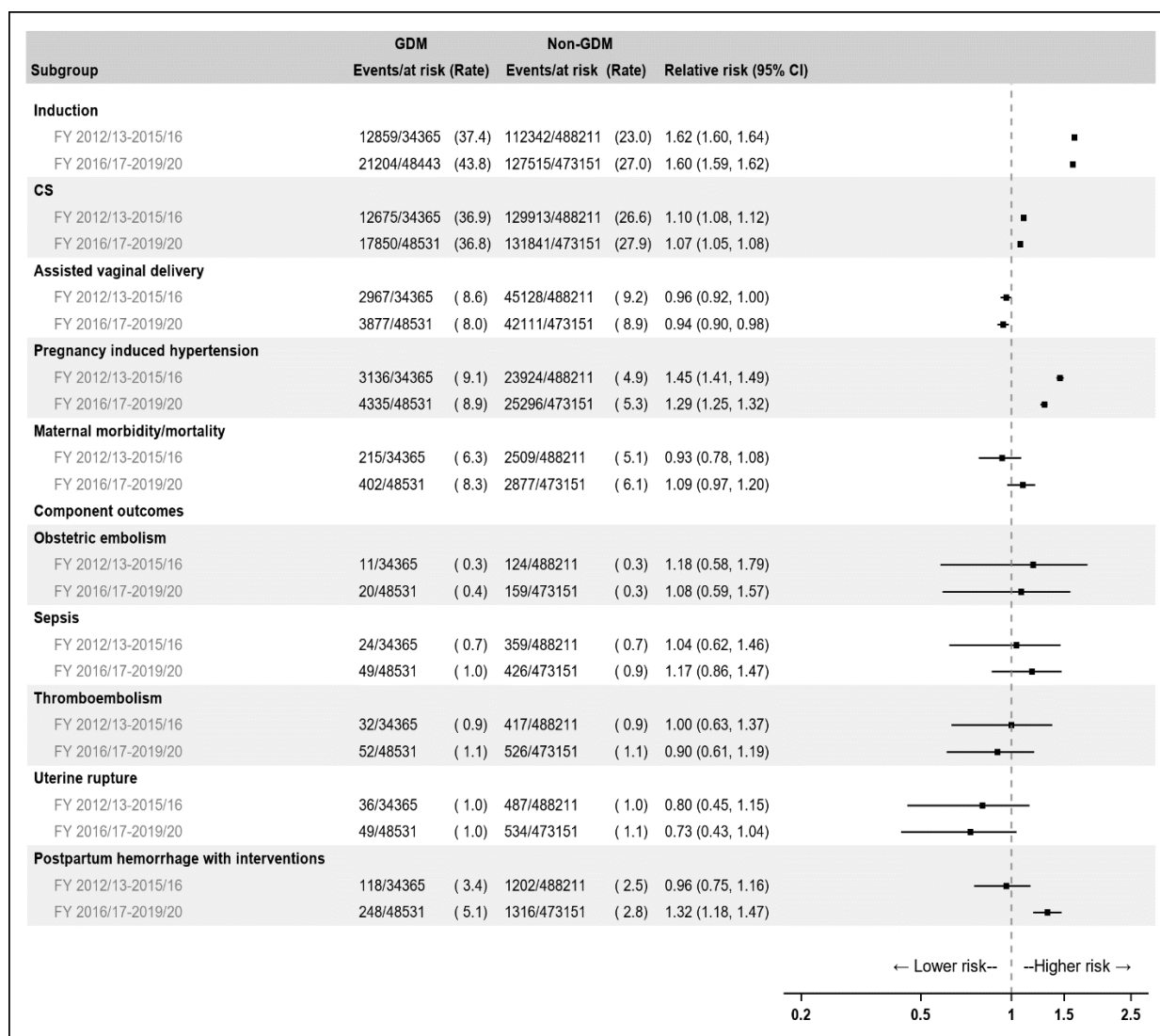


Figure 5.3 Association of GDM and maternal outcomes among singleton deliveries in Ontario, Canada, by time periods of delivery (N= 1 044 258) ^{a,b}

^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, parity, race/ethnicity, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education and antenatal health care providers.

Sensitivity Analyses

Complete-case analysis had generally comparable findings of in the risks of adverse maternal outcomes across different time periods of delivery, as did limiting to first deliveries (Table S9 – S10). 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 S11).

5.6 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, pregnancies with GDM had increased risks of induction, caesarean deliveries, and pregnancy-induced hypertension. Except for postpartum hemorrhage with interventions, the associations between GDM and pregnancy-induced hypertension for GDM decreased over time, while induction, CS, assisted vaginal delivery and other severe maternal outcomes remained stable.

Interpretation

The current analysis, which was 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.¹⁸² However, there is a limited number of studies on 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 was unclear.¹⁷ Our finding that the significantly higher risk of certain maternal outcomes for GDM compared to normoglycemic pregnancies aligns with previous studies showing associations with induction, CS, gestational hypertension or preeclampsia.^{2,171} 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 similar with recent data highlighting the utilization of more obstetrical

interventions for GDM management in clinical practices.^{2,6,21,190} Despite international consensus has not been reached on the optimal timing of delivery for pregnancies with GDM, clinical guidelines has been widely recommending labour induction to GDM pregnancies near term to improve pregnancy outcomes.^{58,92} Consistent to several previous studies,^{6,19–21} we found that the CS rate stayed stable among GDM pregnancies and the risk of CS for GDM compared to non-GDM pregnancies remained similar over the recent years, despite the increased rate of GDM. It was likely reflect the stricter screening and diagnostic criteria of GDM and utilization of intensive medical management and interventions including lifestyle interventions, common use of insulin and metformin as main pharmacotherapy to improve glycemic control, and wide use of induction.^{10,110,191,192} It is possible that inclusion of a mild degree of hyperglycemia together with medical advances in achieving better glucose control in a short period and early term delivery by induction may benefit fetal overgrowth and therefore with no increase in caesarean deliveries.^{192–}

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Similar to the study by Gortazar in Spain from 2006 and 2015,²⁰ the reductions in risks of the pregnancy-induced hypertension 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.¹⁹⁴

Although diagnostic values for GDM are variable and thresholds for treatments are inconsistent, several studies have suggested untreated mild hyperglycemia are at higher risk of poor outcomes compared to normoglycemic pregnancies and improving glycemic control of mild GDM reduces the risk of certain maternal and neonatal outcomes.^{107,195,196} However, contradictory results have been reported where the risk for pregnancy-induced hypertension associated with GDM increased from 1991 and 2003 using the Swedish nationwide birth cohort,¹⁹ which could be due

to the different definitions of pregnancy-induced hypertension and low sensitivity of the screening strategies for GDM used in Sweden.¹⁹⁷

In contrast to previous results that showed no changes in severe maternal outcomes over time,²¹ we found postpartum hemorrhage with hysterectomy or other procedures to control bleeding increased significantly over time for GDM compared to no GDM. It was likely related to the increased rates of known risk factors of postpartum hemorrhage over time among GDM pregnancies, such as placenta-related complications, labour augmentation, and induction.^{198,199} Residual confounding due to insufficient adjustment of these risk factors in the regression models may have overestimated the changes in postpartum hemorrhage with interventions. Variations in prevention and management strategies for early identification and interventions over time might also explain this observation.²⁰⁰

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 despite the increased GDM rate, the risk of adverse maternal outcomes for 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 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 healthcare resource allocation for GDM pregnancies.

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.^{148,183} Furthermore, we were able to control for several key covariates including maternal pre-pregnancy BMI and prenatal healthcare, which were important contributors to the outcomes of pregnancy but were not addressed in some of the previous studies.^{6,20,190}

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 maternal outcomes due to physician misdiagnoses or imperfect ascertainment, which would generally bias the estimates towards the null in cohort studies. Second, information of applied diagnostic guideline or 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, given the nature of retrospective observational study, we were unable to address residual confounding from unmeasured and unknown confounders, such as glycemic control and lifestyle factors, while assessing the changes in the adverse outcomes relating to increasing GDM. Assuming GDM requiring no medical treatments might have better glycemic control, we performed a sensitivity analysis with exclusion of pregnant individuals with medical treatments, and the results indicated the similar trends in outcomes for GDM over time, despite the associations between GDM and maternal outcomes were less strong. Fourth, the impact on severe maternal outcomes was likely underestimated as it was only limited to the severe complications occurring during the immediate perinatal periods in the current study. Lastly, the

nature of public-funded healthcare system and the application of universal screening at 24-28 weeks of gestation for GDM might limit the generalisability of our findings.

5.7 Conclusions

In this large population-based study of singleton hospital deliveries in Ontario, Canada, the recent increase in GDM over the 8-year period was not associated with increases in maternal outcomes. Except for postpartum hemorrhage with interventions, the risk of pregnancy-induced hypertension for GDM, compared to normoglycemic pregnancies, decreased over time while induction, CS, assisted vaginal delivery and other 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 to inform cost-effective healthcare resource allocation for GDM pregnancies.

Acknowledgements

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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.J.C., D.B.F. 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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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 housed at BORN Ontario. Under the Personal Health Information Protection Act (PHIPA), 2004A, BORN Ontario prescribed registry can collect and use personal health information without consent to facilitate and improve healthcare. All data management and analyses were performed within the secure environment at BORN Ontario, aligning with all security and privacy protocols and policies.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed for 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 reasonable request.

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.

Additional files for Chapter 5 can be found in Appendix C

Additional file 1:

Table S1. Datasets used in this analysis

Additional file 2:

Table S2. Canadian guidelines for screening and diagnosis of GDM during 2012 and 2020

Additional file 3:

Table S3. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code outcomes

Additional file 4:

Table S4. Covariates with missing values and strategies handling missing values

Additional file 5:

Table S5. RECORD checklist

Additional file 6:

Table S6. Temporal trends in maternal outcomes among deliveries with and without GDM in Ontario, Canada, fiscal years 2012/13-2019/20

Additional file 7:

Table S7. Interaction tests of GDM with time periods of delivery, Ontario, Canada, fiscal years 2012/13-2019/20

Additional file 8:

Table S8. Risk difference in adverse maternal outcomes among women with GDM and non-GDM in Ontario, Canada, by time periods of delivery (n=1 044 258)

Additional file 9:

Table S9. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery in complete-case analysis

Additional file 10:

Table S10. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals with first delivery

Additional file 11:

Table S11. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals without medical treatments for GDM

Additional file 12:

Figure S1. A Directed Acyclic Graph (DAG) of GDM and adverse maternal outcomes

Additional file 13:

Figure S2. Study flow chart

**Chapter 6. Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational
Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020
(Manuscript)**

6.1 Title Page

Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020

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6.2 Abstract

Background There is conflicting evidence on the impact of the recent increase in GDM rates on adverse neonatal outcomes. This study aimed to describe temporal trends in rates of adverse neonatal outcomes among pregnancies with and without GDM and compare risk of these outcomes for GDM by delivery periods.

Methods We performed a population-based retrospective cohort study using data from Ontario provincial birth registry linked with health administrative databases. All hospital deliveries with a singleton live birth or stillbirth from April 2012 to March 2020 in Ontario, Canada were included. We used modified robust Poisson regression to assess the risks of adverse neonatal outcomes associated with GDM using relative risk (RR) and risk difference (RD) with 95% confidence intervals (CI) by delivery periods.

Results Among 1 044 258 pregnant individuals, there were 82 896 (7.9%) with GDM and 172 442 (16.5%) with one or more diagnoses of severe neonatal morbidity and mortality. The annual rate of GDM increased from 6.1 to 10.5 per 100 deliveries between 2012/13 and 2019/20. Although the rate of severe neonatal morbidity and mortality (SNM) increased over time among pregnancies with and without GDM, the positive association between GDM and SNM was stable between the time periods (adjusted RR, 2012/13-2015/16: 1.50, 95% CI [1.48, 1.52] and 2016/17-2019/20: 1.54, 95% CI [1.52, 1.56]). The strength of the association between GDM and both LGA and macrosomia decreased in 2016/17-2019/20 (2012/13-2015/16: 1.42, 95% CI [1.39, 1.45] and 2016/17-2019/20: 1.31, 95% CI [1.28, 1.34] for LGA; 2012/13-2015/16: 0.98, 95% CI [0.95, 1.02] and 2016/17-2019/20: 0.86, 95% CI [0.83, 0.90] for macrosomia). The associations of GDM with other neonatal outcomes remained similar over time.

Conclusions Our large, population-based study showed that this recent increase in GDM was not associated with increased risks of adverse neonatal outcomes in Ontario, Canada. The magnitude of the association between GDM and overall SNM remained stable. Except for the attenuated association of GDM with LGA and macrosomia, no significant changes were observed in associations of GDM with other individual neonatal outcomes.

Keywords Gestational diabetes mellitus, trend, risk, adverse neonatal outcomes

6.3 Background

Gestational diabetes mellitus (GDM) is a common obstetrical complication resulting from increased insulin resistance in late pregnancy together with impaired pancreatic beta-cells secretion function, with a global prevalence of 14% in 2021 estimated by the International Diabetes Federation (IDF).⁹ GDM is an important public health issue as it has been associated with increased risks of preeclampsia, caesarean delivery, preterm birth, infants born large for gestational age (LGA), neonatal intensive care unit (NICU) admission, birth injuries, and future diabetes and cardiovascular diseases for mothers and their offspring.^{2,170,171} The overall health expenditures of GDM management is substantial.²⁰¹

The rate of GDM has increased worldwide¹¹ and in Canada over the past decade.^{53,182} Although reasons for the rise in GDM are not fully understood, population demographic changes over time together with variation in screening methods and diagnostic thresholds are the contributing factors.^{8,13,131} The diagnosis of GDM has evolved from the initial use of criteria to predict the development of type 2 diabetes within 7-8 years postpartum to the criteria based on the continuous relationship between glycemic values and adverse neonatal outcomes by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.¹⁰ The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended the new set of diagnostic criteria in 2010 based on the neonatal outcomes of HAPO study.⁸⁰ In Canada, Diabetes Canada and the Society of Obstetricians and Gynaecologists of Canada (SOGC) initially had discrepancies between their clinical guidelines; however, updates to Diabetes Canada's and the SOGC's clinical guidelines (in 2013 and 2016, respectively) aligned their recommendations by endorsing universal screening and implementing the one-step and two-step approaches with the same diagnostic cut-off values.^{78,79}

To the best of our knowledge, only a few studies to date have assessed the impact of the increasing rate of GDM on adverse neonatal outcomes, and findings have been inconsistent.^{6,7,15,18–20,105} An earlier study reported that neonatal morbidity increased with the increasing rate of GDM between 2004 and 2014 in Canada.⁶ Yet, several studies observed no significant changes in risks of perinatal outcomes over time despite the increased GDM rate.^{7,19,20} Some other population-based studies only found decreasing rates of LGA and birth trauma for GDM pregnancies over time while GDM rates were increasing.^{15,18,105}

In this study, we described recent trends in a broad range of important neonatal outcomes among deliveries following GDM and non-GDM, and compared the associations between GDM and adverse outcomes by time periods before and after the nation-wide adoption of two different screening and diagnostic approaches using data from the provincial birth registry in Ontario, Canada between 2012 and 2020.

6.4 Methods

Study Design, Population, and Data Sources

We conducted a retrospective, population-based cohort study in Ontario, which is Canada's most populous province with approximately 14.7 million residents and 140 000 births per year.^{202,203}

All residents in Ontario are provided with universal, publicly funded health care, including health services related to prenatal and obstetric care. The province-wide birth registry, Better Outcomes Registry & Network Ontario (BORN), was used to identify all pregnant individuals who had a singleton live birth or stillbirth in Ontario hospitals between April 1, 2012 and March 31, 2020. We excluded neonates born at ≤ 28 weeks; with missing or unclassified information on sex; with implausible gestational age at birth and birth weight combinations; and pregnant individuals < 12 or > 50 years of age at delivery or with pre-existing diabetes. The details of the study population have been described elsewhere.¹⁸²

The BORN Ontario Information System (BIS), an internet-based data platform collecting extensive maternal-neonatal information for all live and stillborn infants ≥ 20 weeks of gestation or with birthweight ≥ 500 grams in real-time from over 250 hospitals, birth centers and midwife practice groups and other health-information custodians across Ontario since 2012.¹⁵¹ Maternal demographics, medical conditions, pregnancy characteristics, labour and birth outcomes are collected from medical records, clinical forms and patient interviews for all births from preconception to the postpartum period.^{151,152} The data quality has been continuously assessed and is of similar quality to other high-quality clinical administrative healthcare databases in Ontario.^{148,152} Using maternal residential postal codes, we linked the study population to Statistics Canada's 2016 Census data to obtain dissemination-level income and education data.

Using deterministic and probabilistic approaches, we linked the study population to hospital delivery records of mothers with the corresponding neonates records from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) to ascertain additional exposure and outcomes. The CIHI-DAD collects sociodemographic, clinical and administrative information on each hospital discharge, including up to 25 medical diagnoses coded by the Canadian version of International Classification of Diseases, tenth Revision (ICD-10-CA) and 20 clinical procedures coded by the Canadian Classification of Interventions (CCI).

Exposure

Presence of GDM in the index pregnancy was the exposure. Diabetes in pregnancy was routinely recorded during prenatal care encounters for pregnant individuals by their healthcare providers using the national clinical practice guidelines. Before 2013, GDM was diagnosed if any two of the following cut-off values were met among negative 50 g glucose challenge test (GCT) (1 hour post <10.3 mmol/L): ≥ 5.3 mmol/L for fasting, ≥ 10.0 mmol/L for 1-hour post, ≥ 8.6 mmol/L for 2-hour post plasma glucose values in the 2-step, 2-hour, 75 g oral glucose tolerance test (OGTT); or ≥ 5.3 or 5.8 mmol/L for fasting, ≥ 10.0 or 10.6 mmol/L for 1-hour post, ≥ 8.6 or 9.2 mmol/L for 2-hour post, ≥ 7.8 or 8.0 mmol/L for 3-hour post plasma glucose values in the 2-step, 3-hour, 100 g OGTT.¹⁰ Since 2013, Diabetes Canada adopted new diagnostic criteria, later endorsed by the SOGC in 2016, where GDM is diagnosed if any of the following cut-off values were met among negative 50 g GCT (1 hour post <11.1 mmol/L): ≥ 5.3 mmol/L for fasting, ≥ 10.6 mmol/L for 1-hour post, ≥ 9.0 mmol/L for 2-hour post plasma glucose values in the 2-step, 2-hour, 75 g OGTT; or ≥ 5.1 mmol/L for fasting, ≥ 10.0 mmol/L for 1-hour post, ≥ 8.5 mmol/L for 2-hour post plasma glucose values in the 1-step, 2-hour, 75 g OGTT.^{78,79}

GDM cases were firstly identified through birth registry-specific variables: "Diabetes and Pregnancy" and "Pregnancy complications". We additionally searched the following codes in CIHI-DAD datasets to supplement GDM cases: obstetrical records with O24.8 or newborn records with P70.0. If any of these codes were identified, the individual was considered to have had GDM during the index pregnancy.

Outcomes

The primary outcome was severe neonatal morbidity and mortality (SNM), which was a composite outcome including any of the following conditions: perinatal mortality (stillbirth and neonatal death within 28 days following live birth), respiratory distress syndrome or transient tachypnea of the newborn, hypoglycemia, newborn sepsis, confirmed seizures, necrotizing enterocolitis, hypoxic–ischemic encephalopathy, cardiopulmonary resuscitation or ventilator support, umbilical-cord-blood arterial pH <7.0, a 5-minute Apgar score <4, admission to NICU, or prolonged hospitalization (≥ 5 days). The types of SNM were selected based on previous literature²⁰⁴ and clinical opinions. Secondary outcomes included each component outcome of SNM, LGA, macrosomia, preterm birth, and birth trauma among live born infants. LGA was determined as >90th percentile of birth weight by infant sex and gestational age in a Canadian reference population.¹⁴⁶ Macrosomia was defined as birth weight ≥ 4000 gram. Preterm birth was defined as a live birth before 37 completed gestational weeks. Specific diagnosis codes used to identify exposure, and outcomes are provided in Table S1 in the Supplement.

Covariates

We prespecified the covariates of interest based on clinical and epidemiological knowledge and data availability, and developed a directed acyclic graph (DAG) (**Figure S1**). Covariates

considered in this study included maternal sociodemographic (maternal age at delivery, neighbourhood-level socioeconomic status, pre-pregnancy body mass index [BMI] and race/ethnicity), pregnancy characteristics (parity, pre-existing medical or obstetrical conditions, conception type, antenatal care provider type, prenatal education and self-reported smoking status in pregnancy), and delivery information (year of delivery, infant sex, birth weight and gestational age at delivery). Pre-pregnancy BMI was calculated by dividing pre-pregnancy weight in kilograms by height in meters squared, where maternal weight was obtained in the Prenatal Screening Ontario (PSO) database and/or the Labour & Birth database within the BIS. Pre-existing medical or obstetrical conditions included any of pre-existing hypertension, autoimmune, cardiac, endocrine conditions, previous stillbirth and previous caesarean delivery. Conception type was classified as spontaneous conception and conception via fertility treatments. Antenatal healthcare was provided by midwife, family physicians, obstetricians and none.

Statistical Analysis

We presented characteristics for the study population overall and by GDM. Continuous variables used means and standard deviations (SDs) or medians and first and third quartiles (Q1, Q3); categorical variables used frequencies (percentages). The distribution of gestational age at delivery over time was visually displayed for pregnancies with and without GDM. We calculated the crude and gestational-age adjusted annual rates of adverse neonatal outcomes per 100 or 1000 deliveries for GDM and non-GDM pregnancies from fiscal year 2012/13 to 2019/20, and assessed the trends using modified Poisson regression.

Considering that the SOGC and Diabetes Canada reached a consensus in 2016 for Canada-wide adoption of the 2-step preferred test and the 1-step alternative test for screening and diagnosing GDM,⁷⁸ we further divided the study period into 2 intervals: 2012/13-2015/16 and 2016/17-2019/20, to compare the associations between GDM and adverse neonatal outcomes by time periods. We used modified Poisson regression with robust standard errors to estimate crude and adjusted relative risks (RRs) with 95% confidence intervals (CIs) for each outcome contrasting GDM with non-GDM pregnancies. We also estimated the statistical significance of the interaction term between GDM and time periods. To assess the absolute burden of GDM, we also computed crude and adjusted risk difference (RD) with 95% CIs for GDM relative to non-GDM in the modified Poisson regression models by specifying an identity link. Multivariable models were adjusted for the minimally sufficient adjustment set identified from the DAG, including maternal age at delivery, neighbourhood-level family income quintiles, neighbourhood-level education quintiles, race, parity, smoking, pre-existing medical or obstetrical conditions, pre-pregnancy BMI, conception type, prenatal education, antenatal care provider, and infant sex. For some extremely rare outcomes, we only adjusted for maternal age and parity to enable convergence.

The percentage of missing values of any individual covariate in the multivariable regression was low to medium (ranges 0-12.3%), with the exception for maternal race/ethnicity, which had 34.4% missing data. Rather than imputing this variable, we coded missing values as a separate category. We assumed the pattern of missing data was random, and used multiple imputation with a fully conditional specification approach to generate five imputation datasets for all regression analyses. The imputations models included all covariates where were used in

multivariable regression models. Estimates were combined across the imputed datasets following Rubin's rules to obtain a single estimate.

We conducted a series of sensitivity analyses to assess the robustness of our main findings: complete-case analysis without imputation for missing values; restricting data to a first delivery if pregnant individuals had multiple deliveries over the study period;⁶⁴ excluding women with eclampsia, severe preeclampsia, mild preeclampsia, and gestational hypertension; and excluding women with medical treatments to control GDM.

We used SAS version 9.4 (SAS Institute, Cary, NC) for all analyses, with a two-tailed p value <0.05 as statistical significance. This study was reviewed and approved by the Research Ethics Boards from the Ottawa Health Science Network (20210400-01H) and the University of Ottawa (H-03-21-6792). Individual patient consent was waived by the Ottawa Health Science Network Research Ethics Board for this study as it involved secondary use of databases held by BORN Ontario. BORN Ontario, as a prescribed provincial birth registry under the province's Personal Health Information Protection Act, 2004A,²⁰⁵ can collect pregnancy, birth and newborn health information aiming to facilitate and improve the provision of perinatal care in Ontario, Canada. We followed the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guideline for reporting cohort studies (Table S2).

6.5 Results

We included 1 044 258 eligible pregnancies in the final analysis; there were 82 896 (7.9%) with GDM and 172 442 (16.5%) with one or more diagnoses of SNM across the entire study period (Table 6.1). Mean maternal age at delivery was 30.7 years, and there were 536 036 (51.3%) male and 508 222 (48.7%) female newborns with a median gestational age of 39.4 weeks.

The distribution of births by gestational age for pregnancies with and without GDM are displayed in Figure 6.1. Despite some fluctuations, it shows a small shift towards shorter gestations for all pregnancies over time. The median gestational age at delivery was lower in GDM pregnancies, at 38.9 weeks, compared to 39.6 weeks in non-GDM pregnancies.

Trends in Rates of GDM and Adverse Neonatal Outcomes

The annual rate of GDM rose from 6.1 (95% CI 5.9-6.2) in 2012/13 to 10.4 (95% CI 10.3-10.6) per 100 deliveries in 2019/20 (Table S3). Figure 6.2 and Table S4 show the crude and gestational-age adjusted rates of adverse neonatal outcomes over time by GDM status. Among GDM pregnancies, the gestational-age adjusted rate of composite SNM increased from 22.9 (95% CI 21.8, 23.9) to 23.9 (95% CI 23.1, 24.8) per 100 deliveries; among non-GDM pregnancies, it increased from 15.1 (95% CI 14.9, 15.3) to 16.8 (95% CI 16.6, 17.0) per 100 deliveries.

Most individual adverse neonatal outcomes remained stable or decreased over time for both GDM and non-GDM pregnancies. However, the rates of adverse respiratory outcomes, hypoglycemia, hypoxic–ischemic encephalopathy, cardiopulmonary resuscitation or ventilator support, and birth trauma increased.

Table 6.1 Maternal and neonatal characteristics in study population in Ontario, Canada, between fiscal years 2012/13-2019/20 (N=1 044 258)

Characteristics	GDM (n=82 897)	Non-GDM (n= 961 362)	Total (N=1 044 258)
Maternal characteristics			
Maternal age at delivery, years			
Mean (SD)	32.9 (4.9)	30.5 (5.2)	30.7 (5.3)
< 25	3 930 (4.7)	128 309 (13.4)	132 239 (12.7)
25-34	47 327 (57.1)	619 143 (64.4)	666 470 (63.8)
≥ 35	31 639 (38.2)	213 906 (22.3)	245 545 (23.5)
Missing	0	<6 (S)	<6 (S)
Neighborhood family income quintile			
Quintile 1 (lowest)	21 303 (25.7)	210 673 (21.9)	231 976 (22.2)
Quintile 2	17 264 (20.8)	192 555 (20.0)	209 819 (20.1)
Quintile 3	17 211 (20.8)	195 465 (20.3)	212 676 (20.4)
Quintile 4	15 056 (18.2)	189 190 (19.7)	204 246 (20.0)
Quintile 5 (highest)	10 546 (12.7)	153 307 (15.9)	163 853 (15.7)
Missing	1 516 (1.8)	20 172 (2.1)	21 688 (2.1)
Neighborhood education level quintile ^a			
Quintile 1 (lowest)	10 830 (13.1)	151 520 (15.8)	162 350 (15.5)
Quintile 2	13 547 (16.4)	172 906 (18.0)	186 453 (17.9)
Quintile 3	17 961 (21.7)	193 944 (20.2)	211 905 (20.3)
Quintile 4	20 554 (24.8)	211 252 (22.0)	231 806 (22.2)
Quintile 5 (highest)	13 976 (16.9)	165 838 (17.3)	179 814 (17.2)
Missing	6 028 (7.3)	65 902 (6.9)	71 930 (6.9)
Nulliparity	31 598 (38.1)	416 611 (43.3)	448 209 (42.9)
Race/Ethnicity			
Non-Asian	31 823 (38.4)	466 654 (48.5)	498 477 (47.7)
Asian	27 675 (33.4)	159 320 (16.6)	186 995 (17.9)
Missing	23 398 (28.2)	335 388 (34.9)	358 786 (34.4)
Pre-pregnancy BMI, kg/m ^{2b}			
Mean (SD)	28.2 (7.1)	25.1 (6.0)	25.3 (6.1)
< 18.5	2 284 (2.8)	52 254 (5.4)	54 538 (5.2)
18.5-24.9	25 210 (30.4)	445 264 (46.3)	470 474 (45.1)
25.0-29.9	20 893 (25.2)	202 872 (21.1)	223 765 (21.4)
≥ 30.0	24 349 (29.4)	143 227 (14.9)	167 576 (16.1)
Missing	10 160 (12.3)	117 745 (12.2)	127 905 (12.3)
Conception type ^c			
Fertility technologies	4 470 (5.4)	29 354 (3.1)	33 824 (3.2)
Spontaneous conception	73 656 (88.9)	885 930 (92.2)	959 586 (91.9)
Missing	4 770 (5.8)	46 078 (4.8)	50 848 (4.9)
Maternal smoking ^d	5 504 (6.6)	89 166 (9.3)	94 670 (9.1)
Pre-existing medical or obstetrical conditions ^e	25 669 (31.0)	220 616 (22.9)	246 285 (23.6)
Prenatal education	16 138 (19.5)	223 879 (23.3)	240 017 (23.0)
Antenatal healthcare provider ^f			

None	147 (0.2)	4 129 (0.4)	4 276 (0.4)
Midwife	7 121 (8.6)	138 096 (14.4)	145 217 (13.9)
Physicians	71 897 (86.7)	783 640 (81.5)	855 537 (81.9)
Missing	3 731 (4.5)	35 497 (3.7)	39 228 (3.8)
Neonatal characteristics			
SNM (primary outcome)	20 976 (25.3)	151 466 (15.8)	172 442 (16.5)
Male Infant	42 935 (51.8)	493 101 (51.3)	536 036 (51.3)
Gestational age at delivery, wks			
Median (Q1, Q3)	38.9 (38.0, 39.4)	39.6 (38.7, 40.4)	39.4 (38.6, 40.3)
Year of delivery			
FY 2012	7 992 (9.6)	123 832 (12.9)	131 824 (12.6)
FY 2013	7 951 (9.6)	122 626 (12.8)	130 577 (12.5)
FY 2014	8 996 (10.9)	121 176 (12.6)	130 172 (12.5)
FY 2015	9 426 (11.4)	120 577 (12.5)	130 003 (12.5)
FY 2016	10 878 (13.1)	119 727 (12.5)	130 605 (12.5)
FY 2017	11 804 (14.2)	118 849 (12.4)	130 653 (12.5)
FY 2018	12 255 (14.8)	118 017 (12.3)	130 272 (12.5)
FY 2019	13 594 (16.4)	116 558 (12.1)	130 152 (12.5)

Note: BMI= body mass index

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).

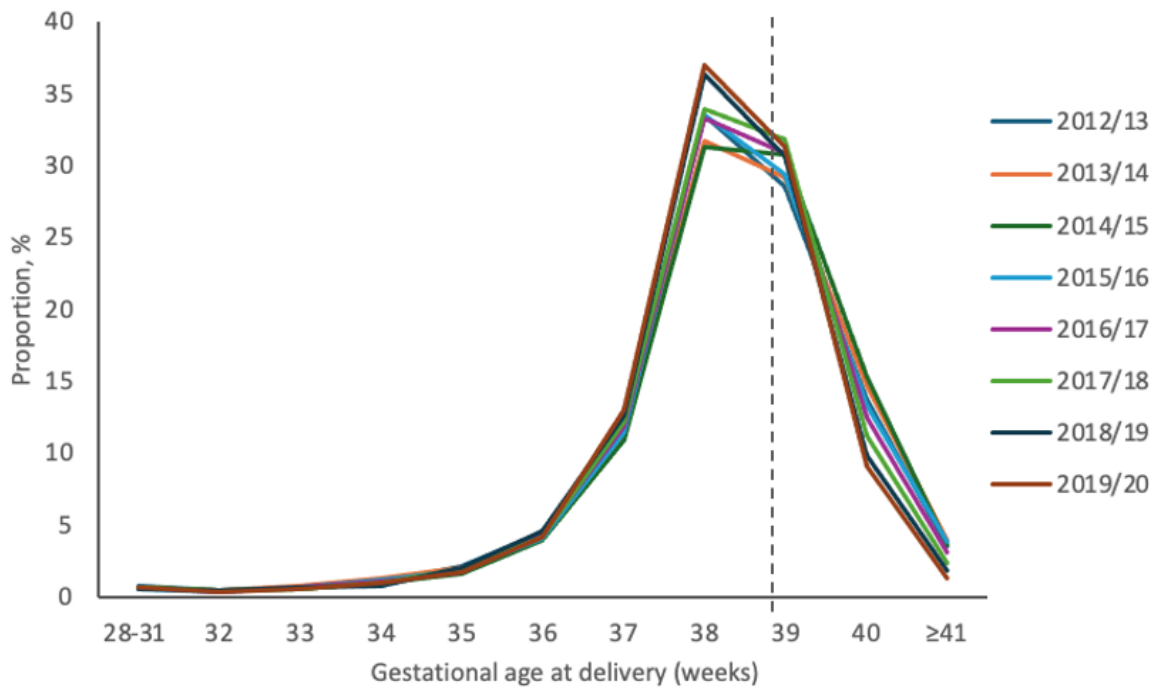
^c Conception type was based on use of fertility technologies. Fertility technologies including assisted reproductive technologies (e.g. IVF, IVF-ICSI and surrogacy) and non-assisted reproductive treatments (e.g. hormonal treatments and insemination).

^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 CS.

^f If a woman had a midwife in addition to other healthcare providers, she was counted into the midwife group and we assumed midwife would have provided most of the antenatal care. Other antenatal healthcare providers including obstetrician only, family physician only and family physician and obstetrician.

A)



B)

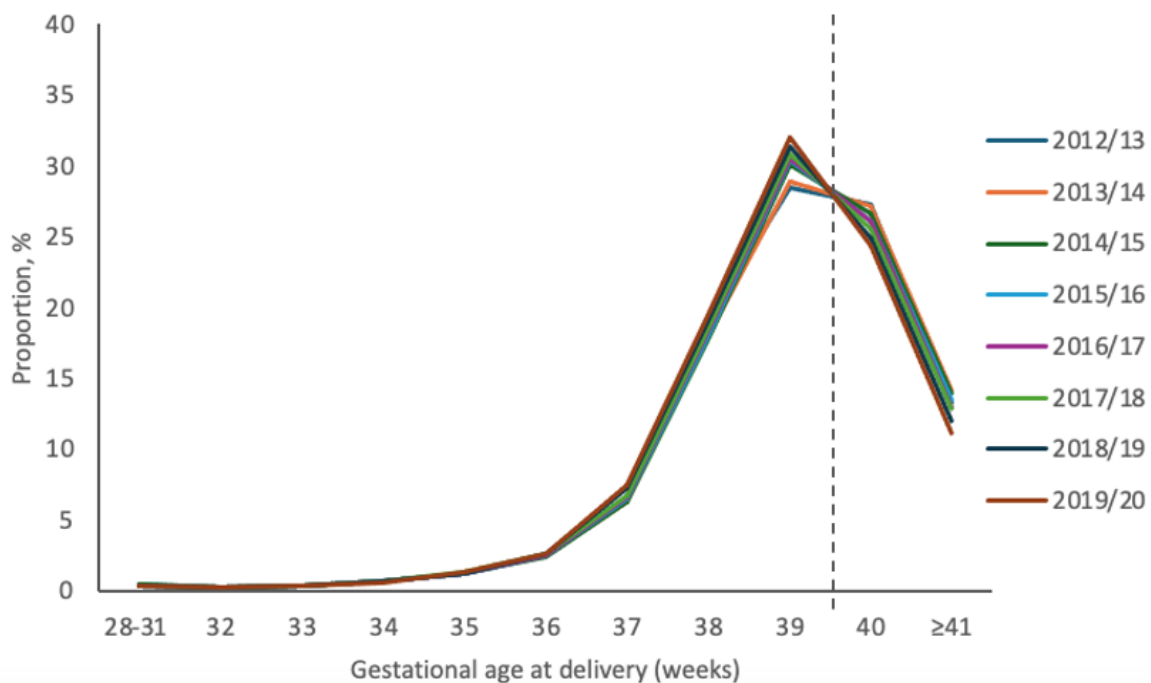
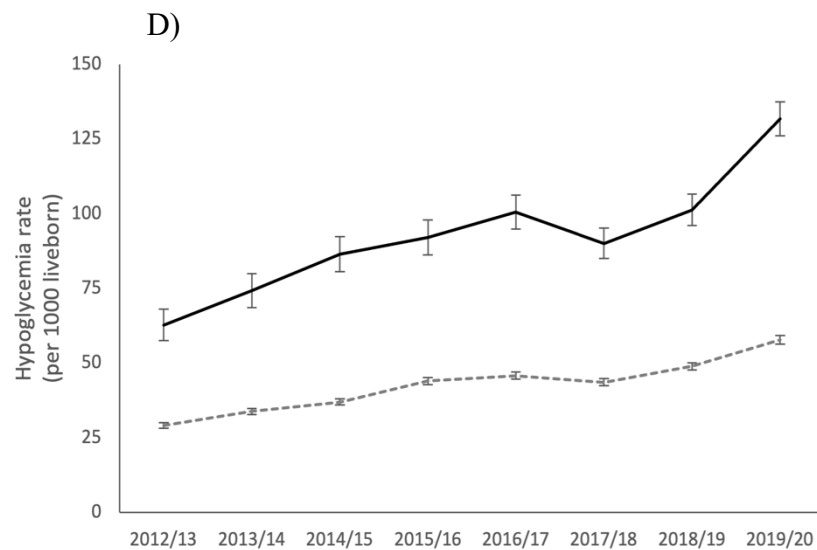
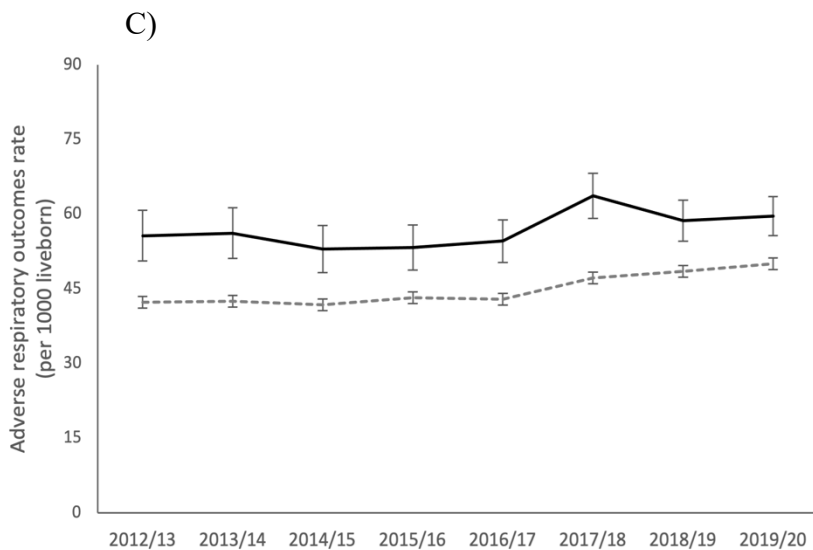
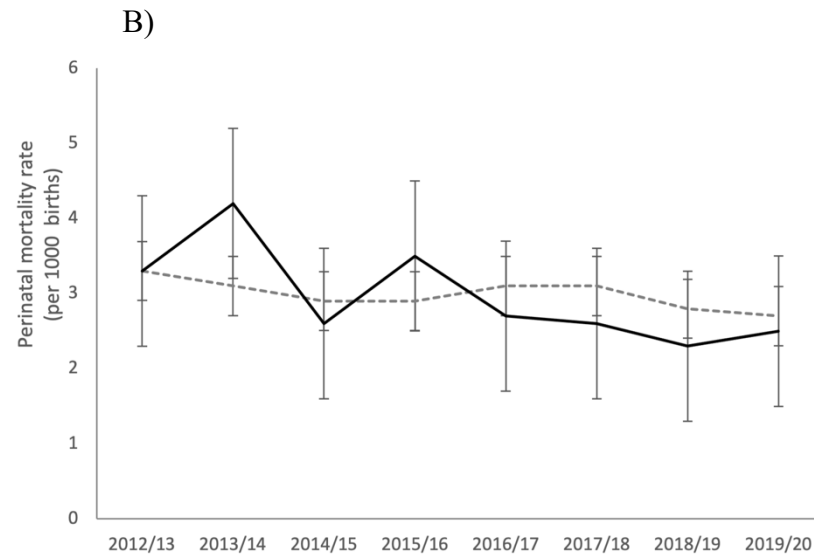
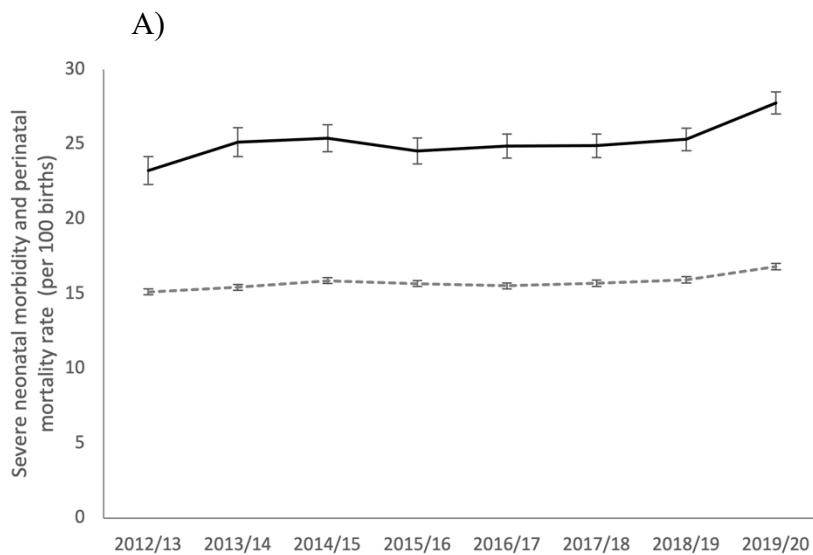
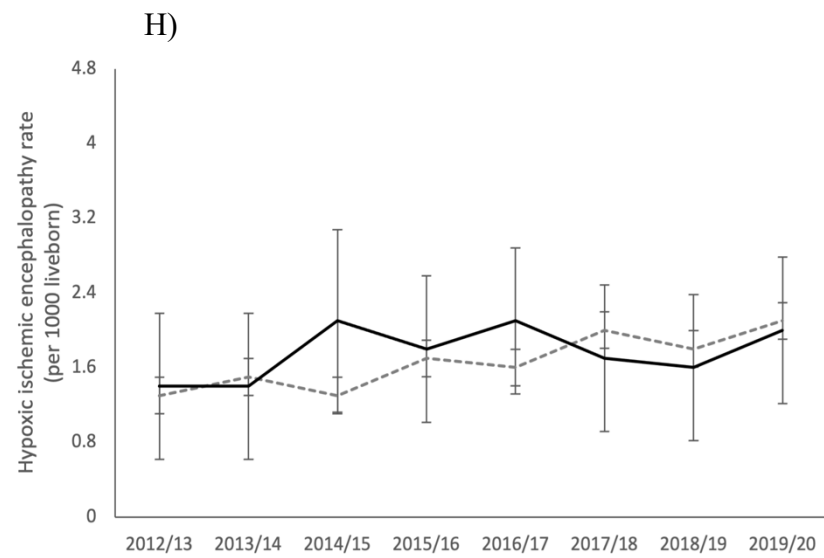
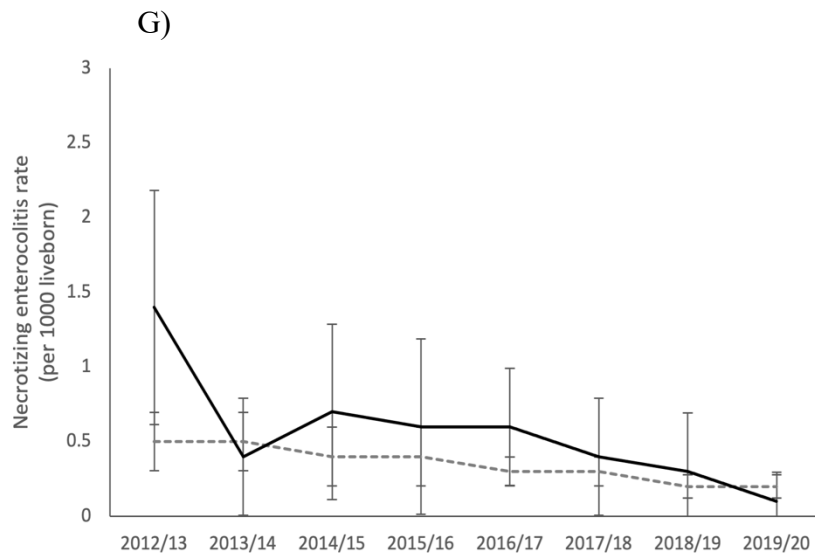
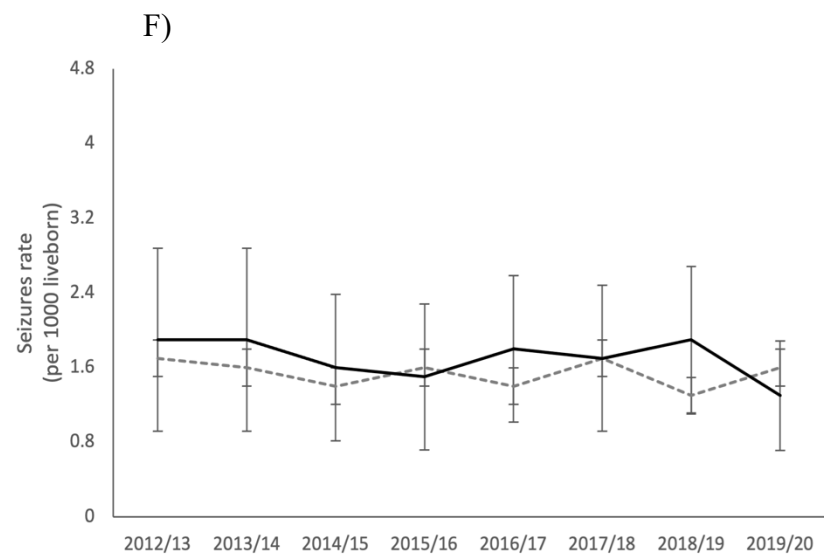
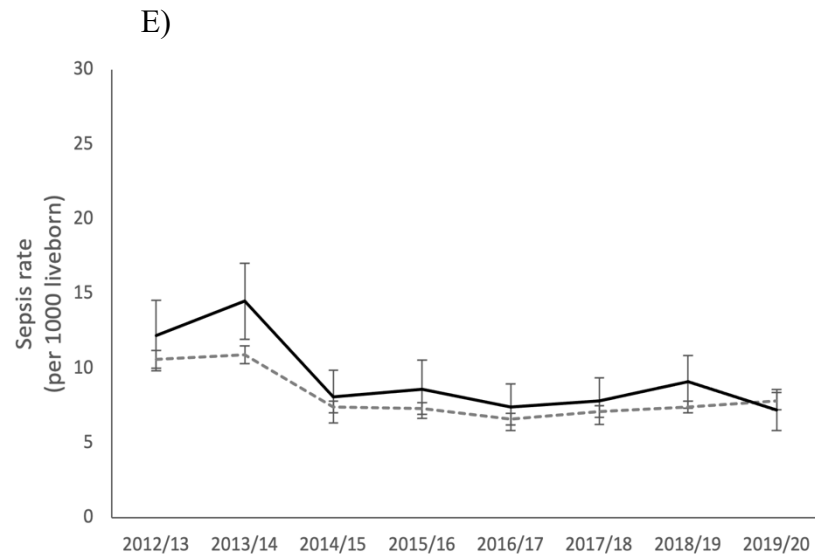
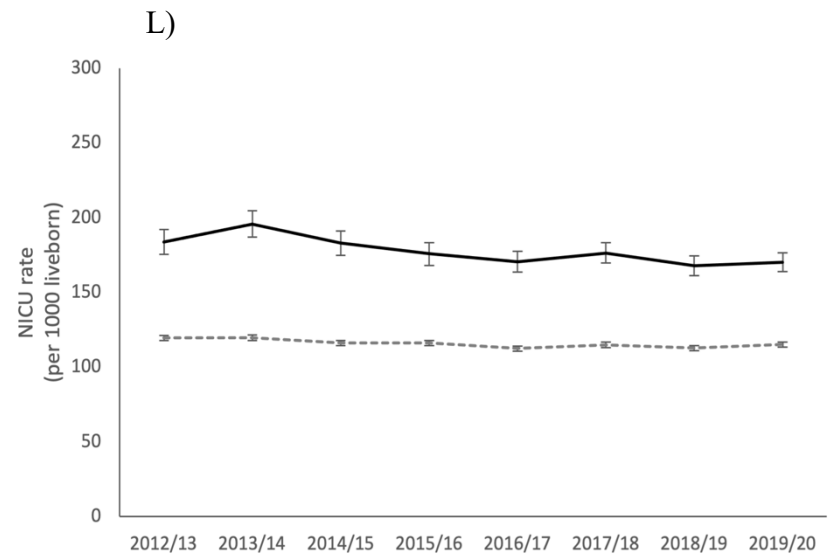
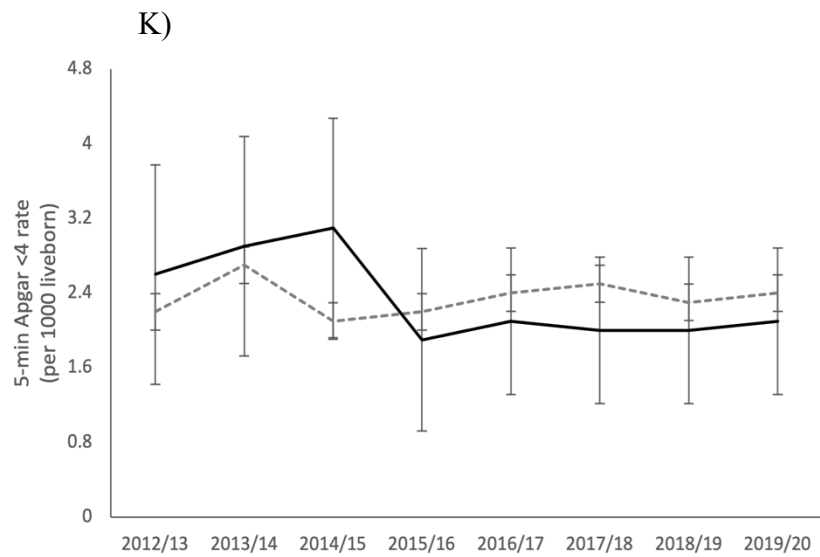
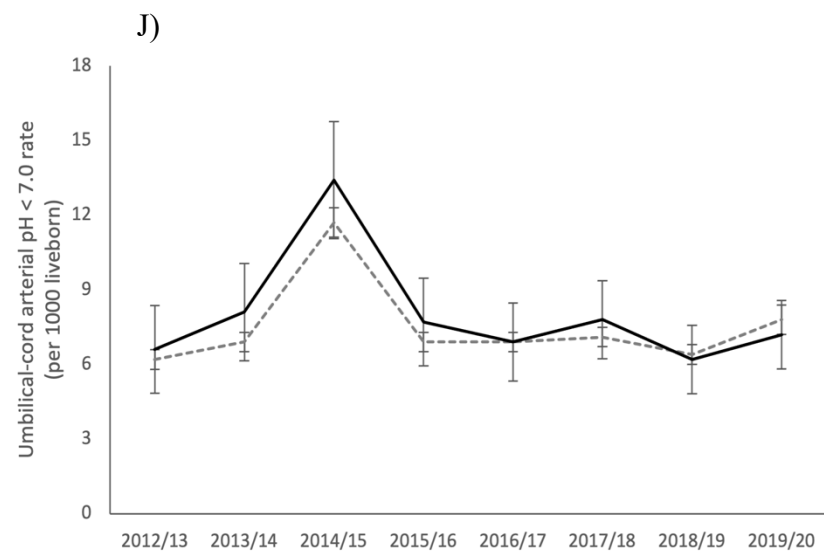
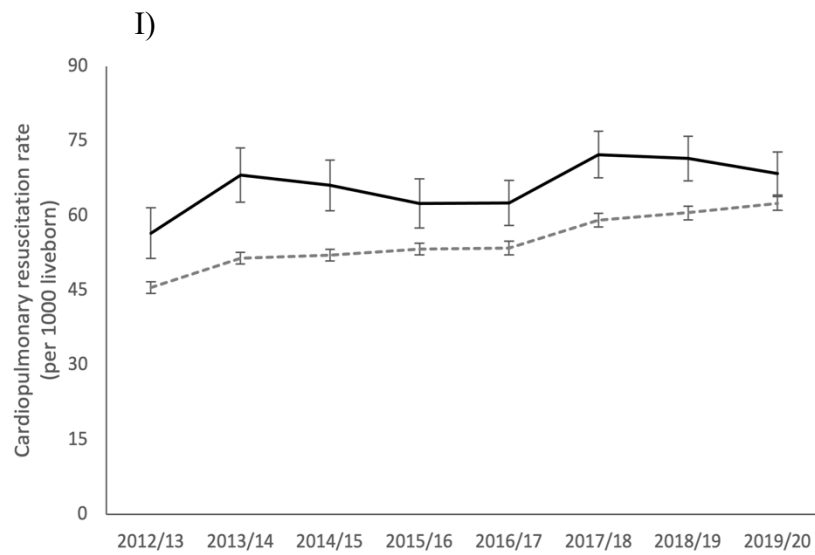


Figure 6.1 Distribution of gestational age at delivery among A) pregnancies with GDM and B) pregnancies without GDM, in Ontario, Canada, fiscal years 2012/13-2019/20 ^a

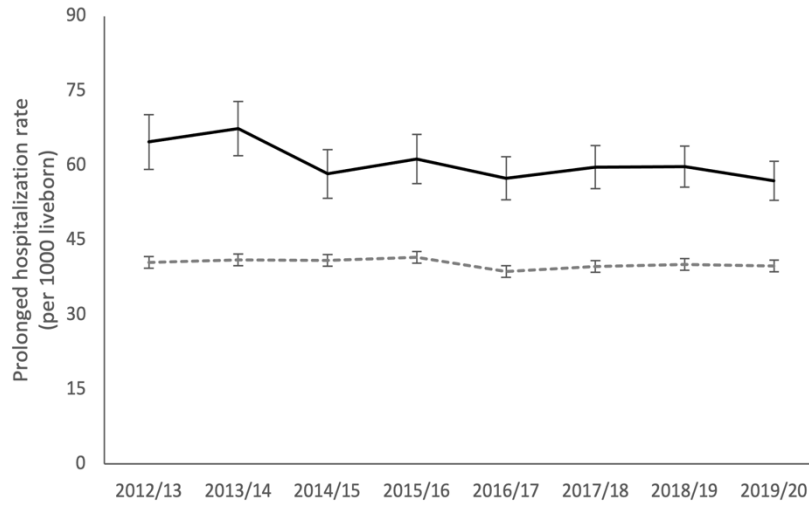
^a Vertical dash lines were median gestational age at birth among pregnancies with and without GDM over the entire study period.



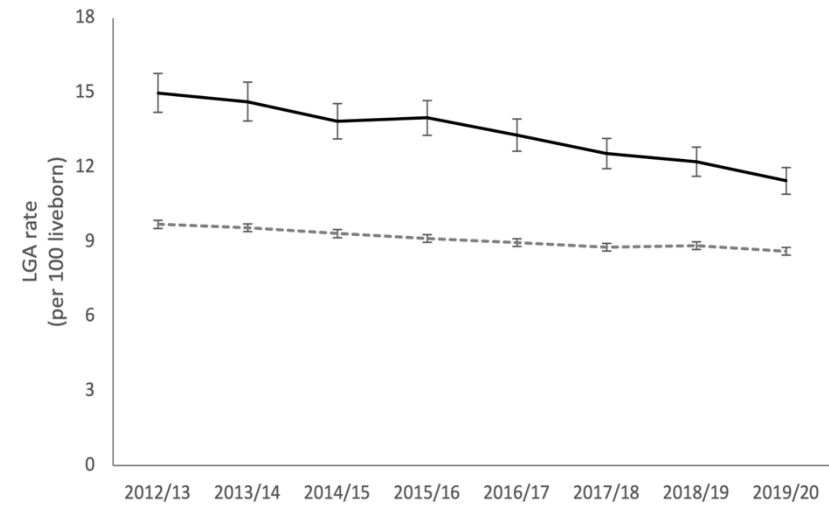




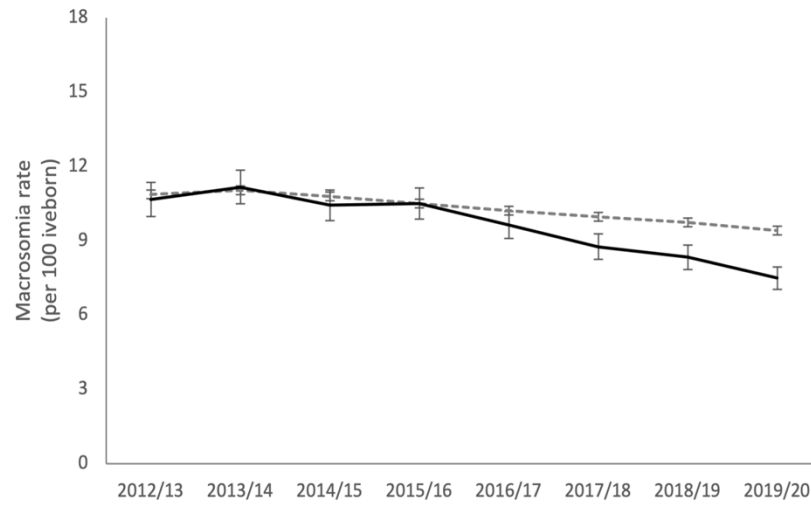
M)



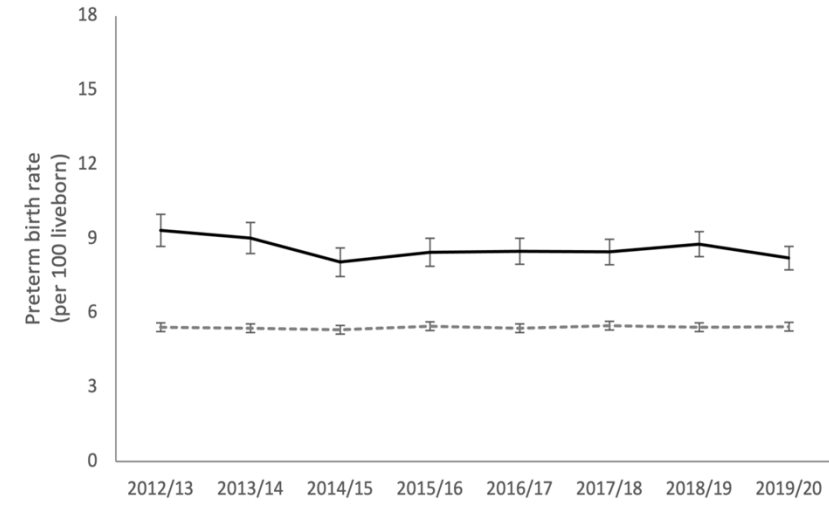
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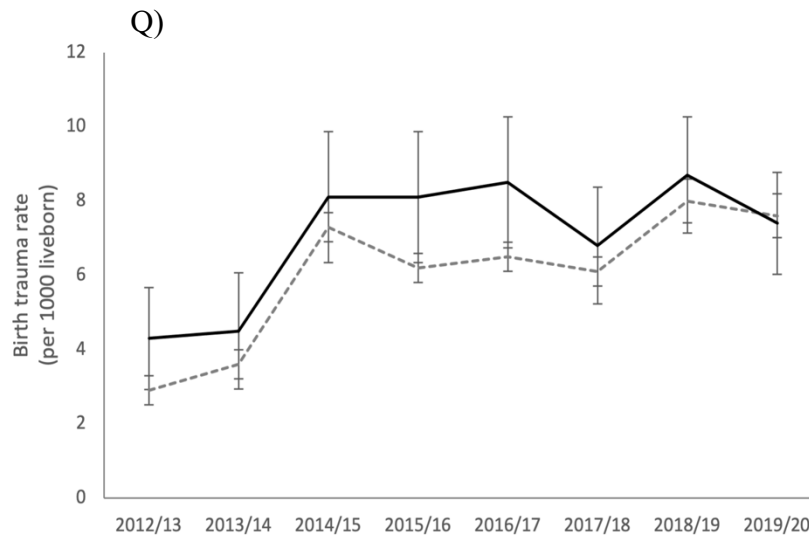


Figure 6.2 Rates of adverse neonatal outcomes A) Severe neonatal morbidity and mortality (SNM); B) Perinatal mortality; C) Adverse respiratory outcomes; D) Hypoglycemia; (E) Sepsis; (F) Seizures; (G) Necrotizing enterocolitis; (H) Hypoxic ischemic encephalopathy; (I) Cardiopulmonary resuscitation or ventilation support; (J) Umbilical-cord arterial pH < 7.0; (K) 5-min Apgar <4; (L) NICU admission; (M) Prolonged hospitalization; (N) LGA; (O) Macrosomia; (P) Preterm birth; (Q) Birth trauma in singleton hospital deliveries in Ontario, Canada, fiscal years 2012/13-2019/20 ^a

^a Crude rate of adverse neonatal outcomes per 100 (1000) gestational diabetic (solid line) and non-gestational diabetic deliveries (dash line).

Comparison of Associations of GDM and Adverse Neonatal Outcomes

We compared the association between GDM and adverse neonatal outcomes by time periods of delivery (Figure 6.3 and Table S5). The association between GDM and overall SNM remained stable in the two time periods; pregnancies with GDM had 1.5 times the risk of SNM compared to those without GDM (2012/13-2015/16: 1.50, 95% CI [1.48, 1.52] and 2016/17-2019/20: 1.54, 95% CI [1.52, 1.56]). Among individual outcomes of the SNM composite, the excess risk of adverse respiratory outcomes, hypoglycemia, and prolonged hospitalization for GDM pregnancies, compared to non-GDM pregnancies, was consistent in both time periods. Despite evidence supporting statistically significant multiplicative interaction for cardiopulmonary resuscitation or ventilation support (P for interaction=0.01), there were no qualitative differences in the magnitude of the adjusted RRs between the two time periods (2012/13-2015/16: 1.19, 95% CI [1.14, 1.24] and 2016/17-2019/20: 1.13, 95% CI [1.09, 1.17]). Similarly, the strength of the association between GDM and NICU admission was similar across time periods (2012/13-2015/16: 1.47, 95% CI [1.44, 1.50] and 2016/17-2019/20: 1.42, 95% CI [1.39, 1.45]). For perinatal mortality, newborn sepsis, confirmed seizures, hypoxic ischemic encephalopathy, umbilical-cord arterial PH<7, and 5-min Apgar <4, both associations with GDM were not statistically significant in either time period; however, for each of these outcomes, the magnitude of the association was lower in the later time period.

With regards to the other secondary outcomes, tests of interaction in the associations of GDM with preterm birth and birth trauma were not statistically significant, and both effect estimates remained relatively stable between the two periods. However, the strength of the association between GDM and LGA was attenuated in the latter period (2012/13-2015/16: 1.42, [95% 1.39,

1.45] and 2016/17-2019/20: 1.31, [95% CI 1.28, 1.34]; P for interaction <0.001). Similarly, the adjusted RR for macrosomia showed a significant reduction for pregnancies with GDM relative to no GDM, with a protective relationship of GDM and macrosomia in the latter period (2012/13-2015/16: 0.98, 95% CI [0.95, 1.02] and 2016/17-2019/20: 0.86, 95% CI [0.83, 0.90]; P for interaction <0.001).

The comparisons in the RDs between GDM and adverse neonatal outcomes in the two time periods of delivery were generally similar to the RRs (Table S5-S6). Interestingly, the excess number of infants with composite SNM increased slightly for GDM pregnancies, compared with non-GDM pregnancies, from 8.05% (95% CI 7.57%, 8.52%) in 2012/13-2015/16 to 8.82% (95% CI 8.41%, 9.23%) in 2016/17-2019/20, which was mainly due to the increase in infants with hypoglycemia. There was a decrease in 2016/17-2019/20 in the excess number of infants who were admitted to NICU (2012/13-2015/16: 57.8‰, 95% CI [53.6‰, 62.0‰] and 2016/17-2019/20: 49.1‰, 95% CI [45.7‰, 52.6‰]), had LGA (2012/13-2015/16: 4.41%, 95% CI [4.03%, 4.80%] and 2016/17-2019/20: 3.10%, 95% CI [2.79%, 3.41%]), and had macrosomia (2012/13-2015/16: -0.33%, 95% CI [-0.67%, 0.02%] and 2016/17-2019/20: -1.48%, 95% CI [-1.75%, -1.21%]) for GDM relative to no GDM.

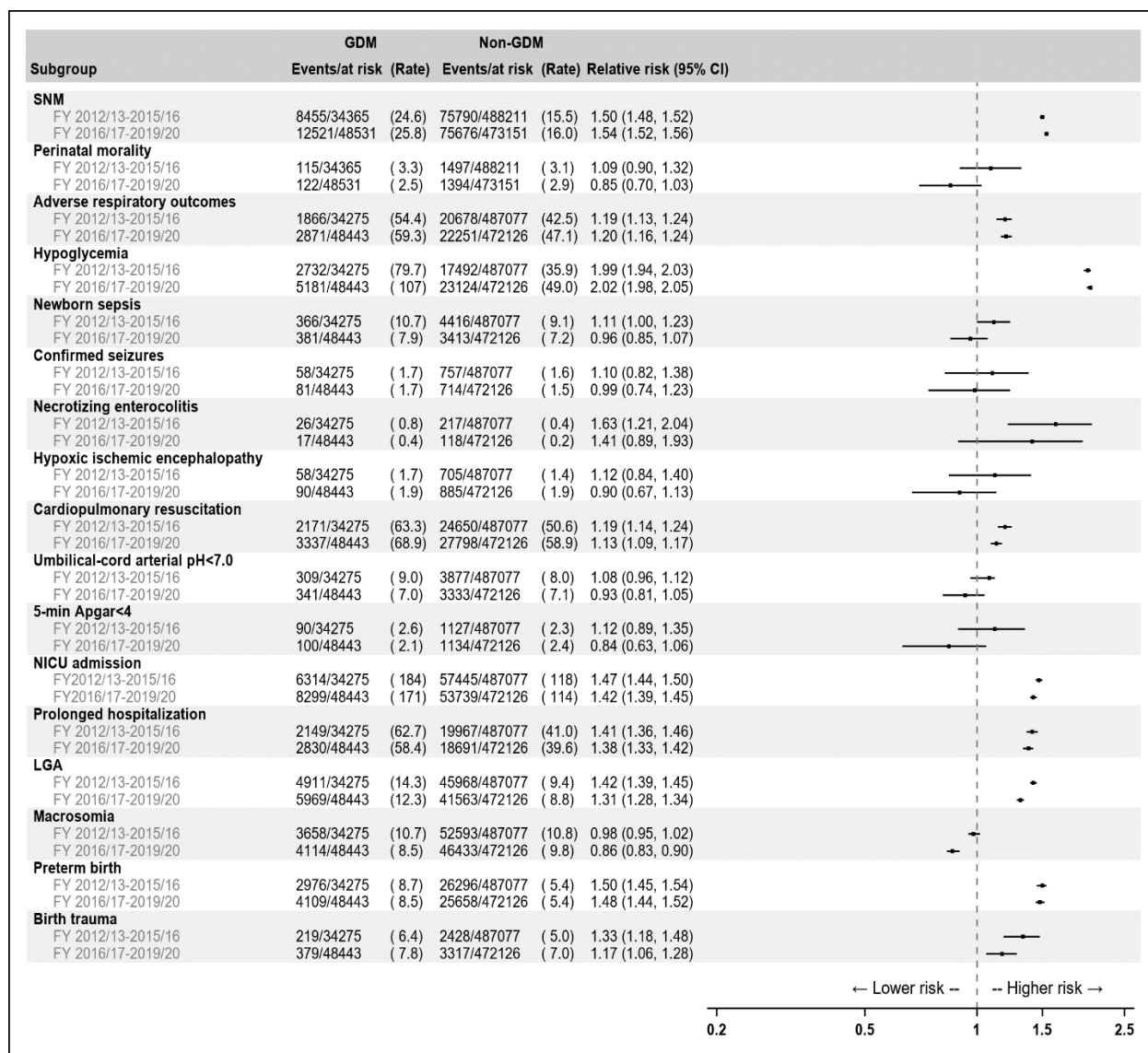


Figure 6.3 Association of gestational diabetes and adverse neonatal outcomes among singleton deliveries in Ontario, Canada, stratified by time periods of delivery (N= 1 044 258) ^{a,b}

^a Rates for each component outcome of SNM and birth trauma were expressed as per1000 deliveries, all other outcomes were expressed as per 100 deliveries; ^b Relative risk was an adjusted relative risk comparing pregnancies with GDM vs. no GDM, which was generated by multivariable regression models using imputed datasets, with adjustment for maternal age at delivery, neighbourhood-level income, neighbourhood-level education, parity, race/ethnicity, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex.

Sensitivity Analyses

Complete-case analysis after removing observations with missing information for covariates yielded generally comparable conclusions for neonatal outcomes over time among pregnancies with and without GDM, as did limiting to pregnancies with pregnancy induced hypertension. Similar findings in the differences of associations of GDM and adverse neonatal outcomes across time periods were also observed by excluding multiple deliveries to the same individuals and GDM cases requiring medical treatments, although the effect estimates of the SNM composite were slightly lower than the main results (Table S7-S10).

6.6 Discussion

In this large population-based cohort study, we observed an increase in GDM rates over the 8-year period in Ontario, Canada. Importantly, despite this increase, the magnitude of the association between GDM and overall SNM remained stable. We observed significant decreases in the magnitude of the association between GDM and both LGA and macrosomia in 2016/17-2019/20 relative to 2012/13-2015/16; however, there were no significant changes in associations of GDM with other individual neonatal outcomes between the two time periods.

Interpretation

Our results are similar to findings of previous studies conducted in Canada and European countries assessing the trends of GDM and neonatal outcomes in earlier periods.^{6,19,20} The excess risk of severe neonatal morbidity and mortality outcomes was not increased in recent years in our study, despite the increasing rate of GDM, which might have reflected the GDM diagnosis by strict criteria and improvement in perinatal health care for GDM pregnancies. Although ongoing global debates continue around when and how to screen and diagnose GDM, several studies have compared birth outcomes of GDM diagnosed by different glucose values. They found that untreated mild GDM identified using the IADPSG criteria had a similar risk of severe neonatal morbidity and mortality compared to normal pregnancies and a lower risk than that of treated GDM identified using other criteria.^{206,207} Advances in clinical management including glucose monitoring, glycemic targets and treatment patterns over time might be another contributing factor to this observation. It has been shown that diagnostic OGTT values were not the most reliable predictors of outcomes but glucose control is closely related to neonatal outcomes.²⁰⁸ Despite no clearly established thresholds for optimal glucose control, tighter glycaemic targets

and stably optimal glycemic control trajectories among GDM pregnancies are associated with a lower risk of serious neonatal morbidity.^{192,209,210}

Contradictory to our findings, an earlier population-based, retrospective study in Canada by Feig et al. reported no change of perinatal mortality among infants born to GDM pregnancies between 1996 and 2010, and GDM had a consistently lower risk of perinatal mortality compared to no GDM.⁷ Similarly, one nationwide cohort study in Sweden reported no change in perinatal mortality for GDM pregnancies but a small decrease in non-GDM pregnancies from 1998 and 2012.¹⁸ The variable findings between studies may be partly due to differing rates of obesity, which is an independent risk factor for perinatal mortality,²¹¹ and the low rate of GDM due to the low sensitivity of the screening and diagnostic strategies used during different periods and countries.^{10,18,197}

We found that hypoglycemia rate increased for all infants, especially for infants born to mothers with GDM in our study, despite the association between GDM and hypoglycemia remained stable. We speculate that such increase in hypoglycemia might be due to the better ascertainment in clinical practice, or the shifts in diagnostic definitions with inclusion of neonates with less severe hypoglycemia.

Our results, that macrosomia and LGA rates reduced more pronouncedly in GDM pregnancies than in their counterpart and the strength of the associations were attenuated in the latter time period, was similar to previous studies.^{18,105} Although infant size at birth has been reported downward trends in the US and elsewhere, reasons for this decline are not fully understood but may be linked to shortened gestational length, improved care for fetal growth, and changes in socio-environmental factors.^{212,213} Advances in antenatal fetal surveillance and ultrasounds

diagnostics and concomitantly wide use of obstetric interventions for earlier delivery of GDM pregnancies may account for the decreases in macrosomia and LGA.^{131,214} Additionally, treatment of mild GDM identified using the new strict cut-offs could benefit excessive fetal growth, which is closely associated with hyperglycemia.²¹⁵ Several studies have found that untreated GDM diagnosed by the IADPSG criteria had higher birthweight than normal pregnancies, and treatment of mild GDM reduced LGA and macrosomia.^{215–217} However, contradictory results have been reported where no significant changes or even increased in birth weight for GDM pregnancies over time, which may be caused by small sample size and residual confounding.^{19,20}

Strengths and Limitations

The main strength of this study was the large, racially diverse obstetric population. This large sample size allowed us to evaluate various adverse neonatal outcomes over time in pregnancies with and without GDM. By linking the provincial birth registry with population-level health administrative databases, we were able to improve ascertainment of GDM and outcomes, thereby reducing potential information bias. Additionally, the BORN Ontario includes extensive data on maternal demographic and pre-existing health conditions as well as obstetrical and prenatal health information which allowed us to adjust for a range of important confounders. The proportion of missing data was low for most covariates, and multiple imputation was used to address missing data to further reduce any potential confounding bias associated with missing information.

Nonetheless, our study has limitations, mainly due to the use of health administrative databases for population-based research.²¹⁸ First, although we identified GDM cases based on BORN

Ontario and delivery hospitalization records, the number of GDM-affected pregnancies might be underestimated since cases diagnosed in outpatient clinics during pregnancy and not documented on the delivery record were not have been identified.²¹⁹ Additionally, due to diagnosis coding errors or imperfect algorithm accuracy, some non-differential misclassification may be present in exposure and/or outcomes, resulting in bias towards the null. Second, due to the less comprehensive data collected in health administrative datasets and retrospective nature, our study may be subject to residual confounding, particularly by factors such as health behaviors, individual-level socioeconomic status and glycosc control. As socioeconomic marginalization and poor health behaviors might be linked with elevated risk of high BMI and excessive weight gain during pregnancy, the potential direction of this residual confounding could have biased the results away from the null. Although history of GDM as one of potential confounder was unavailable in the current analysis, we conducted a sensitivity analysis among individuals with a first delivery and found similar results. Given the lack of data on glucose control and compliance with offered treatments among women with GDM, we cannot rule out that it could affect results and possibly explain changes in adverse outcomes over time. Third, screening and diagnostic criteria have evolved over time in Canada. Unfortunately, given that the current study only included data from 2012 to 2020, it lacked a comprehensive historical context on the evolution of GDM and limited us to assess the long-term trends of GDM and the associated impacts on adverse neonatal outcomes. Lastly, no details regarding the specific diagnostic cut-offs for GDM nor glucose control status were available. Therefore, more mild hyperglycemic cases with a potentially better glycemic control in the latter relative to early period were likely included in our study, which might attenuate the observed impact of the increasing GDM on adverse neonatal outcomes. The findings in our study must be interpreted cautiously and may not be generalizable

to other settings considering no unified standard method exists worldwide, and screening and diagnostic practices and obstetric management for GDM are likely to vary between countries.

6.7 Conclusions

The rate of GDM increased substantially from 2012 to 2020 in Ontario, Canada. This recent increase was, however, not associated with increased risks of adverse neonatal outcomes.

Although the overall rate of SNM increased in the population over the study period, the risk of SNM for GDM compared to no GDM remained stable. The strength of the association between GDM and LGA or macrosomia decreased over time, with no significant changes in associations of GDM with other individual neonatal outcomes. Considering the serious nature and relatively high rates of adverse outcomes in GDM pregnancies, it is critical to prioritize improvements in periconceptional, obstetrical, and neonatal care to address disparities between pregnancies with and without GDM. Meanwhile, future large studies are warranted to more robustly investigate the impact of the increasing GDM trend on adverse neonatal outcomes. Efforts to refine and prioritize diagnostic criteria for sufficiently identifying clinically significant GDM cases should also be enhanced.

Declarations

Ethics approval and consent to participate

Ethics approval for this study were granted by the Ottawa Health Science Network Research Ethics Board (20210400-01H) and the University of Ottawa Research Ethics Board (H-03-21-6792). Individual patient consent was waived by the Ottawa Health Science Network Research

Ethics Board for this study as it involved the secondary use of databases held by BORN Ontario. BORN Ontario, as a prescribed registry under the province's Personal Health Information Protection Act, 2004A, can collect, use and disclose personal health information without patient consent for the purpose to facilitate and improve perinatal care in Ontario, Canada. All data management and analyses for this study were conducted within BORN's secure environment and followed all institutional security and privacy protocols and policies.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

During the conduct of this work, DBF was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute. Although she maintains adjunct appointments at both institutions, she is now employed by Pfizer in an unrelated area. All other authors have no potential competing interests to declare.

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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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Additional files for Chapter 6 can be found in Appendix D

Additional file 1:

Screen shot of revision letter from BMC Pregnancy and Childbirth

Additional file 2:

Table S1. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code outcomes

Additional file 3:

Table S2. RECORD checklist

Additional file 4:

Table S3. Distribution of GDM among singleton hospital deliveries in Ontario, Canada, FY 2012/13-2019/20 (N= 1 044 258)

Additional file 5:

Table S4. Trends of gestational-age adjusted rate of adverse neonatal outcomes among deliveries with and without GDM in Ontario, Canada, fiscal years 2012/13-2019/20

Additional file 6:

Table S5. Interaction tests of GDM with time periods of delivery on adverse neonatal outcomes, Ontario, Canada, fiscal years 2012/13-2019/20

Additional file 7:

Table S6. Risk difference in adverse neonatal outcomes among women with GDM and non-GDM in Ontario, Canada, by time periods of delivery (N=1 044 058)

Additional file 8:

Table S7. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery in complete-case analysis (n=732 870)

Additional file 9:

Table S8. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women with first delivery (n=759 458)

Additional file 10:

Table S9. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women without GH (n= 987 567)

Additional file 11:

Table S10. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women without medical treatments for GDM (n=1 014 228)

Additional file 12:

Figure S1. A directed acyclic graph (DAG) of causal assumptions for the association between GDM and adverse neonatal outcomes

Chapter 7. Comparison of Adverse Maternal and Perinatal Outcomes between Induction and Expectant Management among Women with Gestational Diabetes Mellitus at Term Pregnancy: A Systematic Review and Meta-analysis (Manuscript)

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7.1 Title Page

Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with gestational diabetes mellitus at term pregnancy: A systematic review and meta-analysis

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7.2 Abstract

Background Induction at 38-40 weeks of gestation has been broadly suggested for women with gestational diabetes mellitus (GDM), yet its benefits and risks remain unclear. This study aimed to systematically review and meta-analyze existing evidence on the effect of induction at term gestation among women with GDM.

Methods We searched MEDLINE, EMBASE, Cochrane Libraries, and Web of Science from inception to June 2021. We included randomized controlled trials (RCTs) and observational studies comparing induction with expectant management among GDM term pregnancies. Primary outcomes included caesarean section (CS) and macrosomia. All screening and extraction were conducted independently and in duplicates. Meta-analyses with random-effects models were conducted to generate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) using the Mantel-Haenszel method. Methodological quality was assessed independently by two reviewers using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

Results Of the 4,791 citations, 11 studies were included (3 RCTs and 8 observational studies). Compared to expectant management, GDM women with induction had a significantly lower odds for macrosomia (RCTs: 0.49 [0.30, 0.81]); observational studies: 0.64 [0.54, 0.77]), but not for CS (RCTs: 0.95 [0.64, 1.43]); observational studies: 1.03 [0.79, 1.34]). Induction was associated with a lower odds of severe perineal lacerations in observational studies (0.59 [0.39, 0.88]). No significant difference was observed for other maternal or neonatal morbidities, or perinatal mortality between groups.

Conclusions For GDM women, induction may reduce the risk of macrosomia and severe perineal lacerations compared to expectant management. Further rigorous studies with large sample sizes are warranted to better inform clinical implications.

Keywords

Gestational diabetes mellitus (GDM), term pregnancy, induction, expectant management, caesarean section, macrosomia

7.3 Background

Gestational diabetes mellitus (GDM), characterized as any carbohydrate intolerance with first detection during the late second trimester of pregnancy,²²⁰ has been considered one of the most common pregnancy disorders. Globally, GDM affects 7-10% of all pregnancies, depending on the screening and diagnostic criteria and population profile.²²¹ Although GDM mostly resolves after pregnancy, it imposes an increased risk of adverse outcomes in the short- and long-term, including gestational hypertensive disorders, macrosomia, postpartum type 2 diabetes and cardiovascular disorders for the mother and their offspring.^{2,3,222}

Induction of labour (IOL) has been increasing steadily and approximately 25% of labors are induced in high-income countries.²²³ An increase in induction at term without clinically-accepted indications—termed “elective induction”—appears to be an important contributor to the overall upward trend.²²⁴ Currently, IOL has been broadly suggested for GDM term pregnancies from different professional societies and institutions to improve pregnancy outcomes, despite inconsistent recommendations for timing of induction.^{23–25,78} In Canada, the Society of Obstetricians and Gynaecologists of Canada (SOGC) and Diabetes Canada (DC) recommend offering IOL between 38 and 40 weeks for GDM pregnancies.^{23,78} While in the UK, the National Institute for Health and Care Excellence (NICE) recommends IOL by the 40th week,²⁵ and in the US, the American College of Obstetricians and Gynecologists (ACOG) recommends induction between 39 and 40 weeks for well-controlled GDM pregnancies.²⁴ However, the majority of these recommendations were reached by expert consensus and few were supported by high-quality studies.

There is a paucity of systematic reviews of studies on induction in GDM women, and thus the benefits and risks of induction remain unclear. Previous studies assessing the effect of IOL yielded inconsistent results due to variations in population profile, diagnostic criteria of GDM, comparators and other methodological issues.^{28,30,225} The only three systematic reviews published to date comparing induction versus expectant management in GDM term pregnancies also reported conflicting results, without firm conclusions.^{35,36,226} The inconsistencies are most likely attributed to the differences in data sources and search strategy, inclusion and exclusion criteria, small number of studies and high heterogeneity, and low data quality.

To address this knowledge gap, our systematic review and meta-analysis was conducted to update the evidence pertinent to the benefits and risks of induction versus expectant management for women with GDM, and to explore the potential sources of heterogeneity underlying the inconsistent findings.

7.4 Methods

This systematic review was performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA 2020 statement).²²⁷ This study had no patient or public involvement and data were collected from existing literature, therefore, no ethical approval was required. The study protocol was registered on PROSPERO before starting the review (CRD#42021256268).²²⁸

Searching Strategy and Selection Criteria

We undertook a comprehensive literature search using electronic and manual searching. Four electronic databases, Ovid-MEDLINE (1946 – 2021 June), Ovid-EMBASE (1947 - 2021 June), Cochrane Libraries (inception - 2021 June), and Web of Science (inception - 2021 June), were systematically searched. An initial search strategy was developed in MEDLINE using Medical Subject Headings (MeSH) terms and text words related to the population and exposures of interest in consultation with a professional medical librarian and adapted for the other databases (Appendix S1). The reference lists of all identified articles were examined for potentially additional references. We also searched the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov to identify any ongoing or unpublished trials.

Criteria to identify eligible studies for the current review were guided by the PICOS (Population-Intervention-Comparators-Outcomes-Study design) framework. Studies were considered eligible if: (1) using experimental [i.e. randomized clinical trial (RCT)] or comparative observational (i.e. prospective or retrospective cohort, case-control) study designs; (2) the study comprised women who had a singleton term pregnancy (≥ 37 weeks) and were diagnosed with GDM in the index pregnancy; (3) they compared induction with expectant management; and (4) they addressed any

of the maternal and neonatal outcomes. The primary outcomes comprised: CS and macrosomia (birthweight $\geq 4,000$ grams, or as defined by study authors), while secondary outcomes included: instrumental vaginal delivery (by forceps or vacuum), severe perineal lacerations (third- and fourth-degree perineal tears), intensive care unit (ICU) admission, large-for-gestational-age (LGA) neonates (birthweight higher than the 90th percentile for the same gestational age and sex, or as defined by study authors), shoulder dystocia (delivery requiring additional obstetric manoeuvres to release infant's shoulder after failure of gentle downward traction), neonatal intensive care unit (NICU) admission, 5-min Apgar score < 7 , neonatal acidemia (umbilical cord artery PH < 7 and/or a base deficit > 12 mmol/l, or as defined by study authors), and perinatal mortality (intrauterine fetal death and neonatal death within 28 days following livebirth, or as defined by study authors). For studies involving diabetic pregnant women, if there was no distinction between diabetes types, or less than 90% of subjects had GDM but without subgroup analysis by diabetes type, they were ineligible. Studies published as conference abstracts were deemed eligible if there were sufficient information for data extraction and quality assessment. Narrative reviews, protocols, commentary and correspondence were excluded. Finally, we excluded studies not published in English or if they used a clinically improper comparison including using inappropriate intervention or comparator (e.g. spontaneous vaginal delivery, induction at a later gestational week).

We imported all search records into Mendeley citation manager to remove any duplicates; remaining records were then imported into Covidence for screening. All screenings (title/abstract and full-text reviewing) were conducted independently and in duplicates by two reviewers (R.L. and W.W.). Any disagreement was resolved by discussion with a third reviewer (S.W.W.).

Data Extraction and Risk of Bias Assessment

Two reviewers (R.L. and W.W.) independently extracted the following data into a standard and prespecified form on Microsoft Excel spreadsheet in a duplicate manner: author and publication year, journal, country, study period, study design, population demographics, GDM diagnostic criteria, GDM treatment/subtype, inclusion/exclusion criteria, sample size, definition and ascertainment of interventions and outcomes, number of events, crude and/or adjusted relative effect estimates (relative risk [RR] or odds ratio [OR]) with 95% confidence intervals (CIs) and adjusted variables. Where available, data were also abstracted on induction methods and timing. When the impact of induction was assessed by multiple gestational weeks, only the results of induction at 38 weeks were extracted. The original authors were contacted for further details and clarity when needed.

The methodological quality of each study was independently assessed by two reviewers (R.L. and W.W.) according to the study design. Specifically, RCTs were assessed using the Cochrane Risk of Bias Tool²²⁹ to classify RCTs as having a low, unclear or high risk of bias. The observational studies were assessed using the Newcastle-Ottawa Scale (NOS)²³⁰ to classify the studies as being of poor, fair or good quality. Additionally, the overall quality of evidence for all outcomes across studies was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach²³¹ and rated as very low, low, moderate or high in terms of risk of bias, inconsistency, imprecision and indirectness by the GRADEPro Guideline Development Tool (GDT).

Data Synthesis and Analysis

Data extracted from included studies were compiled into 2X2 tables which consisted of the numbers of events and non-events in intervention and comparison groups. All analyses were

completed in RevMan (version 5.4). Original studies with similar outcomes were pooled together and the 2X2 tables were used to calculate the crude ORs. For studies without explicit event data, we estimated the absolute numbers according to the reported percentages. If no event was recorded in one group, we applied a fixed correction using the default value of 0.5 to each cell of the 2X2 tables to avoid division by zero; if no events were presented in both groups, we excluded those studies from pooled analysis for specific outcomes.

Similarity across studies was assessed in terms of clinical heterogeneity (e.g., clinical characteristics), methodological heterogeneity (e.g., study design) and statistical heterogeneity.²³² We used the I^2 statistic to quantify the magnitude of statistical heterogeneity and high statistical heterogeneity was considered if I^2 was $>75\%$.

Meta-analyses were performed when outcome-specific studies were sufficiently similar in terms of statistical heterogeneity (i.e. $I^2 \leq 75\%$). We used random-effects models with the Mantel-Haenszel method to generate the pooled ORs and 95% CIs for outcomes. We performed prespecified subgroup analyses by study design (RCT vs. observational) for all outcomes. Finally, sensitivity analyses were conducted to assess the robustness of main findings by limiting to studies with the same gestational age at induction and studies with high quality. Additionally, leave-one-out meta-analysis was conducted for cohort studies by removing one study at a time to examine the influence of each individual study on the pooled estimate for primary outcomes. Potential publication bias was assessed graphically using funnel plots.

7.5 Results

Search Results

4,789 citations were identified by bibliographic database searches and an additional two citations were identified through manual searches of related reference lists and other sources (one masters dissertation¹⁴⁴ and one conference abstract²³³). Following de-duplication, 2,920 unique records remained. Through title and/or abstract review, 2,832 records were excluded for nonrelevance or not in English. The subsequent full-text screening against prespecified inclusion criteria further excluded 77 studies, leaving 11 for this systematic review and meta-analysis (Figure 7.1).^{28–30,33,34,144,225,234–237} For the six conference abstracts included in the full-text review,^{233,238–242} we contacted the original authors for additional details, however, all were ultimately excluded due to insufficient information for data extraction and methodological appraisal.

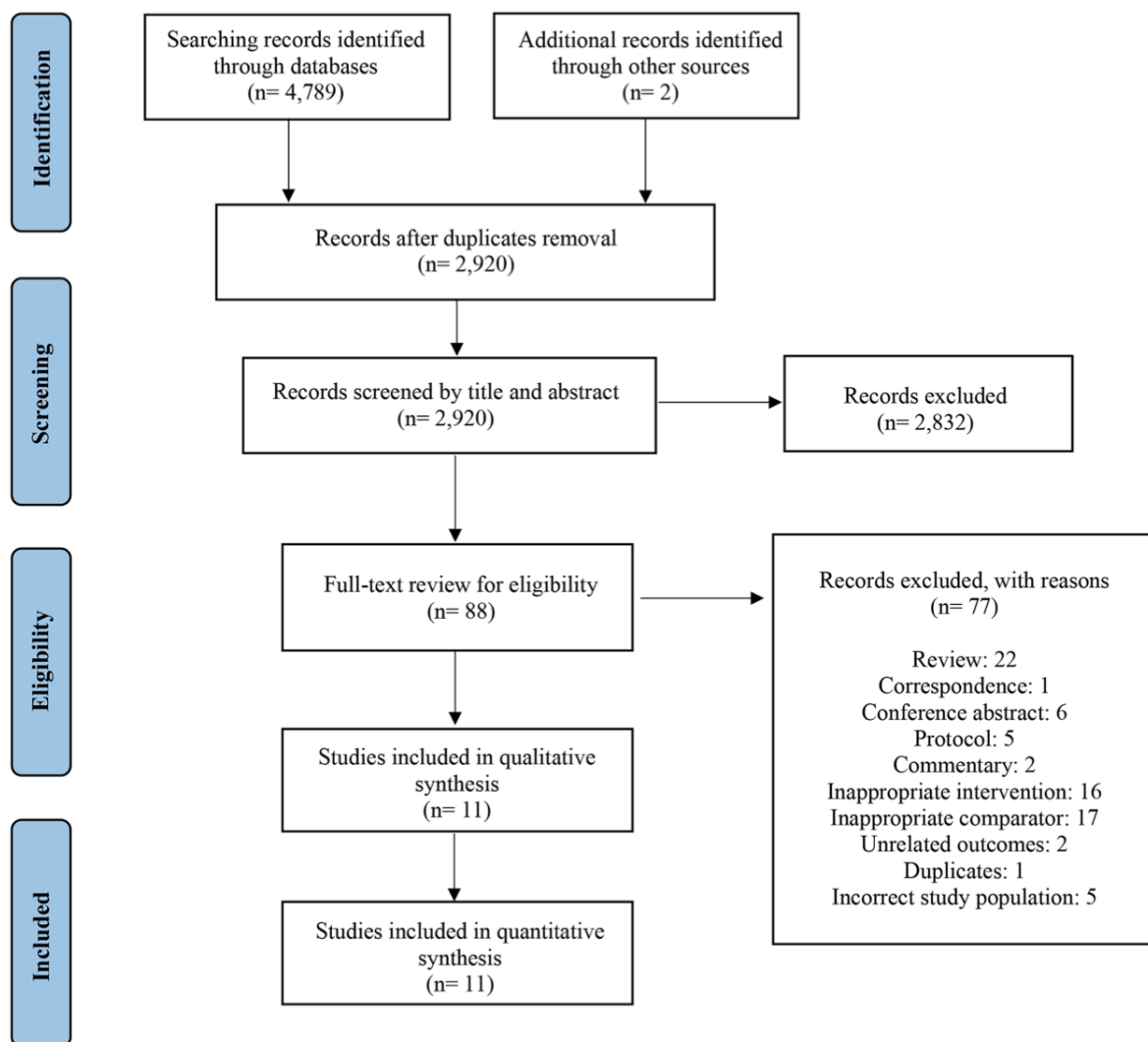


Figure 7.1 PRISMA flowchart diagram for study selection process

Study Characteristics

Descriptive information of the included studies is presented in Table 7.1 and Table S2. Eleven studies met the inclusion criteria,^{28–30,33,34,144,225,234,236,237} resulting in 3,633 GDM women delivered following induction versus 9,984 GDM women with expectant management. The

average age of participants ranged from 26 to 33 years. Studies were published between 1993 and 2019.

General Description of the RCTs

The three included RCTs were conducted in the US,²⁹ India,¹⁴⁴ and Italy,²⁸ respectively. Two were performed in a single academic medical center^{29,144} and the other in multiple centers.²⁸ GDM diagnosis in two of the trials were based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG),^{28,144} while the third didn't report the diagnostic criteria (Table S2).²⁹ Each trial used different study populations: insulin-requiring pre-gestational or GDM women,²⁹ exclusively nutrition-controlled GDM,¹⁴⁴ and women with both GDM subtypes (requiring nutrition therapy or pharmaceutical therapy).²⁸ The trials were relatively small, with sample sizes ranging from 49 to 425 participants. Risk of bias was unclear for two trials,^{29,144} and rated as high for the other (Figure. S1).²⁸

General Characteristics of the Observational Studies

The effect of IOL in GDM term pregnancies was assessed in 7 cohort studies^{30,33,34,225,235–237} and 1 secondary analysis of an RCT.²³⁴ Over half of these studies were conducted in the US,^{34,234–237} and the others in Canada,³⁰ Italy²²⁵ and Israel.³³ Of the observational studies, one included gestational and pre-gestational diabetic women,²³⁷ one only mild GDM,²³⁴ another only insulin-requiring GDM,²³⁵ and the remaining studies included both GDM subtypes.^{30,33,34,225,236} All included studies but one²³⁷ reported GDM diagnosis criteria based on a glucose challenge test (GCT) and/or oral glucose tolerance test (OGTT) (Table S2). More than half of the studies were small (<400 subjects) or medium (400-1,000 subjects) in size. Risk of bias ranged from poor to high, with overall scores of 4 to 9 on a 9-point NOS scale (Table S3).

Table 7.1 Descriptive characteristics of the individual studies meeting inclusion criteria

First author & Publication year	Country & Study period	Study design	Sample size	Inclusion/exclusion criteria	Induction		Expectant management	Outcomes	Risk of bias ^c
					Method	Timing ^b			
Alberico et al, 2017 ²⁶	Italy 2010-2014	RCT	425	GDM women with a singleton, vertex presentation, gestational age at 38-39 weeks were eligible; Patients with previous CS, Bishop score > 7 contraindications to vaginal delivery, or an EFW of > 4000 g were excluded	Dinoprostone	38	IOL at 41 ⁺⁰ weeks	CS, instrumental vaginal delivery, severe perineal tears, ICU, macrosomia, 5-min Apgar score, shoulder dystocia, NICU, perinatal mortality, neonatal acidemia	High
Kjos et al, 1993 ²⁴³	USA 1987-1991	RCT	200	Women with uncomplicated, insulin-requiring diabetes at ≥ 38 weeks and with good blood glucose control were eligible; Patients with contraindications for a trial of vaginal delivery were excluded	Oxytocin/ prostaglandin	38	IOL if EFW ≥ 4200 g or ≥ 42 weeks	CS, LGA, macrosomia, shoulder dystocia, perinatal mortality	Unclear
Singh et al, 2013 ¹⁴⁴	India 2011-2012	RCT	52	Women with GDM well controlled by medical nutritional therapy at 39-40 weeks were eligible; Contradictions to vaginal delivery, suspected EFW > 3.5 kg or < 2.5 kg, multi-gestation, non-cephalic presentation were excluded	Misoprostol/ PGE1	39	IOL ≥ 40 ^{6/7} weeks	CS, instrumental vaginal delivery, severe perineal tear, ICU NICU, macrosomia, perinatal mortality, 5-min Apgar score, neonatal acidemia	Unclear

Alberico et al, 2010 ²²⁵	Italy 1996-2006	Retrospective cohort	99	A1 and A2 GDM pregnancies with fetal growth acceleration at 38 weeks were eligible; an EFW ≥ 4250 g or presence of another indication for elective CS were excluded	PGE2	38	CS if EFW >4250 g	CS, macrosomia, NICU, shoulder dystocia, 5-min Apgar score, perinatal mortality	Low
Melamed et al, 2016 ³⁰	Canada 2012-2014	Retrospective cohort	8392	All women with diagnosed GDM who had a singleton hospital birth at ≥ 38 weeks were eligible	NR ^a	38-39	NR ^a	CS, instrumental vaginal delivery, severe perineal tear, shoulder dystocia, NICU, perinatal mortality, LGA, macrosomia	Low
Vitner et al, 2019 ³³	Israel 2007-2014	Retrospective cohort	2472	GDM women with a singleton gestation who delivered at term were eligible; women with chronic medical conditions or contraindications for a trial of vaginal delivery were excluded	NR ^a	37-40	IOL ≥ 40 weeks	CS, instrumental vaginal delivery, severe perineal tear, shoulder dystocia, perinatal mortality, LGA, macrosomia, 5-min Apgar score, acidemia, NICU	Low
Feghali et al, 2016 ³⁴	USA 2009-2012	Retrospective cohort	863	GDM women with singleton pregnancies, underwent IOL or spontaneous labor at ≥ 37 0/7 were eligible; those with a pre-labor indication for CS were excluded	NR ^a	37-39	NR ^a	CS	Low
Lurie et al, 1996 ²³⁵	USA 1983-1994	Prospective Cohort	260	All insulin-requiring gestational diabetes women were eligible; Multi-gestation, breech presentation and complications of	Balloon catheter/PGE2/oxytocin	38	IOL if EFW >4000 g	Shoulder dystocia, macrosomia, CS, instrumental vaginal delivery, perinatal mortality	High

Rayburn et al, 2005 ²³⁶	USA 2002-2004	Retrospective cohort	280	preeclampsia were excluded GDM women requiring glyburide had a hospital singleton delivery at ≥ 37 weeks were eligible; Those with indications for pre-labor CS were excluded	Oxytocin	38	IOL if ≥ 42 weeks or fetal indications	Shoulder dystocia, CS, macrosomia, perinatal mortality, 5-min Apgar score	High
Sutton et al, 2014 ³²	USA 2002-2007	Secondary analysis of RCT	679	GDM women with cephalic presentation who delivered at term following induced or spontaneous labor were eligible; those had an scheduled CS or previous CS or major fetal anomaly were excluded	NR ^a	37-40	NR ^a	CS, perinatal mortality	Low
Conway et al, 1998 ²³⁷	USA 1993-1995	Prospective cohort	2564	Gestational and pregestational diabetic patients with singleton, cephalic presentation deliveries were eligible; Deliveries before 35 weeks or with intrauterine fetal death were excluded	NR ^a	LGA but EFW < 4250 g	NR ^a	CS, shoulder dystocia, macrosomia, LGA	High

CS: caesarean section; ICU: intensive care unit; LGA: Large-for-gestational-age; NICU: neonatal intensive care unit;

^a Not reported; ^b timing of induction was according to gestational week or estimated fetal weight (EFW); ^c Risk of bias was assessed by the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

Effect of Induction on CS

Eleven studies (3 RCTs^{28,29,144} and 8 observational studies^{30,33,34,225,234–237}) assessed CS following IOL versus expectant management among women with GDM (Table 7.2). Quantitatively, 10 of the 11 studies (3 RCTs^{28,29,144} and 7 observational studies^{30,33,34,225,234–236}) showed no evidence of harmful effect of IOL on CS: the crude effect estimates ranged from 0.41 to 1.75, among which one study reported a significantly decreased odds of CS among women undergoing induction compared to those having expectant management (0.74 [0.63, 0.87]).³⁰ One of the 11 studies found the odds of CS were increased 1.25-fold following induction compared to expectant management (1.25 [1.04, 1.50]).²³⁷ Of the 3 RCTs that compared CS in women with GDM who underwent IOL (n=338) versus expectant management (n=336), the pooled odds of CS were not significantly different between groups (0.95 [0.64, 1.43]; $I^2=0\%$). Similarly, meta-analysis of data from the 8 cohort studies^{30,33,34,225,234–237} (n=3,295 following IOL versus 9,648 expectant management) showed no clear difference in CS (1.03 [0.79, 1.34]), but the studies were heterogeneous ($I^2=70\%$) (Figure. 2A). The GRADE quality of evidence rating was low for RCTs and very low for observational studies (Table S5).

Effect of Induction on Macrosomia

Nine studies (3 RCTs^{28,29,144} and 6 observational studies^{30,33,225,235–237}) compared macrosomia in GDM women who underwent induction versus expectant management (n=3,530 following IOL versus 8,903 expectant management) (Table 7.2). Four studies defined macrosomia as birth weight $\geq 4000\text{g}$,^{28,29,236,237} and the remaining used birth weight $>4000\text{g}$.^{30,33,144,225,235} Notably, one trial had no macrosomic neonates in both groups.¹⁴⁴ All studies consistently reported a lower rate of macrosomia associated with induction with the crude effect estimates ranging from 0.33 to

0.72, among which four studies reporting a significantly decreased odds of macrosomia.^{29,30,33,237}

The pooled summary ORs showed IOL in women with GDM was associated with a reduction in macrosomia compared to expectant management (RCTs: 0.49 [0.30, 0.81]; $I^2=0\%$; observational: 0.64 [0.54, 0.77]; $I^2=0\%$) (Figure. 2B). The GRADE quality of evidence was low for RCTs and very low for observational studies (Table S5).

Table 7.2 Summary of pooled analyses of the effect of induction on adverse maternal and neonatal outcomes in women with GDM

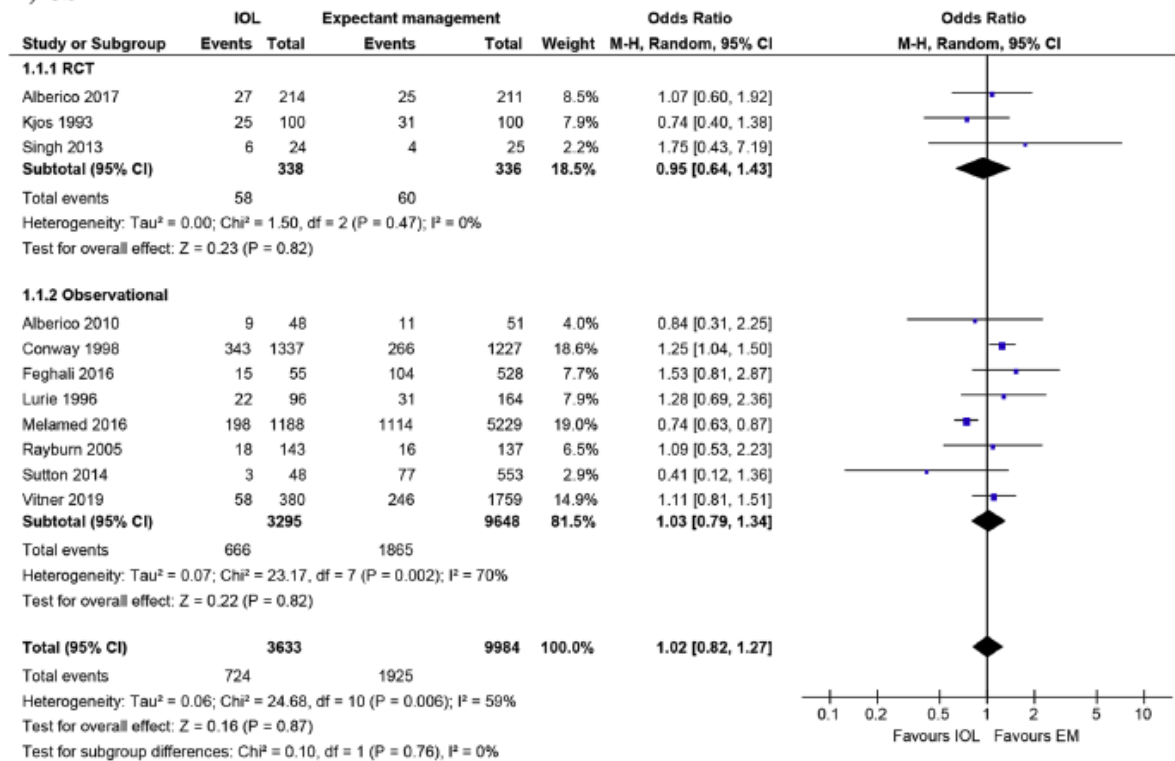
Outcomes	Study design	N of studies	N of Women	Effect estimate (95% CI) ⁱ	I ² (%)
Maternal outcomes					
CS	All	11	13617	1.02 (0.82, 1.27)	59
	RCT	3	674	0.95 (0.64, 1.43)	0
	Observational	8	12943	1.03 (0.79, 1.34)	70
Instrumental vaginal delivery	All	5	9290	0.99 (0.84, 1.17)	0
	RCT	2	474	0.84 (0.47, 1.50)	0
	Observational	3	8816	1.00 (0.85, 1.19)	0
Severe perineal lacerations ^a	All ^b	3	8829	0.57 (0.38, 0.85)	0
	RCT	1	273	0.13 (0.01, 2.52)	NA
	Observational	2	8556	0.59 (0.39, 0.88)	0
ICU	All	1	425	1.49 (0.25, 8.98)	NA
	RCT	1	425	1.49 (0.25, 8.98)	NA
Neonatal outcomes					
Macrosomia ^a	All	8	12384	0.64 (0.55, 0.74)	0
	RCT	2	625	0.49 (0.30, 0.81)	0
	Observational	6	11759	0.64 (0.54, 0.77)	12
LGA	All	4	11320	0.81 (0.63, 1.05)	61
	RCT	1	200	0.37(0.17, 0.83)	NA
	Observational	3	11120	0.88 (0.72, 1.06)	42
Shoulder dystocia ^c	All ^d	7	12232	0.80 (0.49, 1.31)	32
	RCT	2	625	0.75 (0.04, 15.49)	62
	Observational	5	11607	0.79 (0.49, 1.30)	36
NICU ^a	All	4	9080	1.40 (0.90, 2.19)	59
	RCT	1	425	0.99 (0.14, 7.06)	NA
	Observational	3	8655	1.41 (0.85, 2.32)	72
5-min Apgar score <7 ^a	All ^e	4	2943	0.61 (0.17, 2.22)	7
	RCT	1	425	4.98 (0.24, 104.28)	NA
	Observational	3	2518	0.40 (0.10, 1.55)	0
Neonatal acidemia ^a	All ^f	2	2564	1.84 (0.38, 8.92)	14
	RCT	1	425	7.00 (0.36, 136.35)	NA
	Observational	1	2139	1.16 (0.24, 5.48)	NA
Perinatal mortality ^g	All ^h	5	9195	0.64 (0.16, 2.58)	0
	Observational	5	9195	0.64 (0.16, 2.58)	0

CS: caesarean section; ICU: intensive care unit; LGA: Large-for-gestational-age; NICU: neonatal intensive care unit;

^a One RCT (Singh et al 2013) had no events recorded in both induction group and expectant management and were excluded from the final pooled analyses for severe perineal lacerations, macrosomia, NICU, 5-min Apgar score<7 and neonatal acidemia; ^b One RCT (Alberico et al 2017) and one observational study (Vitner et al 2019) had no events recorded in one group and applied a fix correction approach; ^c One observational study (Alberico et al 2010) had no events recorded in both groups and were excluded from the final pooled analyses for shoulder dystocia; ^d One RCT (Kjos et al 1993) had no events recorded in one group and applied a fix correction approach; ^e One RCT (Alberico et al 2017) and two observational studies (Alberico et al 2010; Vitner et al 2019) had no events recorded in one group and applied a fix correction approach; ^f One RCT (Alberico et al 2017) had no events recorded in one group and applied a fix correction approach; ^g Three RCTs (Kjos et al 1993; Singh et al 2013; Alberico et al 2017) and one observational study (Sutton et al 2014) had no recorded events in both groups and were excluded from the final pooled analyses for perinatal mortality; ^h Five observational studies (Alberico et al 2010; Lurie et al 1996; Melamed et al 2016; Rayburn et al 2005; Vitner et al 2019) had no events recorded

in one group and applied a fix correction approach; ⁱ Pooled odds Ratio (OR) was generated by random-effects models with the Mantel-Haenszel method.

A) CS



B) Macrosomia

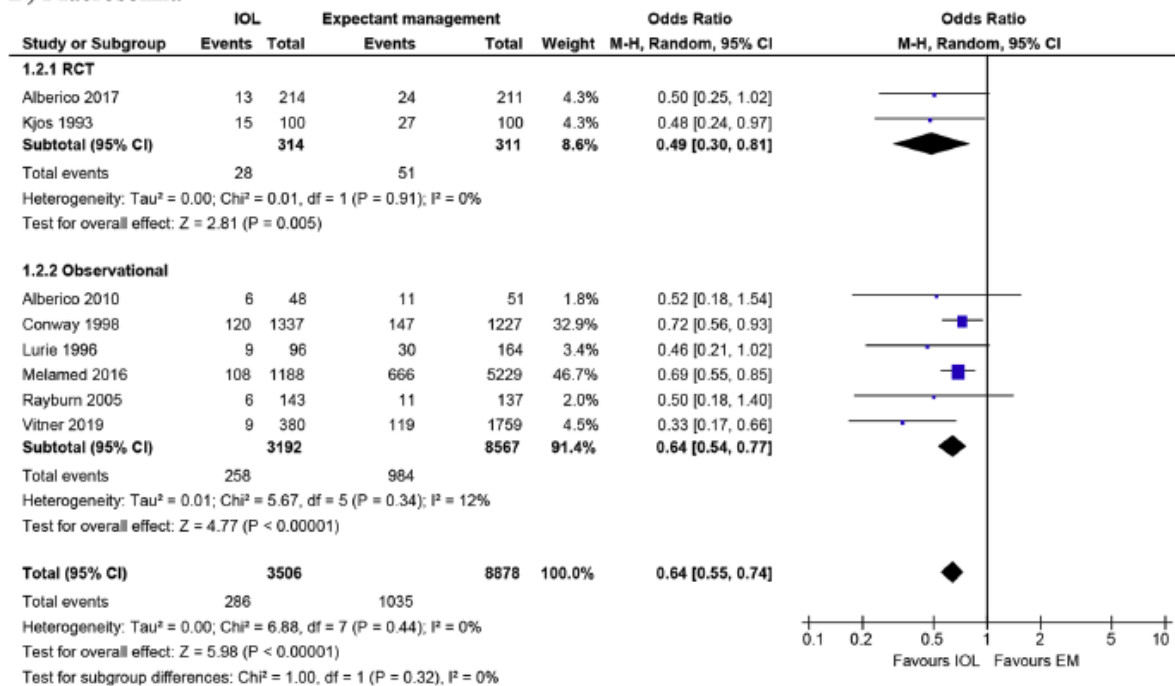


Figure 7.2 Forest plots for primary outcomes A) CS B) Macrosomia comparing IOL with expectant management in women with GDM at term gestation. Reference citations for studies can be found in Table 1. IOL, induction of labour; EM, expectant management

Effect of Induction on Secondary Outcomes

The combined results for severe perineal lacerations from two observational studies significantly favored IOL (0.59 [0.39, 0.88]; $I^2=0\%$) while no significant association was demonstrated in the single trial (0.13 [0.01, 2.52]). For LGA, the trial showed a protective effect of induction (0.37 [0.17, 0.83]) but no significant difference was observed in the pooled results from 3 observational studies (0.88 [0.72, 1.06]; $I^2=42\%$). Additionally, compared with expectant management, induction in GDM women was not significantly associated with instrument vaginal delivery (RCTs: 0.84 [0.47, 1.50]; $I^2=0\%$; observational: 1.00 [0.85, 1.19]; $I^2=0\%$), ICU admission (RCT: 1.49 [0.25, 8.98]), shoulder dystocia (RCTs: 0.75 [0.04, 15.49]; $I^2=62\%$; observational: 0.79 [0.49, 1.30]; $I^2=36\%$), NICU (RCT: 0.99 [0.14, 7.06]; observational: 1.41 [0.85, 2.32]; $I^2=72\%$), 5-min Apgar score <7 (RCT: 4.98 [0.24, 104.28]; observational: 0.40 [0.10, 1.55]; $I^2=0\%$), neonatal acidemia (RCT: 7.00 [0.36, 136.35]; observational: 1.16 [0.24, 5.48]) and perinatal mortality (0.64 [0.16, 2.58]; $I^2=0\%$) (Table 2; Fig. S2-10). The GRADE quality of evidence rating for the secondary outcomes ranged from very low to low (Table S5).

Publication Bias and Sensitivity Analysis

We assessed publication bias using funnel plots and no obvious asymmetry was evident for the primary outcomes (Figure. S11). The results of the sensitivity analyses by limiting studies to high quality or induction at same gestational age for the primary outcomes were similar to the main results (Figure. S12-13). The leave-one-out sensitivity analyses showed similar pooled effect estimates and found Melamed's study had a key contribution to the between-study heterogeneity and the overall effect of induction on primary outcomes (Table S4).

7.6 Discussion

Main Findings

Our study found that comparative studies of adverse maternal and perinatal outcomes following induction at term in women with GDM are limited in number and have yielded inconsistent results. This meta-analysis quantitatively assessed the effect of induction and shows that among women with GDM, induction at term is associated with lower odds of macrosomia and severe perineal lacerations than expectant management, but no evidence of significant difference in CS between groups was found. No significant between-group differences were observed in other maternal or neonatal morbidities, or perinatal mortality. The overall quality of evidence across studies was low to very low due to limited and inconsistent findings from a few studies with mixed study design, precluding our ability to draw firm conclusions.

Strengths and Limitations

This systematic review and meta-analysis used a comprehensive literature search strategy. We included all related comparative studies published on a topic of highly relevant to obstetric clinical decision-making. The risk of bias assessment and data extraction were done independently and in duplicates to minimize assessor bias. Overall, the 11 included studies collectively enrolled over 13,000 women with GDM to answer the research question. To our knowledge, no prior systematic review and meta-analysis on this topic is as extensive and comprehensive as ours, which has quantitatively assessed the effect of induction on various outcomes in GDM women using data from different populations. The review included both randomized and observational study designs to maximize analysis of all available evidence.

Nevertheless, there are several limitations. The most important limitation was the small number of well-designed, adequately powered studies reporting maternal and neonatal outcomes of interest: there were only 3 RCTs, 1 of which had low quality, and the other 2 had unclear risk of bias. As there were no more than 5 studies for most of outcomes, quantitative synthesis may have introduced between-study heterogeneity and affected the validity of pooled results. Among the 11 studies that met inclusion criteria, most were small studies and had imprecise estimates. With the leave-one-out sensitivity analysis, we identified one study with a relatively larger impact on the pooled effect estimates for the primary outcomes.³⁰ Another particular concern was that the included studies were from a wide range of time periods, over which the diagnostic criteria for GDM, induction methods, and obstetrical practice patterns had changed. This may, at least in part, explain the heterogeneity for several outcomes. Additionally, most of the included women were GDM patients with different severity, and the lack of reporting of stratified data of GDM subtypes in original studies prevented us from conducting subgroup analyses by GDM severity. Observational studies, which accounted a substantial proportion of study participants in this study, may be prone to a certain degree of bias that could affect the validity. These include the use of non-concurrent or incomparable control groups in some included studies^{235–237} which may introduce selection bias and exaggerate the observed association away from the null. Expectant management was defined consistently across studies as women who delivered following spontaneous or IOL at later gestational ages, with the exception of one study including spontaneous vaginal delivery at the same week as the induction group.²³⁴ Therefore, the pooled effect estimate for CS might be biased slightly away from the null. Because we do not have access to raw data of the original studies, and given the differences in contents and format of confounding variables in original studies, the lack of adjustment for important confounders

including glycemic control in our meta-analysis also suggests a possibility of residual confounding, which might limit the interpretation of the study findings. The exclusion of non-English language studies in this study might also create language bias. Lastly, publication bias may still exist in the case of small negative unpublished studies. Although it was not detected in this study, the insufficient number of included studies limits the power to detect publication bias.²⁴⁴

Interpretation

In view of the recommendations from many clinical guidelines worldwide that women with GDM should be offered induction at term, the trade-off of benefits and risks of this intervention is of high significance for decision-making by healthcare providers and patients in practice. In this systematic review and meta-analysis, we found induction at term gestation for GDM women was associated with lower odds of macrosomia and severe perineal lacerations compared to expectant management, but no significant differences in CS, instrumental vaginal delivery, LGA or other severe maternal and neonatal outcomes.

The finding of non-significant difference in CS from this updated systematic review and meta-analysis is similar to the results from previous reviews.^{35,36,226} However, the results from the Cochrane review of 1 trial were limited to insulin-treated diabetic pregnant women.³⁶ An earlier systematic review of five studies evaluating the effect of induction in GDM pregnancies was limited by high heterogeneity and methodological concerns, precluding a quantitative synthesis.³⁵ The non-significant difference in CS between groups in our study is likely due to a considerable amount of GDM women expectantly managed ultimately requiring induction or CS at later gestational ages for other indications (e.g. post-term). Additionally, with the increasing

fetal weight, aging placenta and decreasing amniotic fluid associated with advancing pregnancy, women having expectant management might therefore be predisposed to have intrapartum CS due to non-reassuring fetal heart rates.^{141,245} Our finding of a significantly lower odds of macrosomia associated with induction was conflicting with the results from a recent Cochrane review of one trial by Biesty et al, which was an open-label trial including 425 subjects.²²⁶ With exclusion of GDM subjects with suspected macrosomia and severe recruiting challenges,²⁸ it was unable to achieve the target sample size, and therefore underpowered to identify between-group differences.^{28,226} The lower likelihood of macrosomia in GDM pregnancies with induction in our study might be explained based on the modified Pedersen hypothesis of maternal hyperglycemia leading to fetal hyperinsulinemia and increased glucose utilization.²⁴⁶ Consequently, it results in fetal excess protein and fat storage, leading to macrosomia. Moreover, as fetal growth is positively associated with advancing gestational age, expectant management extends the gestation of GDM pregnancy and boosts intrauterine fetal growth, which may further increase the risk of macrosomia.⁹⁹ This finding was also supported by recent evidence of elective induction associated with a lower neonatal birth weight among low-risk pregnancies.²⁴⁵

Nevertheless, we couldn't draw a definite conclusion to guide decisions given the small number and overall low quality of the eligible studies. Results of secondary outcomes, especially for those related to severe neonatal morbidities and perinatal mortality, were underpowered given the rare nature of these outcomes.

Labour and delivery management for pregnancies with GDM, especially with macrosomia, remains an obstetric challenge. Emerging evidence has shed light on the criticality of delivery timing and mode in such pregnancies to maximize health outcomes considering the common tools used for pregnancies monitoring and antenatal fetal surveillance at term, such as

ultrasonography, fetal cardiotocography (CTG) and Doppler studies of umbilical artery (UA) exhibit limited utility in the context of GDM and macrosomia . This is primarily due to the unique fetal growth patterns and increased risk of complications associated with GDM and macrosomia.^{99,101,104} Consequently, there is a growing recognition of the need to necessitate tailored and individualized approaches to deliver these pregnancies which take into account maternal glycemic control status, fetal well-being, and the potential risks linked with prolonged intrauterine exposure to elevated glycemic levels. Comprehensive and well-designed comparative studies with large sample sizes, assessing a wide range of adverse outcomes, are required to generate robust evidence and inform clinical guidance to improve labour and delivery management in GDM pregnancies.

7.7 Conclusions

In this systematic review and meta-analysis, we found induction at term gestation in GDM women may reduce the risk of macrosomia and severe perineal lacerations compared to expectant management, but the effect on CS or severe maternal and neonatal outcomes was inconclusive. Definitive evidence from well-designed studies with large sample sizes are warranted to better inform implications for labour and delivery management in women with GDM.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

All authors have no competing interests to declare.

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Authors' contributions

R.L., M.C.W and S.W.W conceived the study and designed the study. R.L. and W.W. screened studies and extracted data for the systematic review. R.L. analyzed the data and drafted the manuscript. R.L., M.C.W., S.W.W., D.J.C., D.B.F. and M.T. were involved in interpretation of results. M.C.W., S.W.W., D.J.C., D.B.F. 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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Additional files for Chapter 7 can be found in Appendix E

Additional file 1: Search strategy

Additional file 2: PRISMA 2020 checklist

Additional file 3:

Table S1. Articles excluded after full text review and reasons for exclusion (n=77)

Additional file 4:

Table S2. Further characteristics of the included studies

Additional file 5:

Table S3. Quality assessment for the observational studies

Additional file 6:

Table S4. Pooled estimates for the effect of induction on primary outcomes in observational studies

Additional file 7:

Table S5. Summary of findings table (GRADE)

Additional file 8:

Figure. S1 Assessment of risk of bias for RCTs. (A) Summary of risk of bias (+: low risk of bias; -: high risk of bias; ?: unclear risk of bias); (B) Risk of bias graph with each risk of bias item presented as percentages across all included trials

Additional file 9:

Figure. S2-S10 Forest plots for secondary outcomes comparing induction with expectant management in women with GDM.

Additional file 10:

Figure. S11 Funnel plot to assess publication bias for primary outcomes A) CS B) Macrosomia

Additional file 11:

Figure. S12-S13 Sensitivity analysis

Chapter 8. Discussion

As one of the most common endocrinopathies during pregnancy, GDM is a significant clinical and public health challenge. It has been related to short -and long-term adverse health outcomes for both pregnant individuals and their offspring.^{4,96,171} While the definitions and applications of GDM evolved over the past decades, its prevalence has been steadily increasing and is expected to continue rising both in Canada and globally.⁹ The underlying reasons for such increase has not been fully understood. Results from some studies suggested that the increasing GDM rate is partly related to the changes in population demographics and lifestyle risk factors,^{13,14} and partly attributable to the variations in screening methods and uptake of more stringent diagnostic criteria.^{8,11} Additionally, limited studies have investigated the impact of increasing GDM on adverse outcomes, and their findings have been inconclusive.^{6,7,18-21} In Canada, there has been significant population demographic changes over time, however, the contemporary temporal estimates of GDM and related impacts on adverse outcomes over the last decade are lacking.

Labour induction has been widely recommended in Canada and many other countries for pregnancies complicated with GDM at term gestation if spontaneous onset of labour has not occurred, to improve and prevent intrauterine fetal death and other complications particularly related to fetal overgrowth. However, there is a lack of systematic reviews on investigating induction for GDM term pregnancies, and previous studies yielded inconsistent results and had methodological limitations, and no firm conclusions were made regarding the benefits and risks of induction.^{27,35,36}

Thus, a clear understanding of the GDM burden at population level is crucial so that health care interventions can be promptly planned, coordinated, budgeted and delivered. This thesis aimed to address the 7 research questions listed in Chapter 1 through 4 distinct studies (Chapters 4 - 7).

Specially, I started with identifying temporal trends in GDM over the last 8-year period and

contributing factors to the underlying trend in Ontario, Canada, and then focused on investigating trends of adverse maternal and neonatal outcomes associated among pregnancies with and without GDM and comparing the risk of adverse outcomes by time periods of delivery. Finally, I conducted a systematic review and quantified the latest evidence from comparative studies of induction among pregnant individuals with GDM.

8.1 Summary of Research Findings

The first manuscript of this thesis, “ Temporal Trends in Gestational Diabetes Mellitus and Associated Risk Factors in Ontario, Canada, 2012 to 2020: A Population-Based Cohort Study”, aimed to investigate the secular trends of GDM and associated risk factors between April 1 2012 and March 31 2020 in Ontario, Canada.¹⁸² We conducted a retrospective cohort study designed to provide insights of the recent trends in GDM and quantify the contribution of the underlying risk factors to this increase in GDM using data from the provincial birth cohort of over 1.1 million from the BORN linked with the delivery hospitalization records from the DAD.

In this large, racially diverse obstetric population, we found the notable changes in the distribution of maternal demographic characteristics over time, particularly the rise in pre-pregnancy obesity, older age at delivery (≥ 35 years), and Asian ethnicity. The rate of GDM increased from 6.1 in 2012/13 to 10.4 in 2019/20 per 100 deliveries in Ontario, Canada over the 8-year period, with an adjusted RR of 1.53 (95% CI 1.50, 1.56). GDM without pharmaceutical treatments had a larger increase (over 75%) than those requiring pharmaceutical treatments. The decomposition analysis demonstrated changes in the distribution of maternal age at delivery, pre-pregnancy BMI and ethnicity contributed to 27% of the increase in GDM rates over the study period.

Motivated by the recent increase in GDM in Manuscript 1, we further investigated the impact of the increasing GDM on related adverse outcomes. We evaluated the temporal trends in a broad range of adverse neonatal and maternal outcomes among pregnancies with and without GDM and compared if the risk of these outcomes associated with GDM changed by time periods before and after the nationwide adoption of new guidelines using the birth cohort from the BORN Ontario between 2012 and 2020 (Manuscript 2 and 3).

In the second manuscript of the thesis, “Risk of Adverse Maternal Outcomes Among Pregnancies With Gestational Diabetes Mellitus in Ontario, Canada, 2012-2020: a Retrospective Cohort Study”, we found significant increases in the rates of induction over time, from 35.8 (95% CI 34.7 to 36.9) to 46.2 (95% CI 45.3 to 47.0) per 100 deliveries among GDM pregnancies, and from 22.3 (95% CI 22.0 to 22.5) to 29.2 (95% CI 28.9 to 29.4) per 100 deliveries among non-GDM pregnancies. Overall maternal morbidity and mortality had a temporal increase in both pregnancies and reached to a similar level by 2019/20. CS and pregnancy-induced hypertension only increased among non-GDM pregnancies but remained stable among GDM pregnancies. The risk of induction for GDM was 1.6 times higher compared to non-GDM, and remained similar between the two time periods (adjusted RR, 1.62, 95% CI [1.60, 1.64] in 2012/13-2015/16 and 1.60, 95% CI [1.59, 1.62] in 2016/17-2019/20). There was a reduction in the risk of pregnancy-induced hypertension for GDM compared to non-GDM (1.45, 95% CI [1.41, 1.49] in 2012/13-2015/16 and 1.29, 95% CI [2.25, 2.32] in 2016/17-2019/20). The magnitude of the association of GDM with CS (1.10, 95% CI [1.08, 1.12] in 2012/13-2015/16 and 1.07, 95% CI [1.05, 1.08] in 2016/17-2019/20) and assisted vaginal delivery (0.96, 95% CI [0.92, 1.00] in 2012/13-2015/16 and 0.94, 95% CI [0.90, 0.98] in 2016/17-2019/20) remained stable over time. For overall maternal morbidity and mortality (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), the adjusted RR was close to 1 and not statistically significant in either time period. Despite the increased strength of the association with postpartum hemorrhage with interventions to control bleeding, the associations of GDM with other component outcomes of maternal morbidity and mortality remained stable over time. The results were robust in the sensitivity analyses including complete-case analysis, excluding multiple pregnancies to the same pregnant individuals and those GDM cases with pharmaceutical treatments.

In the third study of the thesis, “Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020”, we found that gestational-age adjusted rates of a composite outcome of SNM (perinatal mortality, respiratory distress syndrome or transient tachypnea of the newborn, hypoglycemia, newborn sepsis, confirmed seizures, necrotizing enterocolitis, hypoxic–ischemic encephalopathy, cardiopulmonary resuscitation or ventilator support, umbilical-cord-blood arterial pH <7.0, a 5-minute Apgar score <4, admission to NICU, or prolonged hospitalization (≥ 5 days)) increased over time for both GDM and non-GDM pregnancies – it increased from 22.9 to 23.9 per 100 deliveries among GDM pregnancies and increased from 15.1 to 16.8 per 100 deliveries among non-GDM pregnancies. Most individual adverse neonatal outcomes remained stable or decreased in both pregnancies. Despite the recent increase in GDM, the risk for overall SNM associated with GDM remained stable (1.50, 95% CI [1.48, 1.52] in 2012/13-2015/16 and 1.54, 95% CI [1.52, 1.56] in 2016/17-2019/20). Notably, although the association of GDM and perinatal mortality was not statistically significant in either period, the magnitude of the association was lower in the later time period. The strength of the association between GDM and both LGA and

macrosomia decreased significantly in 2016/17-2019/20 relative to 2012/13-2015/16 (LGA: 1.42, 95% CI [1.39, 1.45] in 2012/13-2015/16 and 1.31, 95% CI [1.28, 1.34] in 2016/17-2019/20, P for interaction <0.001; Macrosomia: 0.98, 95% CI [0.95, 1.02] in 2012/13-2015/16 and 0.86, 95% CI [0.83, 0.90] in 2016/17-2019/20, P for interaction <0.001). No significant changes in associations of GDM with other individual neonatal outcomes between the two time periods. Similar results were also found in the sensitivity analyses including complete-case analysis, first deliveries during the study period, pregnancies without pregnancy-induced hypertension, and excluding GDM cases with pharmaceutical treatments.

The final study of the thesis, “Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with gestational diabetes mellitus at term pregnancy: A systematic review and meta-analysis”, summarized evidence from experimental and observational studies assessing the risks and benefits associated with induction at term gestation among pregnant individuals with GDM up to June 2021.¹³¹ Our study was the first to comprehensively and quantitatively compared induction at a specific gestational week with expectant management until spontaneous onset of labour among GDM term pregnancies. Among the 11 studies included, we found that, compared to expectant management, induction at term gestation among GDM pregnancies was associated with a lower odds of macrosomia (RCTs: 0.49, [95% CI 0.30, 0.81]); observational studies: 0.64, [95% CI 0.54, 0.77]) and severe perineal lacerations (observational studies: 0.59, [95% CI 0.39, 0.88]), but no evidence of significant differences in CS (RCTs: 0.95, [95% CI 0.64, 1.43]; observational studies: 1.03, [95% CI 0.79, 1.34]). There were no significant differences in perinatal mortality or other severe perinatal outcomes. The overall quality of evidence across studies rated from low to very low. Our

sensitivity analyses by study quality, gestational age at induction and leave-one-out showed similar results.

Table 8.1 Summary of research findings from Chapters 4 to 7

Chapter	Main research findings
4	• The distribution of population demographics changed significantly over the study period. The prevalence of age at delivery ≥ 35 years increased from 21.9% to 25.7%, Asian populations increased from 14.9% to 20.0%, pre-pregnancy obesity increased from 17.3% to 19.7%. • The rate of GDM increased substantially from 6.1 to 10.4 per 100 deliveries between 2012/13 and 2019/20, with an adjusted RR of 1.53 • The increased proportion of pregnant individuals with older maternal age at delivery, pre-pregnancy obesity and being Asians accounted 27% of the temporal increase in GDM.
5	• The rate of induction and overall maternal morbidity and mortality increased over time in both pregnancies. Caesarean deliveries and pregnancy-induced hypertension only increased among non-GDM pregnancies. • The adjusted RR of pregnancy-induced hypertension for GDM, compared with non-GDM reduced from 1.45 to 1.29. The strength of the association between GDM and induction, CS and assisted vaginal delivery remained stable between the two time periods. For overall maternal morbidity and mortality, the adjusted RR was close to 1 and not statistically significant in either time period. The association of GDM with each individual component outcome of maternal morbidity and mortality remained stable over time, except for postpartum hemorrhage with interventions.
6	• The gestational-age adjusted rate of composite SNM increased among pregnancies with and without GDM. Most individual adverse neonatal outcomes remained stable or decreased over time for both GDM and non-GDM pregnancies. • The positive association between GDM and SNM was stable between the time periods, and GDM pregnancies had 1.5 times the risk of SNM increased compared to normoglycemic pregnancies. The adjusted RR decreased from 1.42 to 1.31 for LGA, and from 0.98 to 0.86 for macrosomia. No significant changes were observed in associations of GDM with other individual neonatal outcomes between the two time periods.
7	• Among 11 eligible studies, induction at term gestation was associated with a lower odds for macrosomia and severe perineal lacerations among GDM pregnancies. • Between-study heterogeneity could arise from the variations in study quality, sample size and different gestation age at induction.

8.2 Strengths and Limitations

This thesis includes three population-based studies and one systematic review (Chapters 4-7). The three population-based studies fill a much-needed gap in our understanding of the recent temporal trends in GDM and its impact on a full range of related adverse outcomes using a large, validated, diverse obstetrical population and could further guide public health strategies and interventions for GDM management. The systematic review is the first one to quantitatively evaluate the effect of induction at term gestation on perinatal outcomes, comparing it to expectant management, in pregnancies with GDM. It provides valuable insights to inform evidence-based decision-making in clinical settings.

Limitations have been discussed in each manuscript, and additional consideration is provided here to highlight them. One of the main limitations we had through this work is related to the use of healthcare administrative databases. While it is common to use codes in health administrative data to identify diagnoses or procedures for retrospective research, yet these codes are less frequently validated.²⁴⁹ A few studies that assessed the diagnostic codes for GDM using health administrative data indicated imperfect validity, and mostly used clinical diagnosis from medical records or clinical records as a reference.^{148,250–255} Few studies validated diagnostic codes against gold-standard laboratory results from OGTTs. Nevertheless, GDM ascertainment from combined administrative databases shows to have a higher sensitivity and specificity than single data source.^{250,252} In our studies (Chapters 4-6), we therefore measured GDM using any diagnosis documented in either of BIS or CIHI-DAD to increase the probability of GDM ascertainment GDM. Non-differential misclassification of GDM might still occur in these studies and bias the results towards the null.²⁵⁶ The magnitude of temporal trends in GDM and the associations between GDM and adverse outcomes could have been underestimated.

A related issue, known before conducting the studies but worth noting due to its relevance and importance, is the heterogeneity in defining and diagnosing GDM due to the changing screening methods and diagnostic criteria over time in Canada and other countries.^{10,194} The use of universal, one-step approach based on the IADPSG criteria is associated with a 1- to 4-fold increase in GDM prevalence versus baseline criteria.¹⁹⁴ However, the rate of GDM has been reported increasing every year even with a consistent approach for diagnosis.²⁵⁷ In our studies, due to the lack of detailed information on the one-step vs two-step screening methods and diagnostic criteria, and specific glycemic values in the OGTT tests, the temporal estimate in GDM rates were confounded by the changing screening and diagnostic criteria. Similarly, our results were also likely biased by residual confounding of unknown or unmeasured factors, such as patterns in gestational weight change, diet and physical activities during early- to mid-pregnancy, which are important factors associated with GDM and adverse pregnancy outcomes. We were unable to parse out the proportion of increase in GDM attributed to the use of new screening and diagnostic criteria nor its related impact on adverse maternal and neonatal outcomes. Assuming a greater amount of increase due to classifying cases of mild hyperglycemia as GDM, our sensitivity analyses excluding GDM requiring pharmaceutical treatments demonstrated that, there were no significant changes in the risk of adverse outcomes associated with GDM between the two time periods. Additionally, due to the limited time points and data unavailability, our study could not perform an interrupted time series analysis to directly compare the changes in GDM and associated outcomes before and after the implementation of the new screening and diagnostic criteria, nor assess long-term impact of the increasing rate of GDM.

Another limitation to consider was the use of composite maternal and neonatal outcomes in the thesis (Chapters 5-6). Composite measures are useful especially for rare outcomes to increase the study power, as well as to reduce the bias of competing risks by combining both mortality and other serious morbidities into a composite outcome.^{258,259} Nevertheless, it raises concerns with regard to the incomparability of severity, clinical significance, patient relevance, effect sizes, and event rates of each individual outcomes included in the composite outcomes.^{259,260} The unweighted composite measures included in our studies (Chapters 5-6), especially the composite of perinatal mortality, NICU admission, and other serious neonatal outcomes, may have methodological limitations as these individual outcomes have different etiology and severity but are assigned the same weight. The interpretation of the effect estimates of the composite outcome could also be challenging when some component outcomes have substantially different event rate and effect size. Notably, in our studies, we reported both individual components and composite outcomes to ensure appropriate interpretation of the study results and prevent confusion in decision making.

Lastly, in the systematic review and meta-analysis (Chapter 7), due to the heterogeneity in GDM ascertainment/identification and lack of sufficiently powered high-quality studies to assess rare adverse perinatal outcomes relating to induction among pregnancies complicated with GDM, its interpretation and application maybe restricted.

8.3 Implications for Clinical and Public Health and Future Research

The results presented in this thesis offer additional data on the contemporary burden of GDM in Canadian population and help shape the future direction of GDM prevention, surveillance, and management. The evidence on the benefits and risks of labour induction at term gestation among GDM pregnancies helps to guide the decision-making in clinical practice and inform future well-designed clinical trials for labour and delivery management for GDM pregnancies.

In line with the findings from earlier studies conducted in Canada and other countries,^{7,8,13,15,19,21,219} the rates of GDM, especially those without pharmaceutical treatments, have been substantially increased over the recent 8-year period in Ontario. However, the recent increase in GDM did not worsen adverse outcomes. In fact, the risk of macrosomia, LGA, and pregnancy-induced hypertension decreased, and other adverse maternal and neonatal outcomes were stable between the two time periods. Similar to our findings, several studies have found that increases in GDM was not associated with increases in the risk of adverse maternal and neonatal outcomes.^{6,19,20} This is likely to be explained by the larger increase in the number of mild GDM and subsequent benefits from the management of milder form of hyperglycemia in more recent years, together with the advancements in the perinatal health care.^{106,107,181,207,261} Researches have shown that the adverse outcomes of mild GDM may vary depend on the combination of the abnormal values in the IADPSG-defined thresholds. Compared to normal pregnancy, mild GDM only with a higher fasting glucose value exceeding the IADPSG-defined thresholds had a higher risk of LGA, while those with a higher one-hour or two-hour post-load glucose value but normal fasting glucose value were at a higher risk of preterm birth, gestational hypertension, and neonatal hyperbilirubinemia.²⁶²

Currently, the screening and diagnosis criteria to identify the at-risk pregnant individuals of GDM remains controversial. No consensus on a standard diagnosis approach for GDM has been reached, especially in terms of which screening and diagnosis approach is the most clinically benefit or cost-effective. The two-step sequential approach with less strict diagnostic thresholds may miss some cases from benefits of treatment, while the one-step IADPSG criteria may face overtreatment by classifying more pregnancies as having GDM and therefore increasing the need for health interventions and costs.^{263,264} However, the existing evidence is controversial regarding the impact of application of IADPSG on adverse maternal and neonatal outcomes compared to other two-step criteria.⁷⁶ Some observational studies have reported no difference or increase in the adverse maternal and neonatal outcomes,^{206,265–267} whereas some reported a significant reduction in adverse outcomes after the application of the IADPSG criteria for GDM.^{193,268} Recently, one large pragmatic RCT of 23 000 participants compared the impact of the two clinically recommended screening and diagnosis approaches and treatments for GDM (one-step IADPSG versus two-step approach with GCT and 100g OGTT CC criteria) on perinatal outcomes in the US standard clinical care setting.²⁶⁹ They found, despite the higher rate of GDM using the one-step (16.5% versus 8.5%), the risk of LGA, gestational hypertension/preeclampsia, primary caesarean delivery, and the perinatal composite outcome was similar between the groups.²⁶⁹ Compared to the two-step approach, more participants in the one-step approach received medication to manage glucose levels during pregnancy. Moreover, the one-step approach had 39% of GDM diagnosis based on an isolated fasting plasma glucose alone, and half of them were a mild form of hyperglycemia (in the range of 92-94 mg/dl), which may not be diagnosed and treated by the two-step approach.

Emerging evidence have also indicated that mild hyperglycemia who only met the IADPSG criteria but not by other less strict criteria had a higher risk of LGA, increased neonatal adiposity, caesarean delivery, and gestational hypertension and pre-eclampsia, compared to non-GDM pregnancy.^{217,270,271} However, there is a lack of clinical trials comparing the outcomes between treated and untreated GDM cases diagnosed using the IADPSG criteria, and the treatment effects for IADPSG-defined GDM remain unclear.

Identifying the contemporary temporal trends in GDM and its impact on adverse outcomes in our study could help to better understand the current burden of GDM and the underlying reasons driving the rising rates of GDM. While the rate of GDM increased substantially over the past years, the associated adverse outcomes remained relative stable or decreased, supporting the current practice model of identification and management of GDM from 24 - 28 weeks of gestation and up to 6 weeks postpartum. Nonetheless, concerns about overtreatment and health economics of screening and treatments remain.^{17,22} Given the heterogeneity in GDM forms and long-term health consequences for mothers and offspring, a personalized life course approach from preconception to postpartum and onward is needed for prevention, diagnosis and treatments of GDM.²⁷² Meanwhile, public health preventative efforts targeting at the modifiable risk factors of GDM should still be enhanced among at-risk women of reproductive ages. Despite the evidence is limited and the most effective prevention strategy is unclear,^{273–275} health-promoting measures and preventive care should be better tailored and feasible to support lifestyle improvements in achieving and maintaining a normal weight in preconception, during pregnancy, and interpregnancy periods, therefore to reduce the risk of GDM. Future well-designed and sufficiently powered studies evaluating the short-term and long-term health outcomes associated with different glycemic thresholds and treatment effects in GDM are

warranted for prevention and development of more effective screening and diagnosis guidelines for GDM. Given the limited healthcare resources, comprehensive health economic evaluation of various screening approaches of GDM are urgently required to direct effective healthcare resources allocation to ultimately improve patient care.

Among pregnancies with GDM, clinical guidelines from international and national organizations and societies have broadly recommended induction at term gestation to improve pregnancy outcomes if there is no onset of spontaneous labour, based on the expert consensus. However, the supporting scientific evidence is not strong and sufficient; most of the evidence were methodologically limited and yielded inconsistent results.^{28,30,35} The potential risks and benefits associated with induction compared to expectant management revealed by our systematic review and meta-analysis (Chapter 7) provided additional data to guide clinical decisions on the labour and delivery management for pregnancies with GDM. Given the lack of studies in the current body of the literature,¹³¹ future large-scale and well-designed clinical trials are urgently needed to investigate the delivery by induction in patients with different GDM subtypes, taking into account important maternal and fetal factors, such as glycemic control, cervical status, and fetal lung maturity, to generate high-quality evidence that informs best clinical practice. In fact, building on the findings from Chapter 7, we recently successfully received a grant to conduct a multi-center, randomized controlled trial comparing expectant management versus induction at 38 weeks among individuals with GDM (CIHR Number: 505575).

8.4 Final Conclusions

In this doctoral thesis, I have carried out three quantitative studies of the temporal trends of GDM and its related impact on a broad range of adverse maternal and neonatal outcomes, and one systematic review and meta-analysis of the effect of induction at term gestation among pregnancies with GDM. The current findings suggest a substantial temporal increase in GDM in Ontario, Canada, and increased maternal age at delivery, higher pre-pregnancy BMI, and larger proportion of pregnancies from Asian race/ethnicity in recent years contributed to 27% of the overall increase of GDM over time. Importantly, despite the increasing rate of GDM, the strength of the association between GDM and pregnancy-induced hypertension, macrosomia, and LGA decreased, and there were no significant changes in the association of GDM with most severe outcomes over time. Compared to expectant management, induction at term gestation might lower the risk of macrosomia and severe perineal lacerations among GDM pregnancies. Future well-designed clinical trials with large sample sizes are needed to identify the clinically efficient screening and diagnostic thresholds for GDM as well as the benefits and risks associated with induction among GDM term pregnancies.

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Appendix A. Ethics Approval



**Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil
d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)**

Date: June 1, 2021
Principal Investigator: Dr. Mark Walker, TOH/OHRI
Protocol ID: 20210400-01H
Study Title: Gestational diabetes and delivery time: a population-based study in Ontario, Canada
Submission Type: Initial Application
Review Type: Delegated
Date of Approval: May 31, 2021
Approval Expiry Date: May 31, 2022

Dear Dr. Walker,

An **Institutional approval (OHRI) letter is required prior to the conduct of the study** at this site. The institutional approval letter is an indication that you have satisfied ethics, contracts, departmental notifications, as applicable.

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

The **OHSN-REB ethics approval** is applicable only for The Ottawa Hospital.

No deviations from, or changes to, the protocol should be initiated without prior written approval of an appropriate amendment from the OHSN-REB, except when necessary to eliminate immediate hazard(s) to study participants.

REB members involved in the research project do not participate in the review, discussion or decision.

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Report must be received by the OHSN-REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/kc

Appendix B. Additional files for Chapter 4

Additional file 1 - 7:

Table S1. BORN Information system (BIS) and international classification of diseases (tenth revision, Canada) for GDM diagnosis

Table S2. Distribution of variables with missing values in original and imputed datasets

Table S3. GDM rates by fiscal year of delivery from April 1, 2012 to March 31, 2020 (data for Figure 2)

Table S4. Temporal trends in GDM in Ontario, Canada, fiscal years 2012/13-2019/20, in complete-case analysis

Table S5. Temporal trends in GDM among women with first pregnancy in Ontario, Canada, fiscal years 2012/13-2019/20

Figure S1. Directed Acyclic Graph (DAG) of causal assumptions between year of delivery and GDM.

Figure S2. Temporal trends in rates of GDM among all singleton hospital deliveries in Ontario, Canada, April 1, 2012 to March 31, 2020, stratified by maternal age at delivery, (A, B), pre-pregnancy BMI (C,D), and maternal ethnicity (E,F)

Table S1. BORN Information system (BIS) and international classification of diseases (tenth revision, Canada) for GDM diagnosis

Outcome	Data Source	Variable	Coding	Coding description
GDM	BIS	diabetes_and_pregnancy_id	1013490, 1013480, 1013470, 3000001, 1013460, 1013465, 1013450, 1013440, 1013430	Diabetes and pregnancy <i>OR</i>
	BIS	Complication_id	1020270	Complication of pregnancy <i>OR</i>
	CIHI-DAD		Mother: O24.8 and Infant: P70.0, excluding pre-existing diabetes (T1DM: E10.X, O24.5; T2DM:E11.X, O24.6; unspecified type:O24.7, E13.X, E14.X)	Gestational diabetes
GDM with medical treatments	BIS	diabetes_and_pregnancy_id	1013465,1013450,1013460, 1013440	Insulin or oral antihyperglycemic agents <i>OR</i>
	CIHI-DAD		Y42.3	Insulin or oral hypoglycemic agents

Table S2. Distribution of variables in original and imputed datasets (N=1 044 258)

Factors	Non-imputed dataset N (%)	Imputation #1	Imputation #2	Imputation #3	Imputation #4	Imputation #5
Maternal age at delivery category						
<25	132 239 (12.7)	132 240 (12.7)	132 240 (12.7)	132 240 (12.7)	132 239 (12.7)	132 239 (12.7)
25-34	666 470 (63.8)	666 473 (63.8)	666 472 (63.8)	666 472 (63.8)	666 471 (63.8)	666 474 (63.8)
≥35	245 545 (23.5)	245 545 (23.5)	245 546 (23.5)	245 546 (23.5)	245 548 (23.5)	245 545 (23.5)
Missing	<6 (S)	-	-	-	-	-
Neighborhood family income quintile						
Quintile 1 (lowest)	231 976 (22.2)	237 114 (22.7)	237 168 (22.7)	237 159 (22.7)	237 139 (22.7)	237 218 (22.7)
Quintile 2	209 819 (20.1)	214 380 (20.5)	214 329 (20.5)	214 387 (20.5)	214 423 (20.5)	214 293 (20.5)
Quintile 3	212 676 (20.4)	217 262 (20.8)	217 239 (20.8)	217 180 (20.8)	217 149 (20.8)	217 219 (20.8)
Quintile 4	204 246 (19.6)	208 381 (20.0)	208 453 (20.0)	208 294 (20.0)	208 390 (20.0)	208 383 (20.0)
Quintile 5 (highest)	163 853 (15.7)	167 121 (16.0)	167 069 (16.0)	167 238 (16.0)	167 157 (16.0)	167 145 (16.0)
Missing	21 688 (2.1)	-	-	-	-	-
Neighborhood education level quintile ^a						
Quintile 1 (lowest)	162 350 (15.6)	173 538 (16.6)	173 355 (16.6)	173 500 (16.6)	173 303 (16.6)	173 387 (16.6)
Quintile 2	186 453 (17.9)	200 066 (19.2)	200 265 (19.2)	200 267 (19.2)	200 330 (19.2)	199 998 (19.2)
Quintile 3	211 905 (20.3)	227 729 (21.8)	227 808 (21.8)	227 777 (21.8)	227 785 (21.8)	227 935 (21.8)
Quintile 4	231 806 (22.2)	249 685 (23.9)	249 567 (23.9)	249 593 (23.9)	249 721 (23.9)	249 733 (23.9)
Quintile 5 (highest)	179 814 (17.2)	193 240 (18.5)	193 263 (18.5)	193 121 (18.5)	193 119 (18.5)	193 205 (18.5)
Missing	71 930 (6.9)	-	-	-	-	-
Parity						
0	448 209 (42.9)	453 421 (43.4)	453 469 (43.4)	453 475 (43.4)	453 473 (43.4)	453 482 (43.4)
≥ 1	585 339 (56.1)	590 837 (56.6)	590 789 (56.6)	590 783 (56.6)	590 785 (56.6)	590 776 (56.6)

Missing	10 710 (1.0)	-	-	-	-	-
Ethnicity						
Non-Asian	498 477 (47.4)	498 477 (47.4)	498 477 (47.4)	498 477 (47.4)	498 477 (47.4)	498 477 (47.4)
Asian	186 995 (17.9)	186 995 (17.9)	186 995 (17.9)	186 995 (17.9)	186 995 (17.9)	186 995 (17.9)
Missing	358 786 (34.4)	358 786 (34.4)	358 786 (34.4)	358 786 (34.4)	358 786 (34.4)	358 786 (34.4)
Pre-pregnancy BMI category (kg/m²)						
< 18.5	54 538 (5.2)	62 495 (6.0)	62 668 (6.0)	62 466 (6.0)	62 655 (6.0)	62 444 (6.0)
18.5-24.9	470 474 (45.1)	536 944 (51.4)	537 104 (51.4)	536 666 (51.4)	536 794 (51.4)	537 271 (51.5)
25.0-30.0	223 765 (21.4)	254 655 (24.4)	254 345 (24.4)	254 612 (24.4)	254 550 (24.4)	254 429 (24.4)
≥ 30.0	167 576 (16.1)	190 164 (18.2)	190 141 (18.2)	190 514 (18.2)	190 259 (18.2)	190 114 (18.2)
Missing	127 905 (12.3)	-	-	-	-	-
Conception type ^b						
Fertility treatments	33 824 (3.2)	36 299 (3.5)	36 155 (3.5)	36 356 (3.5)	36 350 (3.5)	36 308 (3.5)
Spontaneous conception	959 586 (91.9)	1 007 959 (96.5)	1 008 103 (96.5)	1 007 902 (96.5)	1 007 908 (96.5)	1 007 950 (96.5)
Missing	50 848 (4.9)	-	-	-	-	-
Maternal smoking ^c						
No	900 891 (86.3)	946 128 (90.6)	946 086 (90.6)	946 192 (90.6)	946 170 (90.6)	946 139 (90.6)
Yes	94 670 (9.1)	98 130 (9.4)	98 172 (9.4)	98 066 (9.4)	98 088 (9.4)	98 119 (9.4)
Missing	48 697 (4.7)	-	-	-	-	-
Pre-existing medical or obstetric conditions ^d						
No	764 583 (73.2)	789 485 (75.6)	789 565 (75.6)	789 597 (75.6)	789 426 (75.6)	789 459 (75.6)
Yes	246 285 (23.6)	254 773 (24.4)	254 693 (24.4)	254 661 (24.4)	254 832 (24.4)	254 799 (24.4)
Missing	33 390 (3.2)	-	-	-	-	-
Prenatal education						
No	687 507 (65.8)	770 901 (73.8)	771 202 (73.9)	771 544 (73.9)	771 052 (73.8)	771 154 (73.9)
Yes	240 017 (23.0)	273 357 (26.2)	273 056 (26.2)	272 714 (26.1)	273 206 (26.2)	273 104 (26.2)

Missing	116 734 (11.2)	-	-	-	-	-
Infant sex						
Male	536 036 (51.3)	536 036 (51.3)	536 036 (51.3)	536 036 (51.3)	536 036 (51.3)	536 036 (51.3)
Female	508 222 (48.7)	508 222 (48.7)	508 222 (48.7)	508 222 (48.7)	508 222 (48.7)	508 222 (48.7)
Fiscal year of delivery						
2012/13	131 824 (12.6)	131 824 (12.6)	131 824 (12.6)	131 824 (12.6)	131 824 (12.6)	131 824 (12.6)
2013/14	130 577 (12.5)	130 577 (12.5)	130 577 (12.5)	130 577 (12.5)	130 577 (12.5)	130 577 (12.5)
2014/15	130 172 (12.5)	130 172 (12.5)	130 172 (12.5)	130 172 (12.5)	130 172 (12.5)	130 172 (12.5)
2015/16	130 003 (12.5)	130 003 (12.5)	130 003 (12.5)	130 003 (12.5)	130 003 (12.5)	130 003 (12.5)
2016/17	130 605 (12.5)	130 605 (12.5)	130 605 (12.5)	130 605 (12.5)	130 605 (12.5)	130 605 (12.5)
2017/18	130 653 (12.5)	130 653 (12.5)	130 653 (12.5)	130 653 (12.5)	130 653 (12.5)	130 653 (12.5)
2018/19	130 272 (12.5)	130 272 (12.5)	130 272 (12.5)	130 272 (12.5)	130 272 (12.5)	130 272 (12.5)
2019/20	130 152 (12.5)	130 152 (12.5)	130 152 (12.5)	130 152 (12.5)	130 152 (12.5)	130 152 (12.5)

Note: BMI= body mass index

* Column percentages are presented.

^a Percentage of college and university degrees among adults 25–64 years old.

^b Fertility treatments include assisted reproductive treatments and non-assisted reproductive treatments.

^c A self-reported variable, which was based on smoking status at first prenatal visit.

^d Pre-existing medical or obstetrical conditions were a composite of pre-existing maternal or obstetric health conditions, including any of pre-existing hypertension, autoimmune, cardiac and endocrine conditions, previous stillbirth, and previous cs.

Table S3. GDM rates by fiscal year of delivery from April 1, 2012 to March 31, 2020 (data for Figure 2)

Fiscal year of delivery	No. of deliveries	No. GDM cases		GDM rate per 100 deliveries (95% CI)
		GDM without medical therapy	GDM with medical treatments	
2012/13	131 824	5105	2887	6.1 (5.93-6.19)
2013/14	130 577	4952	2999	6.1 (5.96-6.22)
2014/15	130 172	5695	3301	6.9 (6.77-7.05)
2015/16	130 003	5931	3495	7.3 (7.11-7.39)
2016/17	130 605	6925	3953	8.3 (8.18-8.48)
2017/18	130 653	7545	4259	9.0 (8.88-9.19)
2018/19	130 272	7861	4394	9.4 (9.25-9.57)
2019/20	130 152	8852	4742	10.4 (10.28-10.61)
2012-19	1 044 258	52 866	30 030	7.9 (7.89-7.99)

Table S4. Estimated risk of gestational diabetes mellitus (GDM) in Ontario, Canada, fiscal years 2012/13-2019/20 in complete-case analysis

Fiscal year at delivery	Relative risk (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
2012/13	Ref	ref	Ref
2013/14	0.99 (0.95, 1.04)	0.98 (0.94, 1.03)	0.99 (0.95, 1.03)
2014/15	1.12 (1.08, 1.17)	1.11 (1.07, 1.15)	1.11 (1.06, 1.15)
2015/16	1.23 (1.18, 1.28)	1.17 (1.13, 1.22)	1.17 (1.12, 1.21)
2016/17	1.40 (1.35, 1.45)	1.31 (1.26, 1.35)	1.30 (1.26, 1.35)
2017/18	1.54 (1.48, 1.59)	1.39 (1.34, 1.45)	1.38 (1.33, 1.44)
2018/19	1.58 (1.52, 1.64)	1.41 (1.36, 1.46)	1.40 (1.35, 1.45)
2019/20	1.75 (1.69, 1.81)	1.54 (1.48, 1.59)	1.55 (1.49, 1.60)

^a Crude regression model;

^b Model was adjusted for maternal age at delivery, maternal ethnicity and pre-pregnancy BMI;

^c Model was adjusted for maternal age at delivery, neighbourhood income level, neighbourhood education level, ethnicity, parity, pre-pregnancy body mass index (BMI), conception type, smoking, pre-existing medical or obstetric conditions, prenatal education and infant sex.

Table S5. Estimated risk of gestational diabetes mellitus (GDM) in Ontario, Canada, fiscal years 2012/13-2019/20 among pregnant individuals with first delivery analysis

Fiscal year at delivery	Relative risk (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3
2012/13	Ref	ref	Ref
2013/14	1.01 (0.98, 1.05)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
2014/15	1.19 (1.15, 1.23)	1.15 (1.12, 1.19)	1.15 (1.12, 1.19)
2015/16	1.26 (1.21, 1.30)	1.21 (1.18, 1.25)	1.21 (1.17, 1.25)
2016/17	1.44 (1.39, 1.49)	1.39 (1.35, 1.42)	1.39 (1.35, 1.42)
2017/18	1.55 (1.50, 1.61)	1.47 (1.44, 1.51)	1.47 (1.43, 1.50)
2018/19	1.60 (1.55, 1.66)	1.50 (1.46, 1.53)	1.49 (1.46, 1.53)
2019/20	1.77 (1.71, 1.82)	1.62 (1.59, 1.66)	1.65 (1.62, 1.69)

^a Crude regression model;

^b Adjusted estimates were pooled risk ratios calculated using imputed datasets (n=5) by fully conditional specification approach. Model was adjusted for maternal age at delivery, maternal ethnicity and pre-pregnancy BMI;

^c Adjusted estimates were pooled risk ratios calculated using imputed datasets (n=5) by fully conditional specification approach. Model was adjusted for maternal age at delivery, neighbourhood income level, neighbourhood education level, ethnicity, parity, pre-pregnancy body mass index (BMI), conception type, smoking, pre-existing medical or obstetric conditions, prenatal education and infant sex.

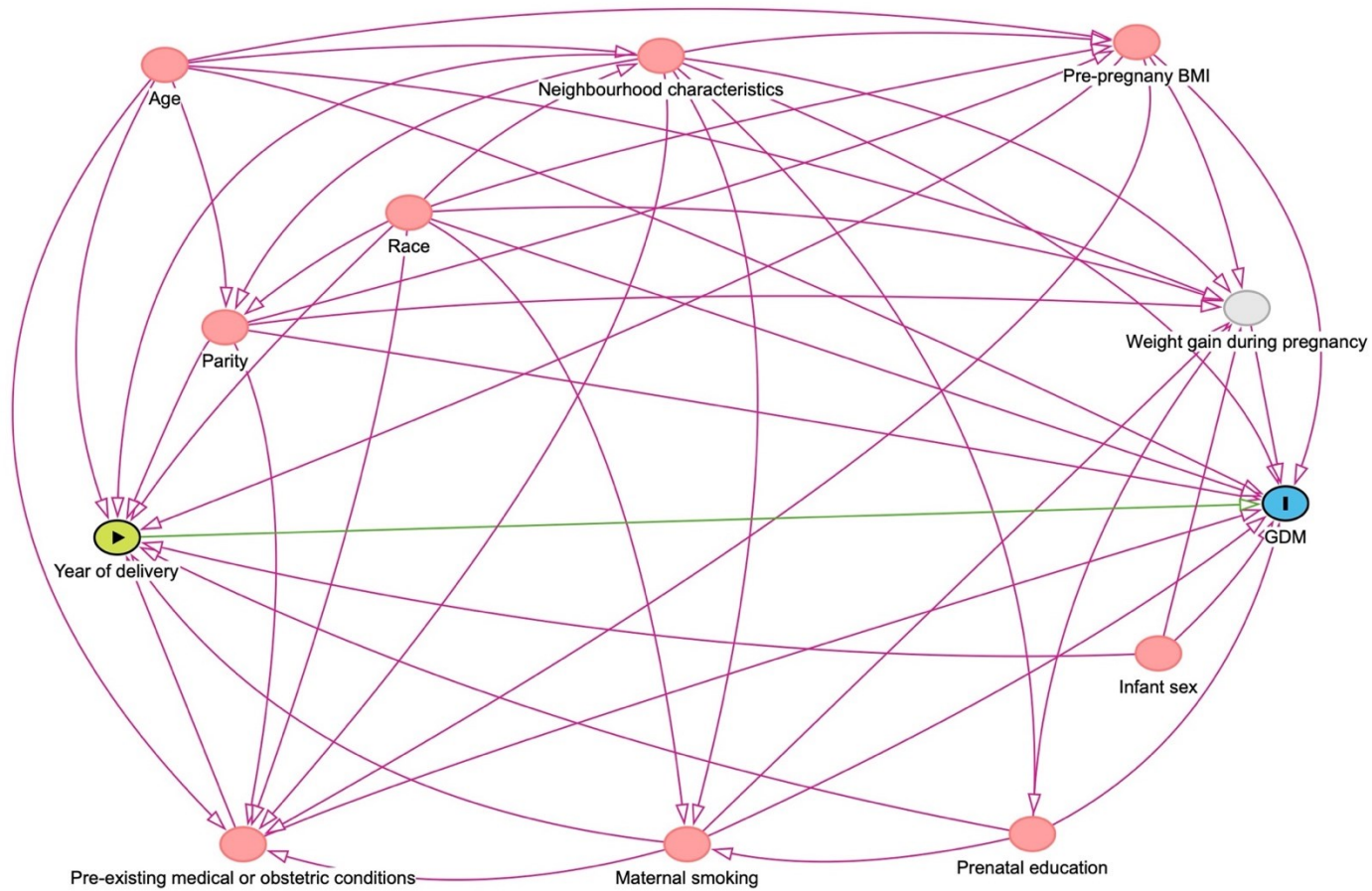
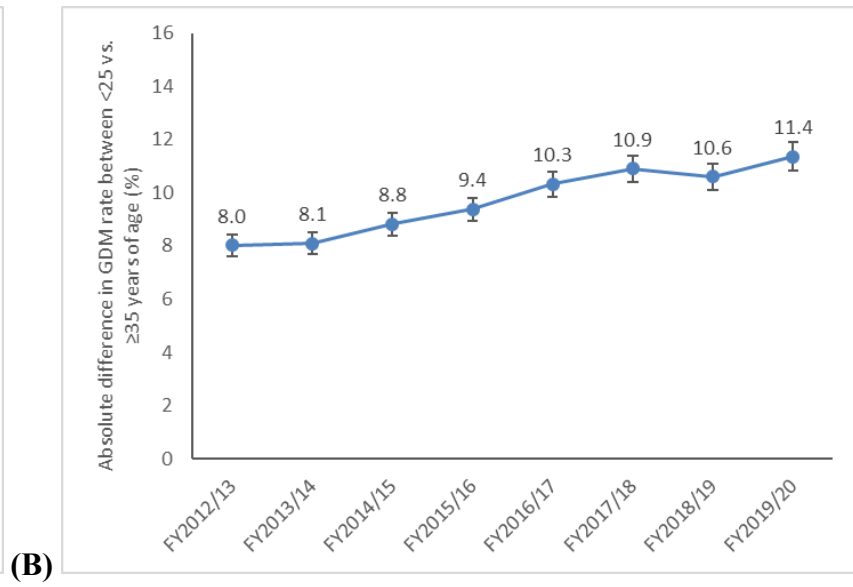
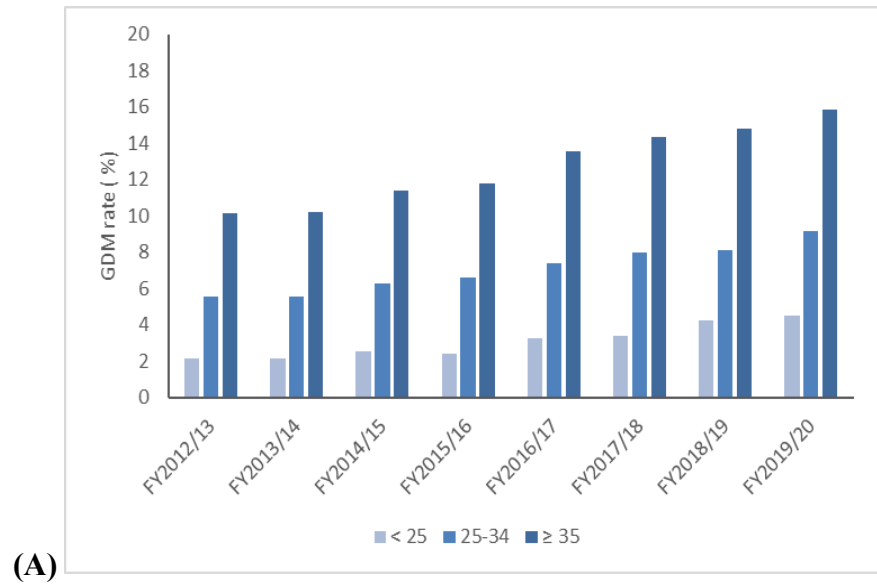


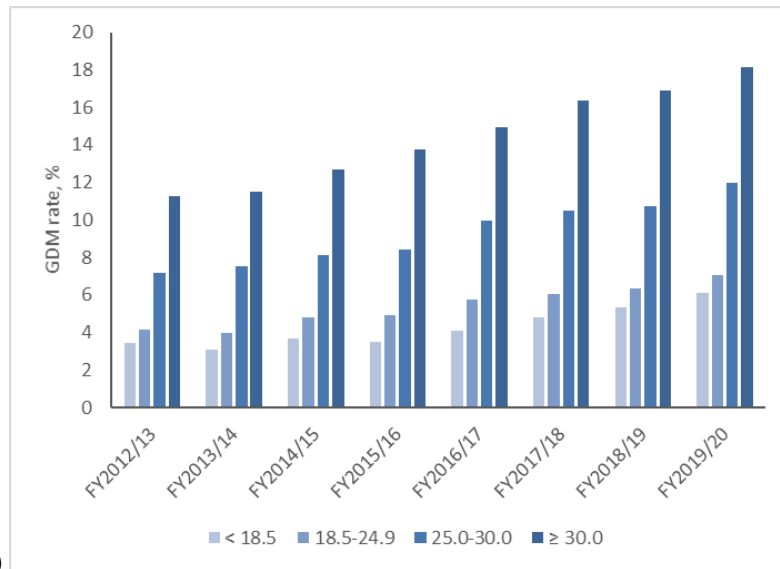
Figure S1. Directed Acyclic Graph (DAG) of causal assumptions between year of delivery and GDM ^{a,b}

^a Neighborhood characteristics include neighborhood-level family income quintiles and education quintiles;

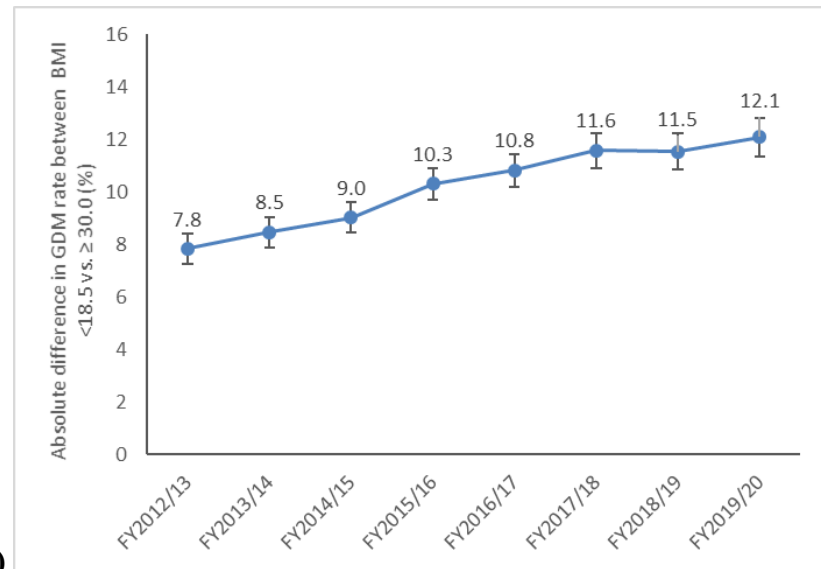
^b Weight gain during pregnancy before GDM diagnosis was an unmeasured variable.



(C)



(D)



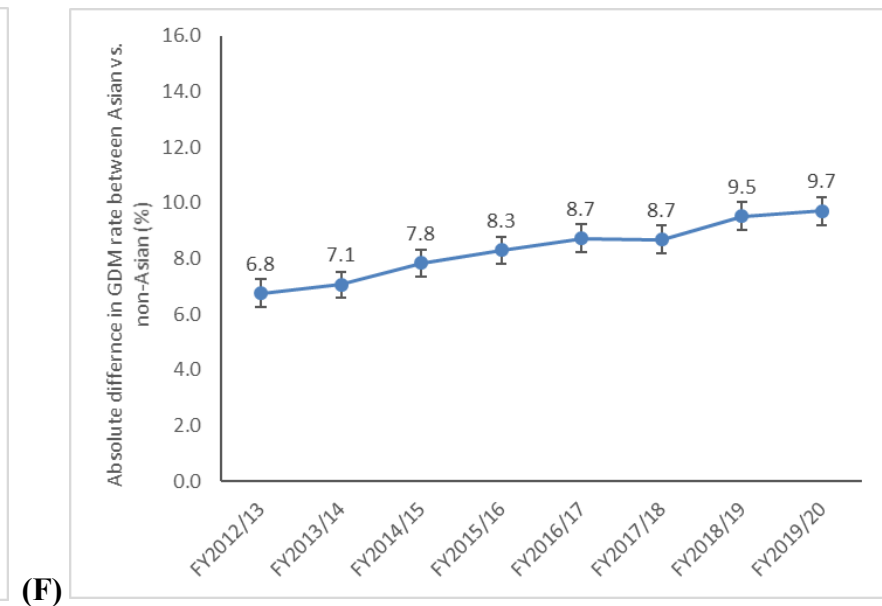
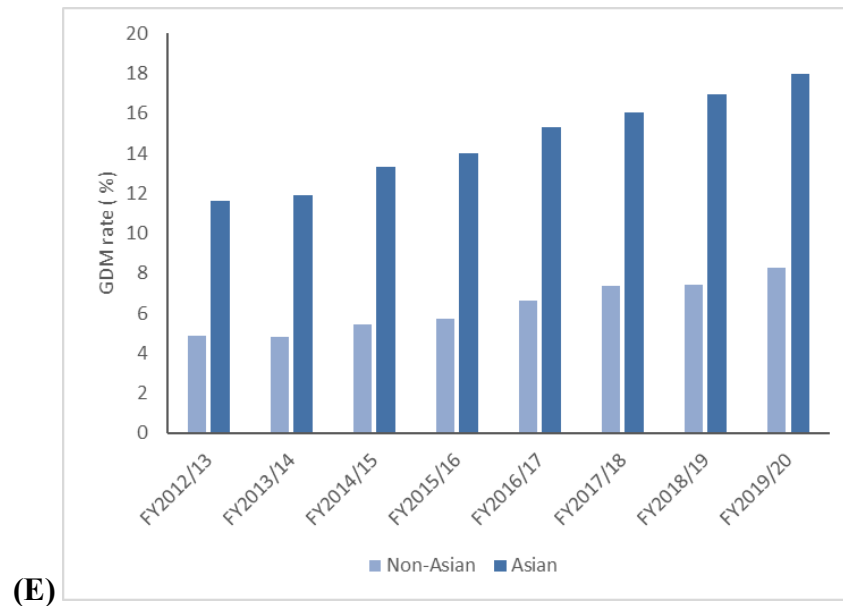


Figure S2. Temporal trends in rates of GDM among all singleton hospital deliveries in Ontario, Canada, April 1, 2012 to March 31, 2020, stratified by maternal age at delivery, (A, B), pre-pregnancy BMI (C,D), and maternal ethnicity (E,F) Panels A, C and E display GDM rates; Panels B, D and F display the absolute differences in rate of GDM between the lowest and highest category. GDM rate was calculated among all deliveries in each fiscal year.

Appendix C. Additional files for Chapter 5

Additional file 1 – 13:

Table S1. Datasets used in this analysis

Table S2. Canadian guidelines for screening and diagnosis of GDM during 2012 and 2020

Table S3. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code outcomes

Table S4. Covariates with missing values and strategies handling missing values

Table S5. RECORD checklist

Table S6. Temporal trends in maternal outcomes among deliveries with and without GDM in Ontario, Canada, fiscal years 2012/13-2019/20

Table S7. Interaction tests of GDM with time periods of delivery, Ontario, Canada, fiscal years 2012/13-2019/20

Table S8. Risk difference in adverse maternal outcomes among women with GDM and non-GDM in Ontario, Canada, by time periods of delivery (n=1 044 258)

Table S9. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery in complete-case analysis

Table S10. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals with first delivery

Table S11. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals without medical treatments for GDM

Figure S1. A Directed Acyclic Graph (DAG) of GDM and adverse maternal outcomes

Figure S2. Study flow chart

Table S1. Datasets used in this analysis

Dataset	Description	Purpose
Better Outcomes Registry & Network (BORN) Ontario	Includes maternal demographics and pregnancy characteristics, conception types, health behaviors, pre-existing medical health conditions, obstetric complications, labor and delivery details and newborn outcomes.	Obtaining study exposure (GDM diagnosis), baseline maternal, obstetric and newborn covariates, and outcomes.
Canada Census profiles (CENSUS)	Includes area-level sociodemographic data from the national census of population questionnaire on income, education, and other topics.	Obtaining dissemination area-level median family income and education quintiles based on the maternal postal codes and the Postal codes Conversion File Plus (PCCF+).
Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)	Includes administrative, demographic and clinical data for hospital discharge abstract.	Obtaining supplementary data for exposure, data for primary and secondary outcomes in the study

Table S2. Canadian guidelines from the Diabetes Canada and the SOGC for GDM screening and diagnosis during 2012 and 2020

Year, Organization	Screening method	Screening Test	GCT	OGTT				
			1h PG (mmol/l)	FPG (mmol/l)	1h PG (mmol/l)	2h PG (mmol/l)	3h PG (mmol/l)	No. of abnormal diagnostic values
Diabetes Canada								
2008, DC	Universal	2-step 2h 75g OGTT ^{\$}	7.8-10.2	5.3	10.6	8.9	-	2
2013, DC	Universal	2-step 2h 75g OGTT ^{\$\$}	7.8-11.0	5.3	10.6	9.0		1
		1-step 2h 75g OGTT		5.1	10.0	8.5	-	1
2018, DC	Universal	2-step 2h 75g OGTT ^{\$\$}	7.8-11.0	5.3	10.6	9.0	-	1
		1-step 2h 75g OGTT		5.1	10.0	8.5	-	1
SOGC								
2002, SOGC	Selective	2-step 2h 75g OGTT ^{\$}	7.8-10.2	5.3	10.0	8.6	-	2
		2-step 3h 100g OGTT [#]		5.3/5.8	10.0/10.6	8.6/9.2	7.8/8.0	2
2016, SOGC	Universal	2-step 2h 75g OGTT ^{\$\$}	7.8-11.0	5.3	10.6	9.0	-	1
		1 step 2h 75g OGTT		5.1	10.0	8.5	-	1
2019, SOGC	Universal	2-step 2h 75g OGTT ^{\$\$}	7.8-11.0	5.3	10.6	9.0	-	1
		1 step 2h 75g OGTT		5.1	10.0	8.5	-	1

Note: GCT= glucose challenge test; OGTT= Oral glucose tolerance test; FPG= fasting plasma glucose; PG, plasma glucose;

[§] If the 1 hour post-glucose plasma glucose ≥ 10.3 (mmol/l) in a 50g GCT, it indicates GDM diagnosis without a subsequent 75g OGTT; if the 1 hour post-glucose plasma glucose in 50g GCT is between 7.8-10.2 mmol/l, a subsequent 75g OGTT test will be followed; A single abnormal value in OGTT test indicated impaired glucose tolerance;

^{\$\$} If the 1 hour post-glucose plasma glucose ≥ 11.1 (mmol/l) in a 50g GCT, it immediately diagnoses GDM without a subsequent 75g OGTT; if the 1 hour post-glucose plasma glucose in 50-g glucose challenge test (GCT) is between 7.8-11.0 mmol/l, a subsequent 75g OGTT test will be followed;

[#] Diagnostic cut-off values based on the Carpenter–Coustan (CC) and National Diabetes Data Group (NDDG) criteria.

Table S3. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code exposure and outcomes

Variables	Source	Variable	Coding	Coding description
GDM	BIS OR	Diabetes and Pregnancy, Pregnancy complications		Gestational diabetes
	ICD-10-CA		Mother: O24.8; Infant: P70.0 (excluding T1DM: E10.X, O24.5; T2DM: E11.X, O24.6; unspecified type:O24.7, E13.X, E14.X)	
Induction	BIS	Type of Labour		Induction
Mode of delivery	BIS	Type of Birth		Caesarean delivery, assisted vaginal delivery
Gestational hypertensive disorders	BIS	Hypertensive Disorders of Pregnancy, All indication(s) for Caesarean birth, All Indications for Induction of Labour		Gestational hypertension or pregnancy induced hypertension
Maternal death	BIS OR	Maternal Outcome		Maternal death prior discharge
	ICD-10-CA OR		O95, O97	
	CIHI-DAD	Discharge disposition		
Maternal morbidity	BIS OR	Labour and Birth Complications, Postpartum Complication		Obstetric embolism
	ICD-10-CA		O88	
	ICD-10-CA		O75.1, R57, T80.5, T88.6	Obstetric shock
	BIS OR	Labour and Birth Complications, Postpartum Complication		Postpartum hemorrhage (due to retained products, uterine atony or

	ICD-10-CA <i>AND</i>		O72.0-O72.3	other causes) with hysterectomy or other procedures to control bleeding
	CCI		5.MD.60.KE, 5.MD.60.RC, 5.MD.60.CB, 5.MD.60.RD, 1.RM.87.LAGX, 1.RM.89.LA, 5.PC.91.LA, 1.KT.51 or 1.RM.13 without 1.PL.74, 1.RS.80, 1.RS.74	
	ICD-10-CA		O75.3, O85	Sepsis
	BIS <i>OR</i>	Labour and Birth Complications		Thromboembolism
	ICD-10-CA		G08, I26, I80.1, I80.2, I80.3, I80.8, I80.9, I82, K55.0, K55.9, K75.1, N28.0, O07.2, O07.7, O08.2, O22.3, O22.8, O22.9, O87.1, O87.9, O88.2	
	BIS <i>OR</i>	Labour and Birth Complications, All indication(s) for Caesarean birth		Uterine rupture
	ICD-10-CA		O71.0, O71.1	

Table S4. Covariates with missing values and strategies handling missing values

Characteristics	No. (%) of missing values [#]		
	Total N = 1 044 258	GDM	Non-GDM
Maternal age at delivery	<6 (S)	0 (0)	<6 (S)
Neighborhood family income quintile	21688 (2.1)	1 516 (1.8)	20 172 (2.1)
Neighbourhood education level quintile	71930 (6.9)	6 028 (7.3)	65 902 (6.9)
Nulliparity	10710 (1.0)	906 (1.1)	9 804 (1.0)
Race/ethnicity	358786 (34.4)	23398 (28.2)	335388 (34.9)
Pre-pregnancy BMI category	127 905 (12.3)	10 160 (12.3)	117 745 (12.2)
Conception type	50 848 (4.9)	4 770 (5.8)	46 078 (4.8)
Maternal smoking	48 697 (4.7)	4 282 (5.2)	44 415 (4.6)
Pre-existing medical or obstetrical conditions	33 390 (3.2)	2 966 (3.6)	30 424 (3.2)
Prenatal education	116 734 (11.2)	10 001 (12.1)	106 733 (11.1)
Antenatal healthcare provider	39 228 (3.8)	3 731 (4.5)	35 497 (3.7)

[#] Column percentages of missingness were presented for deliveries with GDM and non-GDM.

Considering the high amount of missing data in maternal race/ethnicity variable, we used missing as a category for those with missing race in our main analyses. For other variables with missing values, we used multiple imputation with fully conditional specification (FCS) approach. With the assumption that data was missing at random (MAR), a unique multivariable model was applied to impute missing data for discrete and continuous covariate.¹ Maternal age at delivery, neighborhood income and education level, pre-pregnancy BMI and antenatal healthcare provider were imputed using a generalized logit model. Nulliparity, smoking at first prenatal visit, conception type, pre-existing maternal and obstetric health conditions, and prenatal education were imputed using a cumulative logit model. Imputation models included all variables which were used in multivariable regression models. The results from five imputed datasets were combined into a pooled estimate following Rubin's rules for multiple imputed data and best practice.²

References:

1. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16(3):219-242. doi:10.1177/0962280206074463

2. Roderick L, Donald R. Statistical Analysis with Missing Data, Third Edition.; 2019.
<https://onlinelibrary.wiley.com/doi/book/10.1002/9781119482260>

Table S5. RECORD checklist

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, paragraphs 1-2		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, paragraph 3		
Methods					

Study Design	4	Present key elements of study design early in the paper	Methods – Study design and population, paragraph 1		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – Study design and population, paragraph 1		
Participants	6	<i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case	Methods – Study design and population, paragraphs 1-2, supplementary Table S1	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods – Study design and population, paragraphs 1-2, supplementary Table S1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods – Screening and diagnosis of GDM; Outcomes, covariates in the Statistical analysis; supplementary Table	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided	Methods – Screening and diagnosis of GDM; Outcomes, covariates in the Statistical analysis supplementary

		S2	Table S3

Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – Screening and diagnosis of GDM; Outcomes; Supplementary Table S2-S3		
Bias	9	Describe any efforts to address potential sources of bias	Methods – Statistical analysis (multiple imputation, sensitivity analyses)		
Study size	10	Explain how the study size was arrived at	Methods – Study design and population, paragraph 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods – Screening and diagnosis of GDM; Outcomes		
Statistical methods	12	) Describe all statistical methods, including those used to control for confounding) Describe any methods used to examine subgroups and interactions) Explain how missing data were addressed) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed	Methods – statistical analysis		

		<i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods – Study design and population paragraph 2 Methods – Study design and population, paragraphs 1-2
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods – Study design and population paragraph 2, supplementary Table S1
Results					

Participants	13	- Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) - Give reasons for non-participation at each stage. - Consider use of a flow diagram	Results, paragraph 1; Figure S2	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results, paragraph 1; Figure S2
Descriptive data	14	- Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount)	Results, paragraph 1; Table 1		

Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures	Results – Tables 2 and Figure 3		
Main results	16	) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included) Report category boundaries when continuous variables were categorized) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results – Associations between GDM and maternal outcomes, Tables 2, Figure 3 and supplementary Table S8		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results – Sensitivity analyses, Supplementary Table S9-S11		
Discussion					

Key results	18	Summarise key results with reference to study objectives	Discussion, paragraph 1		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion- Strengths and limitations, paragraph 2	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion- Strengths and limitations, paragraph 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion- Interpretation		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion- Strengths and limitations, paragraph 2		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

*Checklist is protected under Creative Commons Attribution ([CC BY](#)) license.

Table S6. Temporal trends in maternal outcomes among deliveries with and without GDM Ontario, Canada, fiscal years 2012/13-2019/20

Outcomes	Total cases	Rate per 100 deliveries		P for trend ^a
		2012/13	2019/20	
GDM deliveries				
Induction	34 063	35.8 (34.7, 36.9)	46.2 (45.3, 47.0)	<0.001
CS	30 525	38.3 (37.3, 39.4)	36.6 (35.8, 37.4)	0.28
Assisted vaginal delivery	6 844	8.42 (7.81, 9.03)	8.22 (7.75, 8.69)	0.002
Pregnancy-induced hypertension	7 471	8.78 (8.16, 9.41)	8.88 (8.41, 9.35)	0.34
Maternal morbidity /mortality ^b	617	6.00 (4.24, 7.76)	7.90 (6.33, 9.47)	0.001
Component outcome ^b				
Obstetric embolism	31	0.38 (-0.02, 0.77)	0.44 (0.05, 0.83)	0.46
Sepsis	73	0.75 (0.16, 1.34)	0.81 (0.42-1.20)	0.19
Thromboembolism	84	1.13 (0.34, 1.91)	1.03 (0.44-1.62)	0.59
Uterine rupture	85	0.63 (0.04, 1.21)	1.03 (0.44, 1.62)	0.69
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	366	3.25 (2.08, 4.43)	5.08 (3.90, 6.25)	<0.001
No GDM deliveries				
Induction	239 857	22.3 (22.0, 22.5)	29.2 (28.9, 29.4)	<0.001
CS	261 754	26.5	28.9	<0.001

		(26.3, 26.8)	(28.6-29.1)	
Assisted vaginal delivery	87 239	9.33 (9.17, 9.49)	8.85 (8.69, 9.01)	<0.001
Pregnancy-induced hypertension	49 220	4.75 (4.63, 4.87)	5.58 (5.44, 5.71)	<0.001
Maternal morbidity /mortality ^b	5 386	5.10 (4.71, 5.49)	6.40 (6.01, 6.79)	<0.001
Component outcome ^b				
Obstetric embolism	283	0.27 (0.17, 0.36)	0.35 (0.16, 0.55)	0.03
Sepsis	785	0.73 (0.53, 0.92)	1.03 (0.83-1.23)	<0.001
Thromboembolism	943	0.61 (0.41, 0.80)	1.07 (0.88, 1.27)	<0.001
Uterine rupture	1 021	0.99 (0.79, 1.18)	1.26 (1.07, 1.46)	0.02
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	2 518	2.71 (2.51, 2.90)	2.84 (2.45, 3.23)	0.002

^a Test for linear trend in proportions based on each year between fiscal years 2012/13 and 2019/20;

^b Rate of maternal morbidity and mortality and its component outcome was expressed as per 1000 deliveries; obstetric shock and maternal death were not presented given few cases in each study year.

Table S7. Interaction tests of GDM with time periods of delivery, Ontario, Canada, fiscal years 2012/13-2019/20

Outcomes	RR	RD
	P-interaction	P-interaction
Induction	0.07	<0.001
CS	<0.001	<0.001
Assisted vaginal delivery	0.13	0.65
Pregnancy-induced hypertension	<0.001	<0.001
Maternal morbidity /mortality	0.28	0.12
Component outcomes		
Obstetric embolism	0.96	0.87
Sepsis	0.92	0.68
Thromboembolism	0.56	0.46
Uterine rupture	0.86	0.64
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	0.02	0.005

Table S8. Risk difference in maternal outcomes among women with GDM and non-GDM in Ontario, Canada, stratified by time periods of delivery (n=1 044 258)

Outcomes	Adjusted RD, % ^a (95% CI)	
	2012/13-2015/16 (n=522 576)	2016/17-2019/20 (n=521 682)
Induction	14.1 (13.6, 14.7)	15.8 (15.4, 16.3)
CS	4.53 (4.03, 5.03)	2.61 (2.23, 3.00)
Assisted vaginal delivery	-0.29 (-0.55, -0.02)	-0.39 (-0.61, -0.17)
Pregnancy-induced hypertension	2.83 (2.53, 3.13)	2.00 (1.75, 2.24)
Maternal morbidity /mortality ^b	-0.12 (-0.87, 0.62)	0.92 (0.15, 1.69)
Component outcome ^{b,c}		
Obstetric embolism	0.01 (-0.17, 0.18)	0.02 (-0.17, 0.21)
Sepsis	-0.04 (-0.31, 0.23)	0.04 (-0.23, 0.32)
Thromboembolism	-0.04 (-0.37, 0.30)	-0.23 (-0.53, 0.07)
Uterine rupture	-0.13 (-0.47, 0.21)	-0.32 (-0.60, -0.05)
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	0.43 (-0.17, 1.03)	1.51 (0.90, 2.12)

Note: CS= caesarean section, RD=Risk difference.

^a Risk difference comparing pregnancies with GDM vs. no GDM was generated by multivariable regression models using imputed datasets (n=5) by fully conditional specification approach, with adjustment for maternal age at delivery, income, education level, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education and antenatal health care providers;

^b Risk difference was expressed as per 1000 deliveries;

^c Risk difference of component outcomes was only adjusted for maternal age and parity to enable convergence in multivariable regression models; effect estimates for obstetric shock and maternal death were not presented given few cases in each study period.

Table S9. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, stratified by time periods of delivery in complete-case analysis

Outcome	Complete-case analysis			
	Adjusted RR ^a (95% CI)		Adjusted RD, % ^a (95% CI)	
	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)
Induction	1.60 (1.57, 1.64)	1.59 (1.57, 1.62)	14.6 (13.9, 15.2)	16.2 (15.7, 16.8)
CS	1.08 (1.05, 1.10)	1.06 (1.04, 1.08)	3.98 (3.43, 4.53)	2.63 (2.18, 3.08)
Assisted vaginal delivery	0.97 (0.92, 1.02)	0.93 (0.89, 0.97)	-0.20 (-0.53, 0.13)	-0.44 (-0.70, -0.19)
Pregnancy-induced hypertension	1.41 (1.35, 1.48)	1.26 (1.21, 1.32)	2.85 (2.50, 3.21)	2.00 (1.70, 2.29)
Maternal morbidity /mortality ^b	0.80 (0.65, 0.97)	1.05 (0.91, 1.21)	-0.49 (-1.34, 0.36)	0.90 (0.02, 1.79)
Component outcome ^{b,c}				
Obstetric embolism	1.12 (0.51, 2.44)	1.16 (0.63, 2.15)	-0.01 (-0.22, 0.20)	-0.02 (-0.20, 0.16)
Sepsis	0.97 (0.55, 1.71)	1.30 (0.88, 1.92)	-0.08 (-0.37, 0.22)	0.10 (-0.21, 0.41)
Thromboembolism	0.90 (0.54, 1.48)	0.84 (0.57, 1.23)	-0.12 (-0.47, 0.24)	-0.27 (-0.60, 0.06)
Uterine rupture	0.71 (0.45, 1.12)	0.79 (0.55, 1.12)	-0.11 (-0.52, 0.30)	-0.22 (-0.57, 0.13)
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	0.80 (0.60, 1.05)	1.23 (1.02, 1.50)	0.19 (-0.50, 0.88)	1.16 (0.49, 1.83)

^a Multivariable regression models were used to generate effect estimates, adjusting for maternal age at delivery, income, education level, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, and antenatal health care providers;

^b Risk difference was expressed as per 1000 deliveries;

^c Risk difference of component outcomes was only adjusted for maternal age and parity to enable convergence in multivariable regression models; effect estimates for obstetric shock and maternal death were not presented given few cases in each study period.

Table S10. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, stratified by time periods of delivery among individuals with first delivery

Outcome	Pregnant individuals with first delivery			
	Adjusted RR ^a		Adjusted RD,% ^a	
	(95% CI)		(95% CI)	
	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)
Induction	1.59 (1.57, 1.62)	1.54 (1.52, 1.57)	14.1 (13.4, 14.9)	16.9 (16.1, 17.7)
CS	1.10 (1.08, 1.13)	1.05 (1.03, 1.08)	4.76 (4.11, 5.41)	2.86 (2.17, 3.56)
Assisted vaginal delivery	0.96 (0.92, 1.01)	0.94 (0.90, 0.98)	-0.18 (-0.49, 0.13)	-0.33 (-0.68, 0.03)
Pregnancy-induced hypertension	1.44 (1.39, 1.48)	1.24 (1.19, 1.29)	4.19 (3.84, 4.55)	3.57 (3.20, 3.95)
Maternal morbidity /mortality ^b	0.95 (0.80, 1.11)	1.04 (0.90, 1.18)	-0.71 (-6.61, 5.19)	0.50 (-0.53, 1.52)
Component outcome ^{b,c}				
Obstetric embolism	1.18 (0.51, 1.85)	1.45 (0.86, 2.04)	0.06 (-0.16, 0.28)	0.14 (-0.12, 0.40)
Sepsis	1.10 (0.67, 1.53)	1.14 (0.78, 1.49)	0.03 (-0.28, 0.34)	0.08 (-0.33, 0.49)
Thromboembolism	0.98 (0.59, 1.37)	0.90 (0.52, 1.27)	0.04 (-0.32, 0.39)	-0.16 (-0.55, 0.23)
Uterine rupture	1.02 (0.66, 1.39)	0.63 (0.17, 1.09)	0.07 (-0.31, 0.45)	-0.34 (-0.65, -0.02)
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	0.95 (0.74, 1.16)	1.24 (1.06, 1.42)	0.46 (-0.18, 1.10)	1.43 (0.62, 2.23)

^a Effect estimates were generated by multivariable regression models using imputed datasets (n=5) by fully conditional specification approach, with adjustment for maternal age at delivery, income, education level, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, and antenatal health care providers;

^b Risk difference was expressed as per 1000 deliveries;

^c Risk difference of component outcomes was only adjusted for maternal age and parity to enable convergence in multivariable regression models; effect estimates for obstetric shock and maternal death were not presented given few cases in each study period.

Table S11. Sensitivity analyses for trends in maternal outcomes associated with GDM in Ontario, Canada, stratified by time periods of delivery among individuals without medical treatments for GDM

Outcome	Pregnant individuals without medical treatments for GDM			
	Adjusted RR ^a (95% CI)		Adjusted RD, % ^a (95% CI)	
	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)
Induction	1.36 (1.34, 1.39)	1.43 (1.41, 1.45)	8.24 (7.62, 8.85)	11.1 (10.6, 11.7)
CS	1.08 (1.06, 1.10)	1.04 (1.02, 1.06)	3.76 (3.16, 4.37)	1.69 (1.24, 2.15)
Assisted vaginal delivery	0.98 (0.94, 1.03)	0.95 (0.90, 0.99)	-0.07 (-0.41, 0.27)	-0.30 (-0.56, -0.03)
Pregnancy-induced hypertension	1.45 (1.40, 1.50)	1.33 (1.29, 1.38)	2.60 (2.25, 2.96)	2.04 (1.74, 2.34)
Maternal morbidity /mortality ^b	1.02 (0.84, 1.19)	1.07 (0.93, 1.21)	0.29 (-0.66, 1.23)	0.76 (-0.15, 1.68)
Component outcome ^{b,c}				
Obstetric embolism	0.54 (0.17, 1.72)	1.43 (0.84, 2.44)	-0.12 (-0.29, 0.05)	0.14 (-0.12, 0.39)
Sepsis	1.28 (0.81, 1.75)	1.09 (0.72, 1.47)	0.12 (-0.25, 0.49)	0.06 (-0.28, 0.39)
Thromboembolism	1.00 (0.54, 1.46)	0.98 (0.63, 1.32)	0.08 (-0.36, 0.52)	-0.10 (-0.46, 0.27)
Uterine rupture	1.07 (0.67, 1.47)	0.83 (0.46, 1.19)	0.10 (-0.36, 0.55)	-0.24 (-0.58, 0.11)
Postpartum hemorrhage with hysterectomy or other procedures to control bleeding	1.18 (0.94, 1.42)	1.37 (1.19, 1.55)	0.61 (-0.13, 1.36)	1.20 (0.49, 1.90)

^a Effect estimates were generated by multivariable regression models using imputed datasets (n=5) by fully conditional specification approach, with adjustment for maternal age at delivery, income, education level, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, and antenatal health care providers;

^b Risk difference was expressed as per 1000 deliveries;

^c Risk difference of component outcomes was only adjusted for maternal age and parity to enable convergence in multivariable regression models; effect estimates for obstetric shock and maternal death were not presented given few cases in each study period.

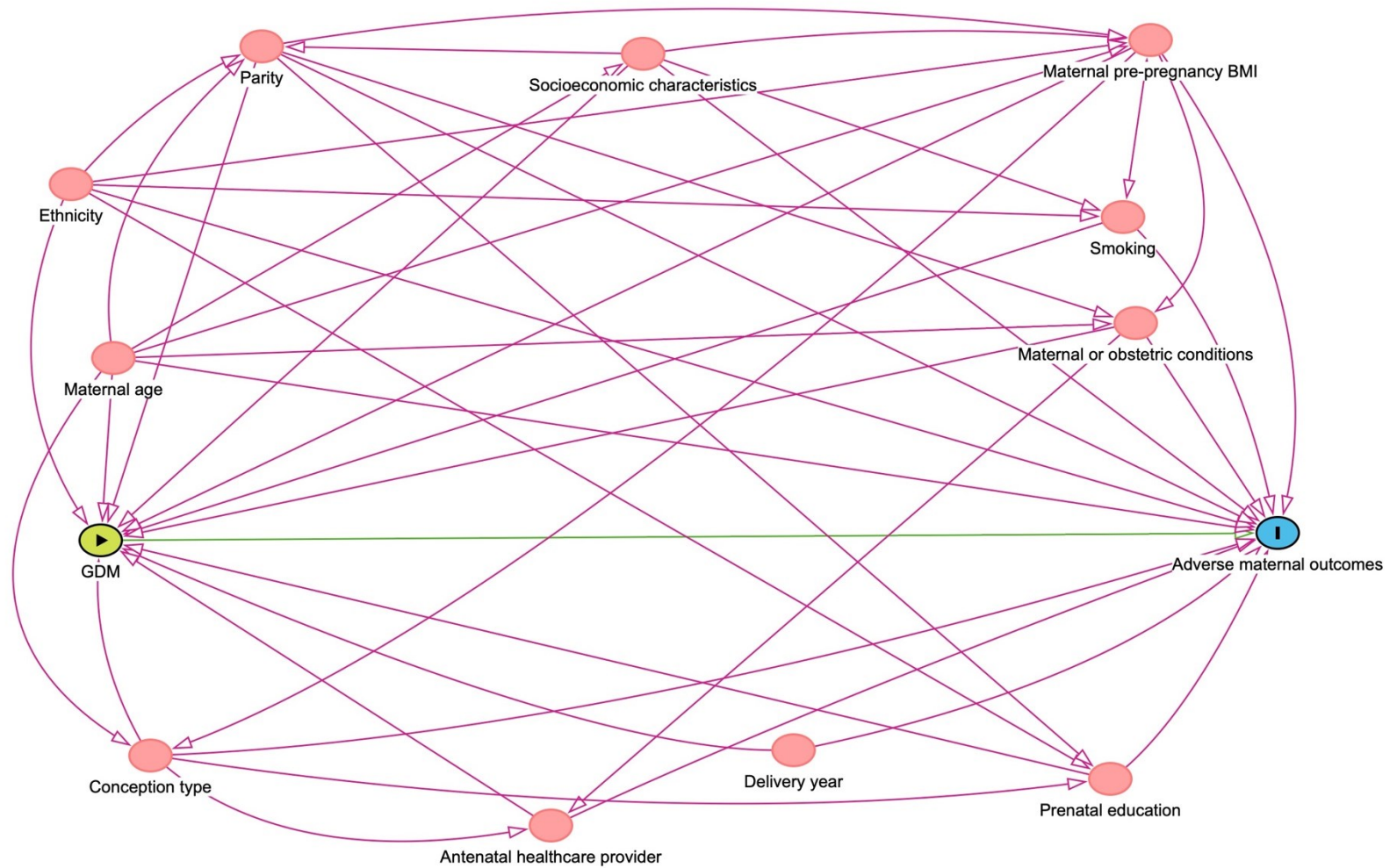


Figure S1. A Directed Acyclic Graph (DAG) of GDM and adverse maternal outcomes

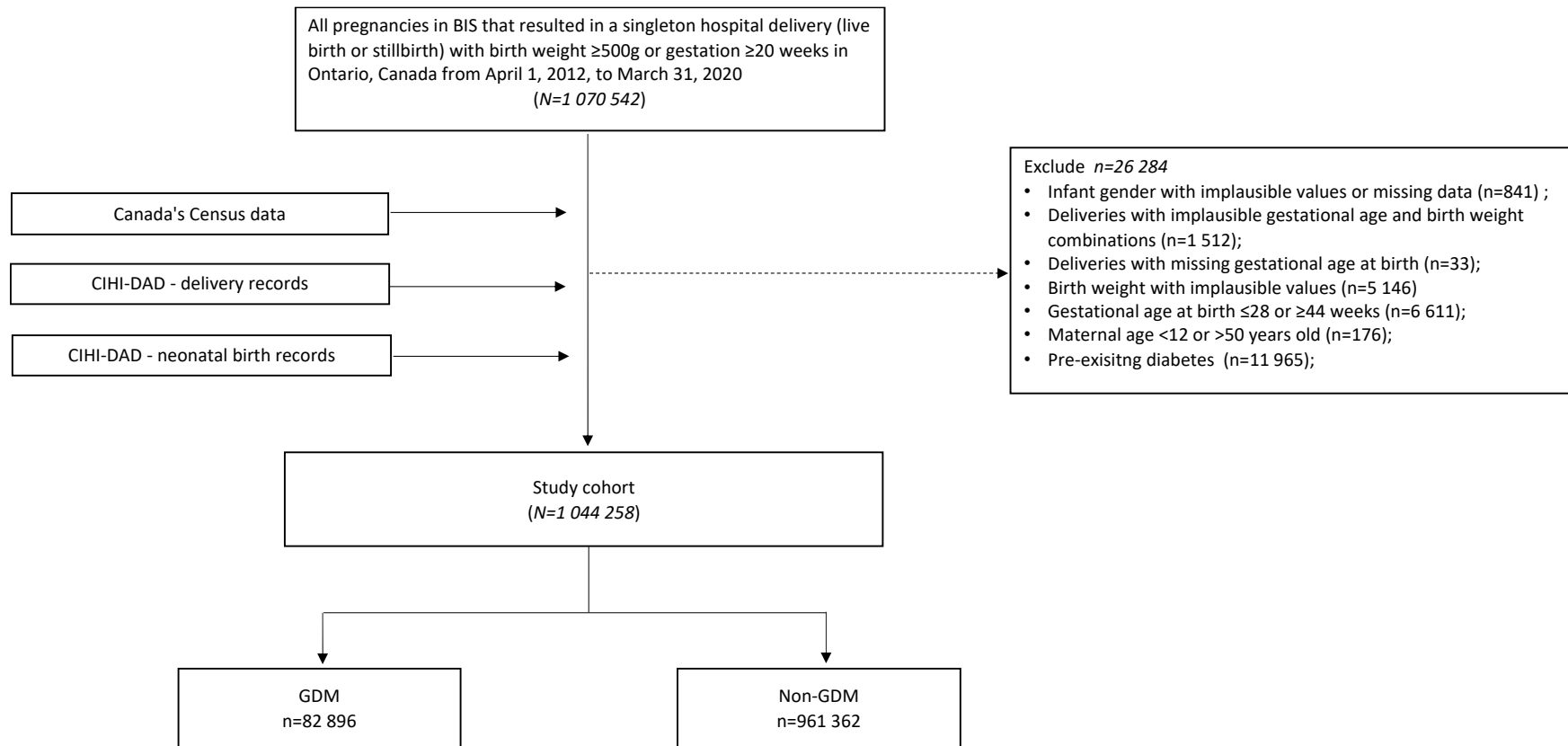


Figure S2. Study flow chart

Appendix D. Additional files for Chapter 6

Additional file 1:

Screenshot of revision letter from BMC Pregnancy and Childbirth

Additional file 2 - 12:

Table S1. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code outcomes

Table S2. RECORD checklist

Table S3. Distribution of GDM among singleton hospital deliveries in Ontario, Canada, FY 2012/13-2019/20 (N= 1 044 258)

Table S4. Trends of gestational-age adjusted rate of adverse neonatal outcomes among deliveries with and without GDM in Ontario, Canada, fiscal years 2012/13-2019/20

Table S5. Interaction tests of GDM with time periods of delivery on adverse neonatal outcomes, Ontario, Canada, fiscal years 2012/13-2019/20

Table S6. Risk difference in adverse neonatal outcomes among women with GDM and non-GDM in Ontario, Canada, by time periods of delivery (N=1 044 058)

Table S7. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery in complete-case analysis (n=732 870)

Table S8. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women with first delivery (n=759 458)

Table S9. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women without GH (n= 987 567)

Table S10. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among women without medical treatments for GDM (n=1 014 228)

Figure S1. A directed acyclic graph (DAG) of causal assumptions for the association between GDM and adverse neonatal outcomes

Additional file 1. Screenshot of revision letter from BMC Pregnancy and Childbirth

BMC Pregnancy and Childbirth: Decision on "Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020"

BP

BMC Pregnancy and Childbirth <do-not-reply@springernature.com>

To: Rong Luo

Tuesday, November 19, 2024 at 5:13 AM

Attention : courriel externe | external email

Dear Dr Luo,

Re: "Risk of Adverse Neonatal Outcomes Following Deliveries with Gestational Diabetes Mellitus: A population-based study in Ontario, Canada, 2012-2020"

The corresponding author has been asked to revise the above submission on which you are listed as a contributing author. Meanwhile, we would be grateful if you would carefully check the author details, including spelling and sequence of given and family names; email and affiliation:

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If you spot any errors, please contact the corresponding author directly to ensure the revision moves smoothly through the submission process.

Kind regards,

Editorial Assistant
BMC Pregnancy and Childbirth

Table S1. BORN Information system (BIS), international classification of diseases (tenth revision, Canada), and Canadian classification of health interventions variables used to code outcomes

Outcomes	Source	Variable	Coding	Coding description
Primary outcomes				
Severe neonatal morbidity and morbidity (SNM)	BIS	Neonatal_health_conditions_id		Adverse respiratory outcomes (respiratory distress syndrome or transient tachypnea of the newborn) OR
	ICD-10-CA		P22.0, P22.1	
	BIS	Neonatal_health_conditions_id		Hypoglycemia OR
	ICD-10-CA		P70.3, P70.4	
	BIS	Neonatal_health_conditions_id		Newborn sepsis OR
	ICD-10-CA		P36	
	BIS	Neonatal_health_conditions_id		Confirmed seizures OR
		Fetal_anomalies_confirmed_id		
	ICD-10-CA		P90, R56	
	BIS	Neonatal_health_conditions_id		Necrotizing enterocolitis OR
	ICD-10-CA		P77	
	BIS	Neonatal_health_conditions_id		Hypoxic ischemic encephalopathy OR
	ICD-10-CA		P91.5, P91.81, P91.6	
	BIS	respiratory_support_id		Cardiopulmonary resuscitation or ventilator support OR
	CCI		1.HZ.30.^, 1.GZ.31.^	
	BIS	Arterial_cord_blood_ph_value	<7	Umbilical-cord blood arterial pH less than 7.0
	BIS	apgar05_id	<4	5-minute Apgar score less than or equal to 3

	BIS	NICU_admission_flag		NICU admission OR
	DAD	Total scu los hours	>0	
	BIS	Length_of_stay_hours	≥120	Prolonged hospitalization greater than or equal to 5 days
	BIS	Pregnancy_outcome_id		Stillbirth (any of the list codes) OR
	DAD	discharge_disposition	09	
		b_rectype	1	
	BIS	Pregnancy_outcome_id AND Neonatal_death_id OR		Livebirth AND Neonatal death OR
	DAD	b_rectype AND discharge_disposition	2, 3 AND 07, 72	Livebirth AND Neonatal death AND
	BIS	Age_at_Neonatal_Death	<28	Neonatal death within 28 days following live births
Secondary outcomes				
Macrosomia	BIS	Birth_weight_grams	>4000	Birthweight ≥ 4000 grams
Large-for-gestational-age	BIS	Complication_id		Complications of pregnancy
Preterm birth	BIS	GA_at_birth_weeks		Gestational age at birth (weeks)
Birth trauma	BIS	Newborn_condition_cmplt_n_id		Intracranial hemorrhage, Subarachnoid hemorrhage, Subdural hemorrhage, Brachial plexus injury, Facial nerve injury, unspecified birth injury, other birth injury OR
	ICD-10-CA		P10.1, P10.2, P10.3, P12.2, P13 (excluding P13.4), P11.5, P11.4, P11.3, P14.0, P14.1, P14.3, P11.4, P14.2, P14.8, P14.9	One of: Hemorrhage (cerebral, intraventricular or subarachnoid, epicranial subaponeurotic) due to birth injury, birth injury to skeleton (excluding fracture of clavicle), birth injury to spine and spinal cord

				or facial nerve, paralysis (Erb's, Klumpke's, phrenic nerve) due to birth injury, other brachial plexus injuries, birth injury to other cranial nerves, birth injury to other perph nervous system

Table S2. RECORD checklist

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, paragraphs 1-3		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, paragraph 4		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods – Study design, Population and data		

			sources, paragraph 1		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – Study design, Population and data sources, paragraph 1		
Participants	6	<i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case	Methods – Study design, Population and data sources, paragraphs 1-2	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods – Study design, Population and data sources, paragraphs 1-2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods – Exposure, Outcomes, Covariates, supplementary Table S1	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided	Methods – Exposure, Outcomes, Covariates, supplementary Table S1

Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – Exposure, Outcomes, Covariates, supplementary Table S1		
Bias	9	Describe any efforts to address potential sources of bias	Methods – Statistical analysis (missingness and multiple imputation, sensitivity analyses)		
Study size	10	Explain how the study size was arrived at	Methods – Study design, population, and data sources, paragraph 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods – Exposure, Outcomes, Covariates, Statistical analysis-paragraph 1		
Statistical methods	12	) Describe all statistical methods, including those used to control for confounding - Describe any methods used to examine subgroups and interactions) Explain how missing data were addressed) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed	Methods – statistical analysis		

		<i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods – Study design, population and data sources, paragraph 2 Methods – Study design, population and data sources, paragraphs 1-2
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods – Study design, population and data sources, paragraph 2
Results					

Participants	13	) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)) Give reasons for non-participation at each stage. Consider use of a flow diagram	Results, paragraph 1;	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results, paragraph 1;
Descriptive data	14	) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders Indicate the number of participants with missing data for each variable of interest) (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount)	Results, paragraph 1-2; Table 1		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures	Results – Tables 1 and Figure 3		

Main results	16	) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included) Report category boundaries when continuous variables were categorized If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results - Trends in Rates of GDM and Adverse Neonatal Outcomes, Comparison of Associations of GDM and Adverse Neonatal Outcomes, Figure 3 and supplementary Table S5-S6		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results – Sensitivity analyses, Supplementary Table S7-S10		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion, paragraph 1		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion- Strengths and limitations, paragraph 2	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion- Strengths and limitations, paragraph 2
Interpretation	20	Give a cautious overall interpretation of results considering	Discussion- paragraph 2-5		

		objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion-Strengths and limitations, paragraph 2		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Availability of data and materials

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Table S3. Distribution of GDM among Singleton deliveries in Ontario, Canada, FY 2012/13-2019/20 (N= 1 044 258)

No. (%) of deliveries	Year of delivery								Total
	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	
GDM	7 992 (6.1)	7951 (6.1)	8996 (6.9)	9426 (7.3)	10878 (8.3)	11804 (9.0)	12255 (9.4)	13594 (10.5)	82 896 (7.9)
Non-GDM	123 832 (93.9)	122 626 (93.9)	121 176 (93.1)	120 577 (92.8)	119 727 (91.7)	118 849 (91.0)	118 017 (90.6)	116 558 (89.6)	961 362 (92.1)

*P-value for GDM trend <0.001 during the study period;

Table S4. Trends of gestational-age adjusted rate of adverse neonatal outcomes among deliveries with and without GDM in Ontario, Canada, fiscal years 2012/13-2019/20

	Fiscal year of delivery								P for trend
	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19	2019/20	
Deliveries with GDM									
SNM	22.9 (21.8, 23.9)	25.0 (23.9, 26.1)	25.8 (24.7, 26.8)	24.7 (23.7, 25.7)	25.0 (24.0, 25.9)	24.9 (24.0, 25.8)	25.1 (24.2, 26.0)	23.9 (23.1, 24.8)	<.001
Component outcome ^a									
Perinatal mortality	3.2 (1.9, 4.4)	4.2 (2.7, 5.6)	2.6 (1.6, 3.7)	3.6 (2.4, 4.9)	2.7 (1.7, 3.7)	2.6 (1.7, 3.5)	2.2 (1.4, 3.1)	2.6 (1.7, 3.4)	0.03
Adverse respiratory outcomes	53.9 (48.9, 58.9)	54.9 (49.8, 60.0)	54.1 (49.2, 58.9)	54.1 (49.4, 58.9)	54.7 (50.3, 59.1)	64.0 (59.4, 68.6)	58.3 (54.0, 62.5)	59.8 (55.6, 63.9)	0.04
Hypoglycemia	62.5 (57.0, 68.0)	74.9 (68.8, 81.0)	87.9 (81.7, 94.1)	92.2 (86.1, 98.4)	100.8 (94.9, 106.8)	90.1 (84.7, 95.5)	99.9 (94.3, 105.4)	130.9 (124.8, 137.0)	<.001
Newborn sepsis	11.7 (9.3, 14.0)	14.0 (11.4, 16.6)	8.2 (6.3, 10.1)	8.7 (6.8, 10.6)	7.3 (5.7, 8.9)	7.8 (6.2, 9.4)	9.0 (7.4, 10.7)	7.4 (5.9, 8.9)	<.001
Confirmed seizures	1.9 (0.9, 2.8)	1.9 (0.9, 2.9)	1.5 (0.7, 2.3)	1.5 (0.7, 2.3)	1.9 (1.0, 2.7)	1.7 (1.0, 2.4)	1.9 (1.1, 2.7)	1.3 (0.7, 1.9)	0.47
Necrotizing enterocolitis	1.3 (0.5, 2.0)	0.4 (0.05, 0.8)	0.7 (0.1, 1.3)	0.7 (0.1, 1.2)	0.5 (0.1, 1.0)	0.4 (0.05, 0.8)	0.3 (0.01, 0.6)	0.2 (0.04, 0.4)	0.001
Hypoxic ischemic encephalopathy	1.4 (0.6, 2.2)	1.4 (0.6, 2.3)	2.1 (1.2, 3.1)	2.5 (1.5, 3.5)	2.1 (1.3, 3.0)	1.7 (1.0, 2.4)	1.6 (0.9, 2.3)	1.9 (1.2, 2.7)	0.53
Cardiopulmonary resuscitation or ventilator support	54.4 (49.4, 59.4)	66.8 (61.2, 72.5)	66.7 (61.3, 72.1)	63.1 (58.0, 68.2)	62.8 (58.1, 67.5)	72.6 (67.8, 77.5)	71.1 (66.4, 75.9)	68.6 (64.1, 73.0)	0.001
Umbilical-cord arterial pH <7.0 d	6.6 (4.8, 8.4)	8.1 (6.1, 10.0)	13.2 (10.8, 15.5)	7.7 (5.9, 9.5)	6.9 (5.3, 8.5)	7.8 (6.2, 9.5)	6.2 (4.8, 7.7)	7.1 (5.7, 8.5)	0.02

5-min Apgar <4	2.6 (1.5, 3.7)	2.9 (1.7, 4.0)	3.2 (2.0, 4.3)	1.9 (1.0, 2.8)	3.1 (2.1, 4.2)	5.4 (4.1, 6.7)	1.9 (1.2, 2.7)	2.2 (1.4, 3.0)	0.07
NICU admission	180.0 (170.7, 189.2)	194.2 (184.5, 203.9)	187.2 (178.1, 196.3)	177.3 (168.7, 185.9)	171.7 (163.9, 179.5)	176.9 (169.3, 184.5)	165.9 (158.7, 173.1)	170.8 (163.8, 177.8)	<.001
Prolonged hospitalization	61.8 (56.5, 67.2)	65.4 (59.9, 71.0)	60.2 (55.0, 65.3)	62.0 (56.9, 67.1)	58.2 (53.6, 62.8)	60.0 (55.5, 64.4)	59.0 (54.7, 63.3)	58.0 (53.8, 62.1)	<.001
LGA	15.1 (14.3, 16.0)	14.8 (13.9, 15.6)	14.0 (13.2, 14.8)	14.0 (13.3, 14.8)	13.3 (12.7, 14.0)	12.5 (11.9, 13.2)	12.1 (11.4, 12.7)	11.2 (10.7, 11.8)	<.001
Macrosomia	10.7 (10.0, 11.5)	11.0 (10.3, 11.7)	10.1 (9.5, 10.8)	10.3 (9.7, 11.0)	9.6 (9.0, 10.1)	8.8 (8.3, 9.3)	8.5 (8.0, 9.0)	7.7 (7.2, 8.2)	<.001
Preterm birth ^b	NA	NA	NA	NA	NA	NA	NA	NA	NA
Birth trauma ^a	4.3 (2.9, 5.7)	4.6 (3.1, 6.1)	8.0 (6.2, 9.8)	8.0 (6.2, 9.8)	8.5 (6.8, 10.2)	6.8 (5.3, 8.3)	8.6 (7.0, 10.3)	7.6 (6.1, 9.1)	<.001
Deliveries without GDM									
SNM	15.1 (14.9, 15.3)	15.5 (15.2, 15.7)	16.0 (15.7, 16.2)	15.7 (15.4, 15.9)	15.6 (15.3, 15.8)	15.7 (15.4, 15.9)	15.9 (15.7, 16.1)	16.8 (16.6, 17.0)	<.001
Component outcome ^a									
Perinatal mortality	3.3 (3.0, 3.6)	3.1 (2.8, 3.4)	2.9 (2.6, 3.2)	2.9 (2.6, 3.2)	3.1 (2.8, 3.4)	3.1 (2.8, 3.5)	2.8 (2.5, 3.1)	2.7 (2.4, 3.1)	0.01
Adverse respiratory outcomes	42.0 (40.8, 43.1)	42.6 (41.4, 43.7)	42.0 (40.8, 43.2)	43.1 (41.9, 44.3)	43.0 (41.8, 44.1)	47.1 (45.8, 48.3)	48.5 (47.2, 49.7)	50.4 (49.1, 51.7)	<.001
Hypoglycemia	29.0 (28.1, 30.0)	34.0 (32.9, 35.0)	37.4 (36.3, 38.5)	44.0 (42.8, 45.2)	45.9 (44.7, 47.2)	43.5 (42.3, 44.6)	48.6 (47.4, 49.9)	57.1 (55.7, 58.4)	<.001
Newborn sepsis	10.5 (10.0, 11.1)	10.8 (10.3, 11.4)	7.4 (6.9, 7.9)	7.3 (6.8, 7.8)	6.6 (6.1, 7.1)	7.1 (6.6, 7.5)	7.4 (6.9, 7.9)	8.0 (7.4, 8.5)	<.001
Confirmed seizures	1.6 (1.4, 1.9)	1.6 (1.4, 1.8)	1.4 (1.2, 1.6)	1.5 (1.3, 1.8)	1.4 (1.2, 1.7)	1.7 (1.4, 1.9)	1.3 (1.1, 1.5)	1.6 (1.4, 1.8)	0.37
Necrotizing enterocolitis	0.5 (0.3, 0.6)	0.5 (0.4, 0.6)	0.4 (0.3, 0.6)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	<.001
Hypoxic ischemic encephalopathy	1.3 (1.1, 1.5)	1.5 (1.3, 1.7)	1.3 (1.1, 1.5)	1.7 (1.4, 1.9)	1.6 (1.4, 1.8)	2.0 (1.8, 2.3)	1.8 (1.6, 2.1)	2.1 (1.8, 2.3)	<.001

Cardiopulmonary resuscitation or ventilator support	45.3 (44.1, 46.5)	51.4 (50.2, 52.7)	52.2 (50.9, 53.5)	53.2 (51.9, 54.5)	53.5 (52.2, 54.9)	59.0 (57.6, 60.4)	60.5 (59.1, 62.0)	63.0 (61.5, 64.4)	<.001
Umbilical-cord arterial pH <7.0	6.2 (5.8, 6.7)	6.9 (6.5, 7.4)	11.7 (11.1, 12.3)	6.9 (6.5, 7.4)	6.9 (6.5, 7.4)	7.1 (6.6, 7.6)	6.5 (6.0, 6.9)	7.9 (7.3, 8.4)	0.09
5-min Apgar <4	2.2 (1.9, 2.5)	2.7 (2.4, 3.0)	2.1 (1.8, 2.4)	2.2 (1.9, 2.4)	2.4 (2.1, 2.6)	2.5 (2.2, 2.8)	2.3 (2.0, 2.6)	2.4 (2.1, 2.7)	0.94
NICU admission	119.2 (117.2, 121.1)	119.9 (118.0, 121.9)	117.0 (115.0, 118.9)	116.1 (114.1, 118.0)	112.8 (110.9, 114.7)	114.7 (112.7, 116.6)	112.5 (110.6, 114.4)	114.9 (113.0, 116.9)	<.001
Prolonged hospitalization	40.4 (39.2, 41.5)	41.1 (40.0, 42.3)	41.4 (40.2, 42.6)	41.4 (40.3, 42.6)	38.8 (37.7, 39.9)	39.6 (38.4, 40.7)	39.9 (38.8, 41.1)	39.8 (38.6, 40.9)	0.002
LGA	9.7 (9.5, 9.9)	9.6 (9.4, 9.7)	9.3 (9.1, 9.5)	9.1 (9.0, 9.3)	9.0 (8.8, 9.1)	8.8 (8.6, 9.0)	8.8 (8.7, 9.0)	8.6 (8.4, 8.8)	<.001
Macrosomia	10.9 (10.7, 11.1)	10.8 (10.6, 11.0)	10.6 (10.4, 10.8)	10.4 (10.2, 10.6)	10.2 (10.0, 10.4)	10.0 (9.8, 10.2)	9.9 (9.7, 10.1)	9.7 (9.6, 9.9)	<.001
Preterm birth ^b	NA	NA	NA	NA	NA	NA	NA	NA	NA
Birth trauma ^a	3.0 (2.6, 3.3)	3.6 (3.2, 3.9)	7.3 (6.8, 7.7)	6.1 (5.7, 6.6)	6.5 (6.0, 6.9)	6.1 (5.6, 6.5)	8.0 (7.5, 8.5)	7.7 (7.2, 8.2)	<.001

^a Rate was expressed as per 1000 deliveries;

^b Not applicable for gestational-age adjusted preterm birth.

Table S5. Interaction tests of GDM with time periods of delivery on adverse neonatal outcomes, Ontario, Canada, fiscal years 2012/13-2019/20

Outcomes	P-interaction (RR)	P-interaction (RD)
SNM	0.31	0.03
Component outcome		
Perinatal mortality	0.07	0.07
Adverse respiratory outcomes	0.49	0.65
Hypoglycemia	0.44	<0.001
Newborn sepsis	0.25	0.16
Confirmed seizures	0.97	1.00
Necrotizing enterocolitis	0.55	0.26
Hypoxic ischemic encephalopathy	0.35	0.37
Cardiopulmonary resuscitation or ventilator support	0.01	0.07
Umbilical-cord arterial pH <7.0	0.13	0.13
5-min Apgar <4	0.06	0.05
NICU admission	0.008	0.0003
Prolonged hospitalization	0.15	0.07
LGA	<0.001	<0.001
Macrosomia	<0.001	<0.001
Preterm birth	0.16	0.18
Birth trauma	0.11	0.32

Table S6. Risk difference in adverse neonatal outcomes among women with GDM and non-GDM in Ontario, Canada, by time periods of delivery (n=1 044 058)

Outcomes	Adjusted RD, % (95% CI) ^a	
	FY 2012/13-2015/16	FY 2016/17-2019/20
SNM	8.05 (7.57, 8.52)	8.82 (8.41, 9.23)
Component outcome ^b		
Perinatal mortality ^c	0.25 (-0.38, 0.88)	-0.44 (-0.91, 0.04)
Adverse respiratory outcomes	8.36 (5.94, 10.8)	8.55 (6.43, 10.7)
Hypoglycemia	43.8 (40.9, 46.8)	58.4 (55.6, 61.3)
Newborn sepsis ^c	2.00 (0.92, 3.09)	1.05 (0.24, 1.86)
Confirmed seizures ^c	0.15 (-0.26, 0.57)	0.13 (-0.23, 0.49)
Necrotizing enterocolitis ^c	0.28 (-0.01, 0.58)	0.12 (-0.07, 0.30)
Hypoxic ischemic encephalopathy ^c	0.20 (-0.22, 0.62)	-0.07 (-0.44, 0.30)
Cardiopulmonary resuscitation or ventilator support	10.0 (7.46, 12.6)	7.30 (5.01, 9.58)
Umbilical-cord arterial pH < 7.0 ^c	0.84 (-0.18, 1.85)	-0.13 (-0.90, 0.65)
5-min Apgar <4	0.34 (-0.21, 0.88)	-0.35 (-0.75, 0.05)
NICU admission	57.8 (53.6, 62.0)	49.1 (45.7, 52.6)
Prolonged hospitalization ^c	21.8 (19.1, 24.4)	18.9 (16.7, 21.1)
LGA	4.41 (4.03, 4.80)	3.10 (2.79, 3.41)
Macrosomia	-0.33 (-0.67, 0.02)	-1.48 (-1.75, -1.21)
Preterm birth	2.89 (2.57, 3.20)	2.70 (2.44, 2.96)
Birth trauma ^b	1.63 (0.78, 2.49)	1.08 (0.30, 1.87)

Note: RD=Risk difference;

^a Risk difference comparing pregnancies with GDM vs. no GDM was generated by multivariable regression models using imputed datasets (n=5), with adjustment for maternal age at delivery, neighborhood-level income, neighborhood-level education, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex;

^b Adjusted risk difference was expressed as per 1000 deliveries;

^c Convergence issues, only adjusted for maternal age at delivery and parity.

Table S7. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery in complete-case analysis (n=732 870)

Outcome	Complete-case analysis			
	Adjusted RR (95% CI) ^a		Adjusted RD, % (95% CI) ^a	
	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)	FY 2012/13-2015/16 (n= 363 946)	FY 2016/17-2019/20 (n= 368 924)
SNM	1.51 (1.47, 1.55)	1.60 (1.55, 1.63)	8.28 (7.71, 8.86)	9.54 (9.05, 10.04)
Component outcome ^b				
Perinatal mortality ^c	0.96 (0.73, 1.25)	0.81 (0.63, 1.04)	0.07 (-0.60, 0.74)	-0.29 (-0.81, 0.23)
Adverse respiratory outcomes	1.19 (1.12, 1.27)	1.19 (1.13, 1.25)	8.63 (5.71, 11.5)	7.54 (5.07, 10.0)
Hypoglycemia	2.02 (1.92, 2.12)	2.10 (2.02, 2.18)	42.7 (39.1, 46.4)	59.7 (56.2, 63.2)
Newborn sepsis ^c	1.13 (0.99, 1.29)	0.91 (0.78, 1.05)	2.01 (0.91, 3.11)	1.08 (0.27, 1.89)
Confirmed seizures ^c	1.07 (0.77, 1.48)	0.97 (0.71, 1.31)	0.17 (-0.26, 0.59)	0.11 (-0.24, 0.47)
Necrotizing enterocolitis ^c	1.59 (1.04, 2.42)	1.43 (0.85, 2.40)	0.27 (-0.03, 0.57)	0.12 (-0.06, 0.30)
Hypoxic ischemic encephalopathy ^c	1.24 (0.90, 1.70)	0.83 (0.62, 1.11)	0.22 (-0.21, 0.65)	-0.08 (-0.45, 0.28)
Cardiopulmonary resuscitation or ventilator support	1.19 (1.12, 1.26)	1.12 (1.07, 1.18)	9.12 (6.07, 12.17)	6.57 (3.94, 9.20)
Umbilical-cord arterial pH <7.0 ^c	1.13 (0.98, 1.31)	0.87 (0.75, 1.01)	0.89 (-0.13, 1.91)	-0.14 (-0.92, 0.63)
5-min Apgar <4	1.20 (0.92, 1.57)	0.85 (0.65, 1.11)	0.36 (-0.19, 0.92)	-0.32 (-0.72, 0.08)
NICU admission	1.47 (1.42, 1.52)	1.45 (1.40, 1.49)	58.4 (53.3, 63.5)	50.2 (46.1, 54.3)
Prolonged hospitalization ^c	1.42 (1.34, 1.50)	1.39 (1.32, 1.47)	18.5 (15.3, 21.6)	15.8 (13.3, 18.3)
LGA	1.38 (1.33, 1.43)	1.29 (1.24, 1.33)	4.46 (4.07, 4.85)	3.09 (2.79, 3.40)
Macrosomia	0.97 (0.92, 1.01)	0.85 (0.81, 0.88)	-0.30 (-0.64, 0.05)	-1.49 (-1.76, -1.22)
Preterm birth	1.48 (1.41, 1.56)	1.51 (1.44, 1.57)	2.59 (2.23, 2.96)	2.65 (2.34, 2.95)
Birth trauma ^b	1.40 (1.19, 1.64)	1.12 (0.98, 1.28)	1.71 (0.84, 2.58)	1.10 (0.31, 1.88)

Note: RR=Relative risk; RD=Risk difference;

^a Effect estimates were expressed by comparing GDM pregnancies with non-GDM pregnancies. Multivariable regression models were adjusted for maternal age at delivery, neighborhood-level income, neighborhood-level education, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex;

^b Adjusted risk difference was expressed as per 1000 deliveries;

^c Only adjusted maternal age at delivery due to convergence issue for computing risk difference.

Table S8. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals with a first delivery (n=759 458)

Outcome	Individuals with first delivery			
	Adjusted RR (95% CI) ^a		Adjusted RD, % (95% CI) ^a	
	2012/13-2015/16 (n= 450 180)	2016/17-2019/20 (n= 309 278)	2012/13-2015/16 (n= 450 180)	2016/17-2019/20 (n= 309 278)
SNM	1.48 (1.46, 1.51)	1.46 (1.44, 1.49)	8.11 (7.60, 8.62)	8.54 (8.01, 9.08)
Component outcome ^b				
Perinatal mortality ^c	0.94 (0.72, 1.15)	0.68 (0.44, 0.93)	0.06 (-0.60, 0.72)	-0.91 (-1.51, -0.32)
Adverse respiratory outcomes	1.17 (1.12, 1.23)	1.12 (1.07, 1.17)	8.25 (5.64, 10.9)	5.84 (3.03, 8.7)
Hypoglycemia	1.97 (1.92, 2.02)	1.84 (1.80, 1.89)	43.67 (40.5, 46.8)	54.34 (50.7, 58.0)
Newborn sepsis ^c	1.12 (1.00, 1.23)	0.88 (0.74, 1.02)	2.20 (0.99, 3.41)	0.36 (-0.74, 1.46)
Confirmed seizures ^c	1.16 (0.88, 1.44)	1.02 (0.75, 1.29)	0.30 (-0.19, 0.79)	0.29 (-0.27, 0.85)
Necrotizing enterocolitis ^c	1.6 (1.16, 2.05)	1.04 (0.34, 1.74)	0.28 (-0.04, 0.6)	0.03 (-0.19, 0.25)
Hypoxic ischemic encephalopathy ^c	1.17 (0.88, 1.46)	0.96 (0.71, 1.22)	0.32 (-0.16, 0.81)	0.15 (-0.45, 0.75)
Cardiopulmonary resuscitation or ventilator support	1.19 (1.14, 1.24)	1.06 (1.02, 1.11)	10.5 (7.64, 13.3)	4.09 (1.01, 7.17)
Umbilical-cord arterial pH <7.0 ^c	1.10 (0.97, 1.23)	0.98 (0.84, 1.12)	1.07 (-0.05, 2.18)	0.13 (-0.97, 1.23)
5-min Apgar <4	1.15 (0.92, 1.38)	0.85 (0.61, 1.09)	0.44 (-0.18, 1.06)	-0.44 (-1.04, 0.15)
NICU admission	1.46 (1.43, 1.49)	1.36 (1.33, 1.39)	58.7 (54.2, 63.2)	48.4 (43.8, 53.0)
Prolonged hospitalization ^c	1.40 (1.35, 1.45)	1.35 (1.30, 1.41)	22.4 (19.5, 25.2)	20.4 (17.5, 23.4)
LGA	1.41 (1.38, 1.45)	1.29 (1.25, 1.34)	4.14 (3.74, 4.54)	2.53 (2.18, 2.89)
Macrosomia	0.97 (0.93, 1.01)	0.82 (0.77, 0.87)	-0.43 (-0.79, -0.07)	-1.56 (-1.88, -1.25)
Preterm birth	1.49 (1.45, 1.54)	1.46 (1.41, 1.50)	2.93 (2.59, 3.26)	2.83 (2.48, 3.17)
Birth trauma ^b	1.29 (1.14, 1.45)	1.18 (1.05, 1.31)	1.49 (0.59, 2.40)	1.40 (0.25, 2.54)

Note: RR=Relative risk; RD=Risk difference;

^a Adjusted estimates were calculated using imputed datasets (n=5) by fully conditional specification approach. Effect estimates were expressed by comparing GDM pregnancies with non-GDM pregnancies. Multivariable regression models were adjusted for maternal age at delivery, neighborhood-level income, neighborhood-level education, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex;

^b Adjusted risk difference was expressed as per 1000 deliveries;

^c Only adjusted maternal age at delivery due to convergence issue for computing risk difference.

Table S9. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals without pregnancy induced hypertension (n= 987 567)

Outcome	Individuals without GH			
	Adjusted RR (95% CI) ^a		Adjusted RD, % (95% CI) ^a	
	2012/13-2015/16 (n= 495 516)	2016/17-2019/20 (n= 492 051)	2012/13-2015/16 (n= 495 516)	2016/17-2019/20 (n= 492 051)
SNM	1.50 (1.47, 1.53)	1.55 (1.53, 1.57)	7.64 (7.15, 8.12)	8.50 (8.07, 8.92)
Component outcome ^b				
Perinatal mortality ^c	0.97 (0.76, 1.18)	0.77 (0.57, 0.98)	0.17 (-0.48, 0.82)	-0.43 (-0.93, 0.06)
Adverse respiratory outcomes	1.18 (1.13, 1.23)	1.18 (1.14, 1.22)	7.80 (5.33, 10.27)	7.57 (5.42, 9.73)
Hypoglycemia	2.11 (2.07, 2.16)	2.16 (2.12, 2.19)	43.1 (40.1, 46.1)	58.1 (55.2, 61.0)
Newborn sepsis ^c	1.10 (0.98, 1.21)	0.95 (0.83, 1.06)	1.69 (0.59, 2.79)	0.85 (0.04, 1.67)
Confirmed seizures ^c	1.08 (0.79, 1.38)	0.96 (0.70, 1.22)	0.04 (-0.37, 0.45)	0.03 (-0.32, 0.37)
Necrotizing enterocolitis ^c	1.86 (1.42, 2.30)	1.41 (0.80, 2.03)	0.33 (0.02, 0.64)	0.09 (-0.08, 0.26)
Hypoxic ischemic encephalopathy ^c	1.12 (0.82, 1.42)	0.95 (0.71, 1.18)	0.15 (-0.27, 0.57)	-0.09 (-0.45, 0.28)
Cardiopulmonary resuscitation or ventilator support	1.19 (1.14, 1.24)	1.10 (1.07, 1.14)	9.20 (6.57, 11.8)	6.00 (3.68, 8.32)
Umbilical-cord arterial pH <7.0 ^c	1.10 (0.97, 1.22)	0.93 (0.81, 1.06)	0.78 (-0.27, 1.82)	-0.14 (-0.94, 0.66)
5-min Apgar <4	1.09 (0.85, 1.33)	0.80 (0.56, 1.03)	0.18 (-0.37, 0.72)	-0.48 (-0.86, -0.10)
NICU admission	1.46 (1.43, 1.49)	1.41 (1.39, 1.44)	53.1 (48.9, 57.4)	45.6 (42.0, 49.1)
Prolonged hospitalization ^c	1.40 (1.35, 1.45)	1.36 (1.32, 1.41)	18.4 (15.8, 21.1)	15.3 (13.2, 17.5)
LGA	1.41 (1.37, 1.44)	1.29 (1.26, 1.32)	4.12 (3.73, 4.52)	2.86 (2.54, 3.18)
Macrosomia	0.97 (0.93, 1.01)	0.85 (0.82, 0.89)	-0.52 (-0.88, -0.16)	-1.59 (-1.87, -1.31)
Preterm birth	1.49 (1.44, 1.54)	1.45 (1.41, 1.50)	2.55 (2.23, 2.86)	2.31 (2.04, 2.57)
Birth trauma ^b	1.25 (1.09, 1.41)	1.16 (1.04, 1.29)	1.21 (0.35, 2.06)	0.96 (0.16, 1.77)

Note: RR=Relative risk; RD=Risk difference;

^a Adjusted estimates were calculated using imputed datasets (n=5) by fully conditional specification approach. Effect estimates were expressed by comparing GDM pregnancies with non-GDM pregnancies. Multivariable regression models were adjusted for maternal age at delivery, neighborhood-level income, neighborhood-level education, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex;

^b Adjusted risk difference was expressed as per 1000 deliveries;

^c Only adjusted maternal age at delivery due to convergence issue for computing risk difference.

Table S10. Sensitivity analyses for trends in neonatal outcomes associated with GDM in Ontario, Canada, by time periods of delivery among individuals without medical treatments for GDM (n=1 014 228)

Outcome	Individuals without medical treatments for GDM			
	Adjusted RR (95% CI) ^a		Adjusted RD, % (95% CI) ^a	
	2012/13-2015/16 (n=509 894)	2016/17-2019/20 (n=504 334)	2012/13-2015/16 (n=509 894)	2016/17-2019/20 (n=504 334)
SNM	1.44 (1.41, 1.47)	1.51 (1.48, 1.53)	7.03 (6.46, 7.60)	8.20 (7.71, 8.69)
Component outcome ^b				
Perinatal mortality ^c	1.16 (0.94, 1.39)	0.88 (0.66, 1.10)	0.73 (-0.10, 1.56)	-0.18 (-0.79, 0.42)
Adverse respiratory outcomes	1.19 (1.13, 1.26)	1.16 (1.11, 1.22)	8.00 (5.08, 10.92)	7.34 (4.79, 9.89)
Hypoglycemia	1.83 (1.77, 1.88)	2.00 (1.96, 2.04)	35.4 (31.9, 38.8)	55.3 (51.9, 58.8)
Newborn sepsis ^c	1.04 (0.90, 1.19)	0.95 (0.81, 1.09)	1.01 (-0.28, 2.3)	0.73 (-0.25, 1.71)
Confirmed seizures ^c	0.97 (0.61, 1.33)	0.90 (0.60, 1.21)	0.11 (-0.57, 0.36)	0.05 (-0.39, 0.49)
Necrotizing enterocolitis ^c	1.87 (1.39, 2.35)	1.16 (0.47, 1.84)	0.40 (0.001, 0.79)	0.05 (-0.15, 0.25)
Hypoxic ischemic encephalopathy ^c	0.95 (0.59, 1.32)	0.93 (0.66, 1.20)	-0.11 (-0.56, 0.35)	0.02 (-0.45, 0.50)
Cardiopulmonary resuscitation or ventilator support	1.22 (1.17, 1.28)	1.13 (1.08, 1.18)	11.1 (7.92, 14.3)	7.53 (4.76, 10.3)
Umbilical-cord arterial pH <7.0 ^c	1.11 (0.96, 1.26)	0.98 (0.83, 1.12)	0.87 (-0.40, 2.14)	-0.01 (-0.96, 0.94)
5-min Apgar <4	1.16 (0.89, 1.43)	1.00 (0.76, 1.24)	0.35 (-0.33, 1.04)	-0.02 (-0.55, 0.51)
NICU admission	1.39 (1.36, 1.43)	1.36 (1.33, 1.39)	46.9 (41.9, 51.9)	41.3 (37.2, 45.4)
Prolonged hospitalization ^c	1.37 (1.31, 1.43)	1.37 (1.32, 1.42)	18.5 (15.3, 21.7)	17.5 (14.9, 20.2)
LGA	1.31 (1.27, 1.35)	1.17 (1.14, 1.21)	2.83 (2.38, 3.28)	1.55 (1.20, 1.90)
Macrosomia	1.01 (0.96, 1.05)	0.87 (0.83, 0.92)	-0.35 (-0.77, 0.07)	-1.48 (-1.8, -1.16)
Preterm birth	1.52 (1.47, 1.57)	1.49 (1.45, 1.53)	2.96 (2.58, 3.35)	2.72 (2.40, 3.04)
Birth trauma ^b	1.23 (1.04, 1.41)	1.12 (0.98, 1.26)	1.17 (0.14, 2.20)	0.54 (-0.38, 1.46)

Note: RR=Relative risk; RD=Risk difference;

^a Adjusted estimates were calculated using imputed datasets (n=5) by fully conditional specification approach. Effect estimates were expressed by comparing GDM pregnancies with non-GDM pregnancies. Multivariable regression models were adjusted for maternal age at delivery, neighborhood-level income, neighborhood-level education, parity, race, pre-pregnancy BMI, smoking, pre-existing medical or obstetrical conditions, conception type, prenatal education, antenatal health care providers and infant sex;

^b Adjusted risk difference was expressed as per 1000 deliveries;

^c Only adjusted maternal age at delivery due to convergence issue for computing risk difference.

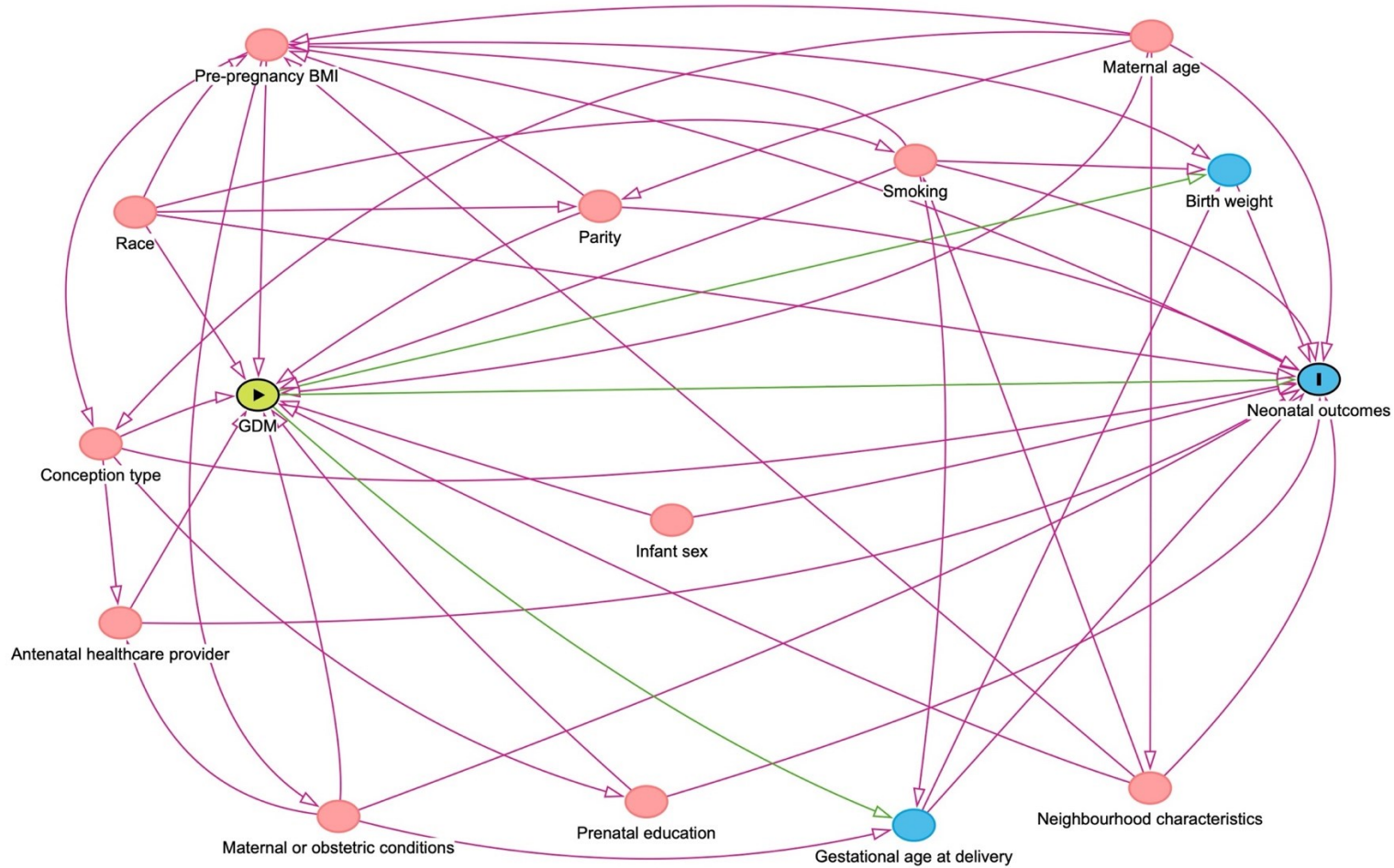


Figure S1. A directed acyclic graph (DAG) of causal assumptions for the association between GDM and adverse neonatal outcomes. Adapted from Kariniemi et al., 2024

Appendix E. Additional files for Chapter 7

Additional file 1:

Search strategy

Additional file 2:

PRISMA 2020 checklist

Additional file 3 – 11:

Table S1. Articles excluded after full text review and reasons for exclusion (n=77)

Table S2. Further characteristics of the included studies

Table S3. Quality assessment for the observational studies

Table S4. Pooled estimates for the effect of induction on primary outcomes in observational Studies

Table S5. Summary of findings table (GRADE)

Figure. S1 Assessment of risk of bias for RCTs. (A) Summary of risk of bias (+: low risk of bias; -: high risk of bias; ?: unclear risk of bias); (B) Risk of bias graph with each risk of bias item presented as percentages across all included trials

Figure. S2-S10 Forest plots for secondary outcomes comparing induction with expectant management in women with GDM

Figure. S11 Funnel plot to assess publication bias for primary outcomes A) CS B) Macrosomia

Figure. S12-S13 Sensitivity analysis

Additional file 1. Search strategy

Databases	ID	Search
Ovid MEDLINE	1	exp Diabetes, Gestational/
	2	((gestation* adj3 diabet*) or (diabet* adj2 pregnan*)).tw,kf.
	3	gdm.tw,kf.
	4	(hyperglyc?emia adj2 pregnan*).tw,kf.
	5	1 or 2 or 3 or 4
	6	exp Labor, Induced/
	7	exp Obstetric labor/
	8	((labor or labour or deliver*) adj3 induc*).tw,kf.
	9	IOL.tw,kf.
	10	exp Watchful Waiting/
	11	(expectant* adj2 manage*).tw,kf.
	12	(spontaneous* adj2 (deliver* or birth* or labo?r)).tw,kf.
	13	((elective* or plan* or expectant* or active*) adj2 (deliver* or birth*)).tw,kf.
	14	(tim* adj2 (birth* or deliver*)).tw,kf.
	15	Delivery, Obstetric/ and (gestation* age adj2 (deliver* or birth*)).tw,kf.
	16	(gestation* age adj2 deliver*).tw,kf.
	17	Delivery, Obstetric/ and gestational age/
	18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
	19	5 and 18
	20	exp animals/ not humans/
	21	19 not 20
	22	limit 21 to english language
Ovid Embase	1	exp *pregnancy diabetes mellitus/
	2	((gestation* adj3 diabet*) or (diabet* adj2 pregnan*)).tw.
	3	gdm.tw.
	4	(hyperglyc?emia adj2 pregnan*).tw.
	5	1 or 2 or 3 or 4
	6	exp Labor, Induced/
	7	exp labor/
	8	((labor or labour or deliver*) adj3 induc*).tw.
	9	IOL.tw.
	10	Watchful Waiting/
	11	(expectant* adj2 manage*).tw.
	12	(spontaneous* adj2 (deliver* or birth* or labo?r)).tw.
	13	((elective* or plan* or expectant* or active*) adj2 (deliver* or birth*)).tw.
	14	(tim* adj2 (birth* or deliver*)).tw.
	15	Delivery, Obstetric/ and (gestation* age adj2 (deliver* or birth*)).tw.
	16	(gestation* age adj2 deliver*).tw.
	17	Delivery, Obstetric/ and gestational age/
	18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
	19	5 and 18
	20	exp animals/ not exp humans/
	21	19 not 20
	22	limit 21 to english language
	23	conference abstract.pt.
	24	22 not 23
	1	TS=GDM

Web of Science	2	TS=(Gestation* NEAR/3 diabet*)
	3	TS=(Diabet* NEAR/2 pregnan*)
	4	TS=(hyperglyc?emia NEAR/2 pregnan*)
	5	#4 OR #3 OR #2 OR #1
	6	TS=(IOL)
	7	TS=(Obstetric labo?r)
	8	TS=((labor or labour or deliver*) NEAR/3 induc*)
	9	TS=((induced NEAR/0 labo?r) or (labo?r NEAR/1 induction) or (induc* labo?r))
	10	TS=(Watchful* NEAR/1 Wait*)
	11	TS=(expectant* NEAR/2 manag*)
	12	TS=(spontaneous* NEAR/2 (deliver* or birth* or labo?r))
	13	TS=((elective* or plan* or expectant* or active*) NEAR/2 (deliver* or birth*))
	14	TS=(tim* NEAR/2 (deliver* or birth*))
	15	TS=(Deliver* AND obstetric)
	16	TS=((gestation* NEAR/0 age) NEAR/2 (deliver* or birth))
	17	#16 AND #15
	18	TS=(gestational NEAR/0 age)
	19	#18 AND #15
	20	#15 AND #14
	21	#20 OR #19 OR #17 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6
	22	#21 AND #5
	23	TS=animals NOT TS=humans
	24	#22 NOT #23
	25	(#24) AND LANGUAGE: (English)
Cochrane Library	1	MeSH descriptor: [Diabetes, Gestational] explode all trees
	2	((gestation* NEAR/2 diabet*) or (diabet* NEAR/2 pregnan*)):ti,ab,kw
	3	(GDM or (gestational NEXT diabetes NEXT mellitus)):ti,ab,kw
	4	(hyperglyc?emia NEAR/2 pregnan*):ti,ab,kw
	5	#1 or #2 or #3 or #4
	6	MeSH descriptor: [Labor, Induced] explode all trees
	7	MeSH descriptor: [Labor, Obstetric] explode all trees
	8	((labo?r NEXT of NEXT induction) or (IOL)):ti,ab,kw
	9	((labor or labour or deliver*) NEAR/3 induc*):ti,ab,kw
	10	MeSH descriptor: [Watchful Waiting] explode all trees
	11	(expectant* NEAR/2 manage*):ti,ab,kw
	12	(spontaneous* NEAR/2 (deliver* or birth* or labo?r)):ti,ab,kw
	13	((elective* or plan* or expectant* or active*) NEAR/2 (deliver* or birth*)):ti,ab,kw
	14	(tim* NEAR/2 (birth* or deliver*)):ti,ab,kw
	15	MeSH descriptor: [Delivery, Obstetric] explode all trees
	16	((gestation* NEXT age) NEAR/2 (deliver* or birth*)):ti,ab,kw
	17	#15 AND #16
	18	((gestation* NEXT age) NEAR/2 deliver*):ti,ab,kw
	19	MeSH descriptor: [Gestational Age] explode all trees
	20	#15 AND #19
	21	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #17 OR #18 OR #20
	22	#5 AND #21

Additional file 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p9

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p10-12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p11
Study characteristics	17	Cite each included study and present its characteristics.	p12-14
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p13-14
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p18-22
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p18-22
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for	p18-22

Section and Topic	Item #	Checklist item	Location where item is reported
		each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p18-22
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p22
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P22
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p18-22
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p23
	23b	Discuss any limitations of the evidence included in the review.	p23-25
	23c	Discuss any limitations of the review processes used.	p23-25
	23d	Discuss implications of the results for practice, policy, and future research.	P25-26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p29
Competing interests	26	Declare any competing interests of review authors.	p29
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p28

Table S1. Articles excluded after full text review and reasons for exclusion (n=77)

Articles	Exclusion reasons
Olerich et al: Cesarean section rates by induction of labor indication in diabetic pregnancies	Inappropriate comparator
Vilchez et al: Pregnancy, Labor and Neonatal Outcomes and Optimal Timing for Induction of Labor in Gestational Diabetes	Inappropriate comparator
Rayburn et al: Effect of labor induction on cesarean rates in diabetic pregnancies	Inappropriate comparator
Hamel et al: Labor Induction and Cesarean Delivery Risk in Women with Gestational Diabetes Mellitus	Inappropriate comparator
Mantovani et al: Early diagnosis, active management and early induction of labour in pre-existing and gestational diabetes: Effects on pregnancy and delivery outcomes	Inappropriate comparator
Mirghani et al: A simplified management of diabetic pregnant women	Inappropriate intervention
Schwartz et al: Elective Delivery of Large Infants in Diabetic Pregnancies: Consequences and Implications	Inappropriate intervention
Sirota et al: Is Pharmacological Therapy during Induction of Labor in Gestational Diabetes Mellitus Patients Needed?	Inappropriate intervention
Maso et al: "GINEXMAL RCT: Induction of labour versus expectant management in gestational diabetes pregnancies".	Protocol
Bas-Lando et al: Elective induction of labor in women with gestational diabetes mellitus: an intervention that modifies the risk of cesarean section	Inappropriate comparator
Mashini et al: Indications for and timing of delivery in diabetic pregnancies	Inappropriate comparator
Kapustin et al: Time and mode of delivery in diabetic pregnancy: a review	Review
Vilchez et al: Labor and neonatal outcomes after term induction of labor in gestational diabetes	Inappropriate comparator
Hochberg et al: Perinatal outcome following induction of labor in patients with good glycemic controlled gestational diabetes: does timing matter?	Inappropriate comparator
Metcalfe et al: Timing of delivery in women with diabetes: A population-based study	Unrelated outcomes

Worda et al: Randomized controlled trial of induction at 38 weeks versus 40 weeks gestation on maternal and infant outcomes in women with insulin-controlled gestational diabetes	Inappropriate comparator
Wimberley et al: When a pregnant women is diabetic: intrapartal care	Review
Liner et al: Induction of labor in patients with diabetes mellitus	Correspondence
Thung et al: Fetal surveillance and timing of delivery in pregnancy complicated by diabetes mellitus	Review
Witkop et al: Active compared with expectant delivery management in women with gestational diabetes: a systematic review	Review
Leeman et al: Induction of labour at 37-38 weeks in women with large fetuses decreases the likelihood of shoulder dystocia; however, overall benefit of early-term delivery has not been demonstrated	Incorrect patient population
Sugiyama et al: Management of gestational diabetes mellitus	Review
Grabowska et al: Labour in women with gestational diabetes mellitus	Inappropriate comparator
Zara et al: Medical and elective induction: A prospective randomized study	Incorrect patient population
Nicholson et al: Therapeutic management, delivery, and postpartum risk assessment and screening in gestational diabetes	Review
Herranz et al: Elective delivery in women with gestational diabetes mellitus	Review
Karmon et al: Decreased perinatal mortality among women with diet-controlled gestational diabetes mellitus	Inappropriate intervention
Crippa et al: Outcome of induction of labour in women with gestational diabetes and comparison with general obstetric population	Inappropriate comparator
Yogev et al: Active induction management of labor for diabetic pregnancies at term; mode of delivery and fetal outcome--a single center experience	Inappropriate comparator
Jiang et al: Effects of gestational diabetes mellitus on time to delivery and pregnancy outcomes in full-term pregnancies with dinoprostone labor induction	Inappropriate intervention

Atad et al: Induction of labor in gestational diabetes	Review
Boulvain et al: Elective delivery in diabetic pregnant women	Review
Arnold et al: Induction of labour in pregnant diabetics using vaginal prostaglandin E2 pessaries	Inappropriate intervention
Gawlik et al: Timing of elective repeat caesarean does matter: Importance of avoiding early-term delivery especially in diabetic patients	Inappropriate intervention
Duryea et al: The effect of expectant management of mild gestational diabetes at term on perinatal morbidities	Inappropriate comparator
Fraser et al: Gestational diabetes: After the ACHOIS trial	Review
Wagner et al: Association between time of delivery and composite adverse outcomes in pregnancies complicated by diabetes	Inappropriate intervention
Schwarz et al: Timing of delivery in the pregnant diabetic patient	Unrelated outcomes
Gabbe et al: General obstetric management of the diabetic pregnancy	Review
Khonjandi et al: Gestational diabetes: the dilemma of delivery	Inappropriate intervention
Huang et al: Intrapartum Results on Differing Degrees of Ketonuria in Nulliparous Women with Gestational Diabetes Mellitus during Spontaneous Labor	Inappropriate intervention
Dude et al: Association between Sonographic Estimated Fetal Weight and the Risk of Cesarean Delivery among Nulliparous Women with Diabetes in Pregnancy	Inappropriate intervention
Berger et al: Timing of delivery in women with diabetes in pregnancy	Review
Biesty et al: Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants	Review
Garabedian et al: Delivery (timing, route, peripartum glycemic control) in women with gestational diabetes mellitus	Review
Biesty et al: Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants	Review

Korkmazer et al: Gestational Diabetes: Screening, Management, Timing of Delivery	Review
Arnold et al: Induction of labor in pregnant diabetics using vaginal prostaglandin-E2 pessaries	Inappropriate intervention
Levy et al: Effect of labor induction on cesarean section rates in diabetic pregnancies	Inappropriate comparator
Hod et al: Antepartum management protocol: Timing and mode of delivery in gestational diabetes	Inappropriate intervention
Egan et al: A Review of the Pathophysiology and Management of Diabetes in Pregnancy	Review
Landon et al: Fetal surveillance and timing of delivery in pregnancy complicated by diabetes mellitus	Review
Boulvain et al: Elective delivery in diabetic pregnant women	Review
Sacks et al: Induction of labor versus conservative management of pregnant diabetic women	Review
Visser et al : Management of diabetes in pregnancy: antenatal follow-up and decisions concerning timing and mode of delivery	Review
Hersh et al: Induction of labor at 39 weeks of gestation versus expectant management for low-risk nulliparous women: a cost-effectiveness analysis	Incorrect patient population
Henry et al: Randomized trial of elective induction vs expectant management in diabetics	Conference abstract
Nayeri et al: Labor induction at 38 weeks versus expectant management of insulin-requiring diabetics in pregnancy: a cost effective analysis	Conference abstract
No name: Gestational Diabetes: induction Versus Expectant Management of Labour	Protocol
Alberico et al: Fulfilling professional responsibilities when counselling patients about Zika infection	Commentary
No name: Insulin Dependent Gestational Diabetes Mellitus: randomized Trial of Induction of Labour at 38 and 40 Weeks of Gestation	Protocol
No name: The Best Timing of Delivery in Women With GDM Study	Protocol

Niu et al: Timing of induction of labor among women with gestational diabetes (GDM)	Conference abstract
Rosenstein et al: The risk of stillbirth and infant death stratified by gestational age in women with gestational diabetes	Inappropriate intervention
Nau et al: Induction Compared to Expectant Management for Women With Gestational Diabetes at Term	Conference abstract
McElwee et al: The risk of perinatal mortality by week of expectant management in pregnancies complicated by diabetes	Conference abstract
No name: To understand whether in women diagnosed with gestational diabetes well controlled on diet therapy at term (39-40 gestational weeks) would be better to induce labour or expect the spontaneous onset of labour	Protocol
Cheng et al: Women with gestational diabetes mellitus: induction or spontaneous labor?	Conference abstract
Niu et al: What is the optimal gestational age for women with gestational diabetes type A1 to deliver?	Inappropriate intervention
Boulvain et al: Elective delivery in diabetic pregnant women	Review
Harper et al: Gestational Age of Delivery in Pregnancies Complicated by Diabetes	Incorrect patient population
Leaphart et al: Labor induction with a prenatal diagnosis of fetal macrosomia	Incorrect patient population
Peled et al: Gestational diabetes mellitus--implications of different treatment protocols	Inappropriate comparator
Hod et al: Antepartum management protocol. Timing and mode of delivery in gestational diabetes	Inappropriate comparator
Lurie et al: Outcome of pregnancy in class A1 and A2 gestational diabetic patients delivered beyond 40 weeks' gestation	Inappropriate intervention
Lyons et al: Timing of Delivery in Women with Diabetes: A Population-Based Study	Commentary
Alberico et al: Immediate delivery or expectant management in gestational diabetes at term: the GINEXMAL randomised controlled trial	Duplicate

Table S2. Further characteristics of the included studies

Study	Study Population			GDM subtypes	GDM Diagnosis criteria	Timing of diagnosis (weeks)	Measurement of gestational age
	Maternal age (y) ^a	Nulliparity ^b	Obesity ^c				
Alberico et al. 2017	32.3 ± 6.1 32.4 ± 5.6	127 (59.4) 104 (49.3)	NR ^d	A1GDM/A2GDM	IADPSG	NR ^d	LMP and Ultrasonography
Kjos et al. 1993	32.1 ± 0.61 31.9 ± 0.56	NR ^d	NR ^d	A2GDM/Pre-existing DM	NR ^d	NR ^d	LMP and Ultrasonography
Singh et al. 2013	26.0 ± 4.9 26.1 ± 4.22	14 (58.0) 12 (48.0)	NR ^d	A1GDM	IADPSG	NR ^d	LMP and Ultrasonography
Alberico et al. 2010	33.3 ± 4.9 32.7 ± 5.1	39 (63.0) 30 (59.0)	18 (37) 11 (21)	A1GDM/A2GDM	2000-2010 ADA diagnostic criteria	24-28	NR ^d
Melamed et al. 2016	32.5 ± 5.1 32.5 ± 5.0	483 (40.7) 2632 (50.3)	529 (44.5) 1650 (31.5)	A1GDM/A2GDM	2008 and 2013 CDA guideline	NR ^d	NR ^d
Vitner et al. 2019	33.0 ± 4.8 32.7 ± 4.8	150 (39.5) 670 (38.1)	NR ^d	A1GDM/A2GDM	2001 ACOG diagnostic criteria	24-28	LMP and Ultrasonography
Feghali et al. 2016	31.0 ± 5.2	90 (48.9)	NR ^d	A1GDM /A2GDM	CC criteria	NR ^d	NR ^d
Lurie et al. 1996	32.5 ± 6.1 31.1 ± 5.0	NR ^d	NR ^d	A2GDM	O'Sullivan and Mahlan ACOG	NR ^d	LMP and Ultrasonography
Rayburn et al. 2005	30.0 ± 6.5 30.0 ± 6.8	26 (18.0) 42 (31.0)	NR ^d	A1GDM/A2GDM	diagnostic criteria	NR ^d	Ultrasonography
Sutton et al. 2014	28.9 ± 5.5	38 (26.2)	NR ^d	Mild GDM	CC Criteria	24-30	NR ^d
Conway et al. 1998	28.5 ± 6.6 28.8 ± 6.8	NR ^d	NR ^d	GDM/Pre-existing DM	NR ^d	NR ^d	NR ^d

^a presented as mean ± SD for intervention and control groups; ^b presented as number (%) for intervention and control groups; ^c refers to maternal BMI >30 mg/m², presented as number (%) for intervention and control groups; ^d NR: Not reported; LMP: Last menstrual period; ADA: American Diabetes Association; CC: Carpenter and Coustan criteria; IADPSG: The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria; CDA: Canadian Diabetes Association; ACOG: American Committee of Obstetrics and Gynaecology;

Table S3. Quality assessment for the observational studies

Study	Selection			Comparability		Outcome			NOS Score	
	1	2	3	4	5 _a	5 _b	6	7		8
Alberico et al, 2010	*	*	*	*	*	*	*	*	*	9
Feghali et al, 2016	*	*	*	*	*	*	*	*	*	9
Lurie et al, 1996	*	-	-	*	-	-	*	*	*	5
Melamed et al, 2016	*	*	*	-	*	*	*	*	*	8
Rayburn et al, 2005	*	-	*	*	-	-	*	*	*	6
Sutton et al, 2014	*	*	-	*	*	*	-	*	*	7
Vitner et al, 2019	*	*	*	*	*	*	*	*	*	9
Conway et al, 1998	*	-	-	*	-	-	-	*	*	4

NOS: Newcastle-Ottawa Scale;

1. Representativeness of the exposed cohort; 2. Selection of the non-exposed cohort; 3. Ascertainment of exposure; 4. Demonstration that outcome of interest was not present at start of study; 5_a Comparability of cohort: control selected (the most important factor); 5_b study controls for additional factor; 6. Assessment of outcome; 7. long enough follow- up for outcomes; 8. Adequacy of follow-up

Table S4. Pooled estimates for the effect of induction on primary outcomes in observational studies

Observational study	Events/Total, n/N		OR (95% CI)	Sensitivity analysis		
	IOL	EM		Q	I ² (%)	Pooled OR * (95% CI)
CS						
Alberico et al, 2010	9/48	11/51	0.84 (0.31, 2.25)	23.1	74	1.04 (0.79, 1.37)
Conway et al, 1998	343/1337	266/1227	1.25 (1.04, 1.50)	12.4	52	0.97 (0.74, 1.28)
Feghali et al, 2016	15/55	104/528	1.53 (0.81, 2.87)	21.1	72	0.99 (0.75, 1.30)
Lurie et al, 1996	22/96	31/164	1.28 (0.69, 2.36)	22.4	73	1.00 (0.76, 1.33)
Melamed et al, 2016	198/1188	1114/5229	0.74 (0.63, 0.87)	4.69	0	1.19 (1.04, 1.38)
Rayburn et al, 2005	18/143	16/137	1.09 (0.53, 2.23)	23.08	74	1.02 (0.77, 1.36)
Sutton et al, 2014	3/48	77/553	0.41 (0.12, 1.36)	21.1	72	1.07 (0.82, 1.39)
Vitner et al, 2019	58/380	246/1759	1.11 (0.81, 1.51)	22.4	73	1.01 (0.74, 1.39)
No exclusion	666/3295	1865/9648	1.06 (0.96, 1.17)	23.2	70	1.03 (0.79, 1.34)
Macrosomia						
Alberico et al, 2010	6/48	11/51	0.52 (0.18, 1.54)	5.5	27	0.63 (0.51, 0.78)
Conway et al, 1998	120/1337	147/1227	0.72 (0.56, 0.93)	4.8	16	0.57 (0.43, 0.75)
Lurie et al, 1996	9/96	30/164	0.46 (0.21, 1.02)	4.9	18	0.65 (0.53, 0.79)
Melamed et al, 2016	108/1188	666/5229	0.69 (0.55, 0.85)	5.4	26	0.56 (0.40, 0.78)
Rayburn et al, 2005	6/143	11/137	0.50 (0.18, 1.40)	5.4	26	0.63 (0.51, 0.78)
Vitner et al, 2019	9/380	119/1759	0.33 (0.17, 0.66)	1.7	0	0.68 (0.58, 0.80)
No exclusion	258/3192	984/8567	0.68 (0.59, 0.78)	5.7	12	0.64 (0.54, 0.77)

Sensitivity analysis was performed by leaving out one observational study; * Pooled OR referred to the OR where a corresponding study was excluded at one time by a random-effects model with the Mantel-Haenszel method;

Table S5. Summary of findings table (GRADE)

Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with GDM at term pregnancy					
Patient or population: Women with GDM at term pregnancy Intervention: IOL Comparison: Expectant Management					
Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EM	Risk difference with IOL
CS	674 (3 RCTs)	⊕⊕○○ Low ^{a,b,c,d,e}	OR 0.95 (0.64 to 1.43)	179 per 1,000	7 fewer per 1,000 (56 fewer to 59 more)
	12943 (8 observational studies)	⊕○○○ Very low ^{f,g}	OR 1.03 (0.79 to 1.34)	193 per 1,000	5 more per 1,000 (34 fewer to 50 more)
Macrosomia	625 (2 RCTs)	⊕⊕○○ Low ^{b,c,e}	OR 0.49 (0.30 to 0.81)	164 per 1,000	76 fewer per 1,000 (108 fewer to 27 fewer)
	11759 (6 observational studies)	⊕○○○ Very low ^{f,h}	OR 0.64 (0.54 to 0.77)	115 per 1,000	38 fewer per 1,000 (49 fewer to 24 fewer)
LGA	200 (1 RCT)	⊕⊕○○ Low ^{d,e,i}	OR 0.37 (0.17 to 0.83)	230 per 1,000	130 fewer per 1,000 (182 fewer to 31 fewer)
	11120 (3 observational studies)	⊕○○○ Very low ^j	OR 0.88 (0.72 to 1.06)	117 per 1,000	13 fewer per 1,000 (30 fewer to 6 more)
Instrumental vaginal delivery	474 (2 RCTs)	⊕⊕○○ Low ^{b,e}	OR 0.84 (0.47 to 1.50)	119 per 1,000	17 fewer per 1,000 (59 fewer to 49 more)
	8714 (3 observational studies)	⊕⊕○○ Low ^{k,l}	OR 1.00 (0.84 to 1.18)	114 per 1,000	0 fewer per 1,000 (16 fewer to 18 more)

Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with GDM at term pregnancy

Patient or population: Women with GDM at term pregnancy

Intervention: IOL

Comparison: Expectant Management

Outcomes	N ^o of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EM	Risk difference with IOL
Severe perineal lacerations	273 (1 RCT)	⊕⊕○○ Low ^{b,e}	OR 0.13 (0.01 to 2.52)	23 per 1,000	20 fewer per 1,000 (23 fewer to 33 more)
	8556 (2 observational studies)	⊕○○○ Very low ^e	OR 0.59 (0.39 to 0.88)	29 per 1,000	12 fewer per 1,000 (18 fewer to 3 fewer)
ICU	425 (1 RCT)	⊕⊕○○ Low ^{b,e}	OR 1.49 (0.25 to 8.98)	9 per 1,000	5 more per 1,000 (7 fewer to 70 more)
Shoulder dystocia	625 (2 RCTs)	⊕⊕○○ Low ^{b,e}	OR 0.75 (0.04 to 15.49)	13 per 1,000	3 fewer per 1,000 (12 fewer to 155 more)
	11660 (5 observational studies)	⊕○○○ Very low ^{f,g}	OR 0.79 (0.48 to 1.30)	23 per 1,000	5 fewer per 1,000 (12 fewer to 7 more)
NICU	425 (1 RCT)	⊕⊕○○ Low ^{b,e}	OR 0.99 (0.14 to 7.06)	9 per 1,000	0 fewer per 1,000 (8 fewer to 54 more)
	8655 (3 observational studies)	⊕○○○ Very low ^{h,m}	OR 1.41 (0.85 to 2.32)	96 per 1,000	34 more per 1,000 (13 fewer to 102 more)
5-min Apgar score <7	425 (1 RCT)	⊕⊕○○ Low ^{b,e}	OR 4.98 (0.24 to 104.28)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

Comparison of adverse maternal and perinatal outcomes between induction and expectant management among women with GDM at term pregnancy

Patient or population: Women with GDM at term pregnancy

Intervention: IOL

Comparison: Expectant Management

Outcomes	N ^o of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with EM	Risk difference with IOL
Neonatal acidemia	2518 (3 observational studies)	⊕○○○ Very low ^{e,n}	OR 0.40 (0.10 to 1.55)	6 per 1,000	4 fewer per 1,000 (6 fewer to 3 more)
	425 (1 RCT)	⊕⊕○○ Low ^{b,e}	OR 7.00 (0.36 to 136.35)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
	2139 (1 observational study)	⊕○○○ Very low ^e	OR 1.16 (0.24 to 5.48)	5 per 1,000	1 more per 1,000 (3 fewer to 20 more)
Perinatal mortality	9195 (5 observational studies)	⊕○○○ Very low ^{e,i,o}	OR 0.64 (0.16 to 2.58)	2 per 1,000	1 fewer per 1,000 (1 fewer to 3 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. 2 trials with unclear risk for most domains (Kjos 1993, Singh 2013)

b. 1 trial (Alberico 2017) was open label, unable to blind women and healthcare professionals to the intervention, with high risk of performance and detection bias

- c. 1 trial only included GDM women controlled by medical nutrition therapy (Singh 2013)
- d. 1 trial only included insulin-treated GDM (Kjos 1993)
- e. Relatively small sample size and a wide confidence interval
- f. 3 studies had high risk of bias and no adjustment for the outcome, of which two had a historical comparison group (Lurie 1996, Conway 1998), and the other one with incomparable control group (Rayburn 2005);
- g. Point effect estimate varied in direction while most of the studies included null value
- h. 1 study with relatively small sample size (Alberico 2010)
- i. The trial with unclear risk of bias for most of the domains (Kjos 1993)
- j. 1 study (Conway 1998) had a historical comparison and no adjustment for the outcome (Conway 1998)
- k. 1 study had high risk of bias, with a historical comparison and no adjustment for the outcome (Lurie 1996)
- l. All of the studies included null value
- m. Two studies showed a significantly protective effect (Melamed 2016, Vintner 2019)
- n. 1 study had high risk of bias, with a historical comparison group and no adjustment for the outcome (Rayburn 2005)
- o. 2 studies had high risk of bias, with a historical comparison group and no adjustment for the outcome (Lurie 1996, Rayburn 2005)

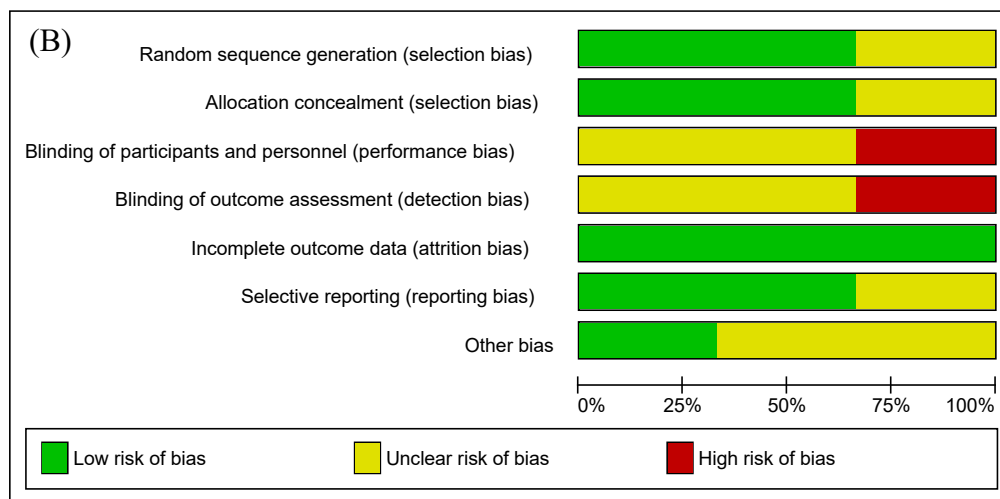
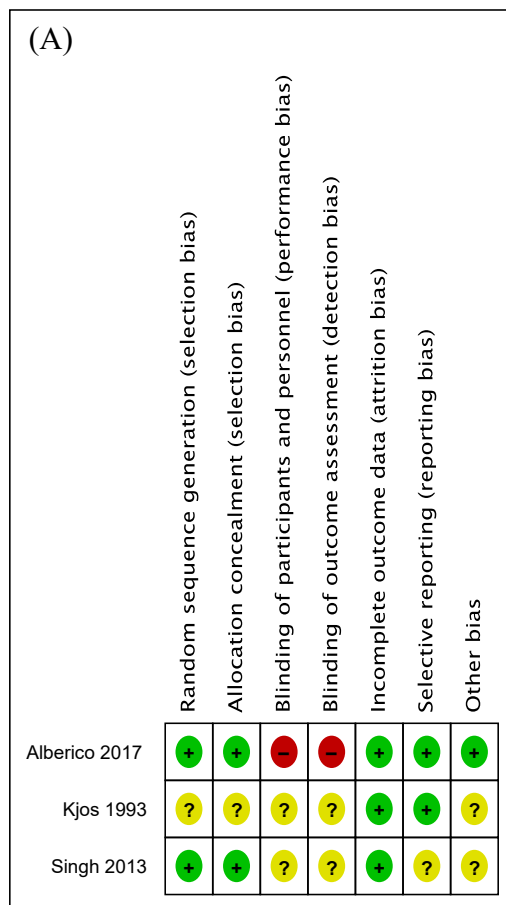


Figure. S1 Assessment of risk of bias for RCTs. (A) Summary of risk of bias (+: low risk of bias; -: high risk of bias; ?: unclear risk of bias); (B) Risk of bias graph with each risk of bias item presented as percentages across all included trials

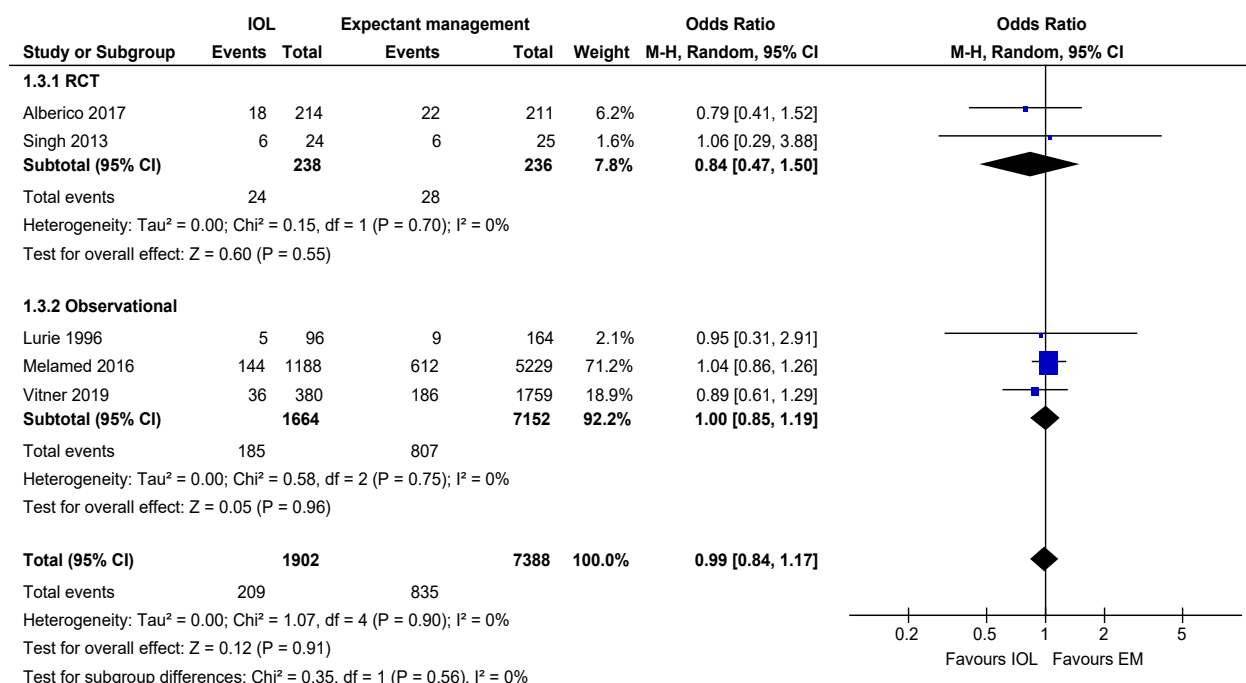


Figure. S2 Forest plot for instrumental vaginal delivery comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. IOL, induction of labour; EM, expectant management

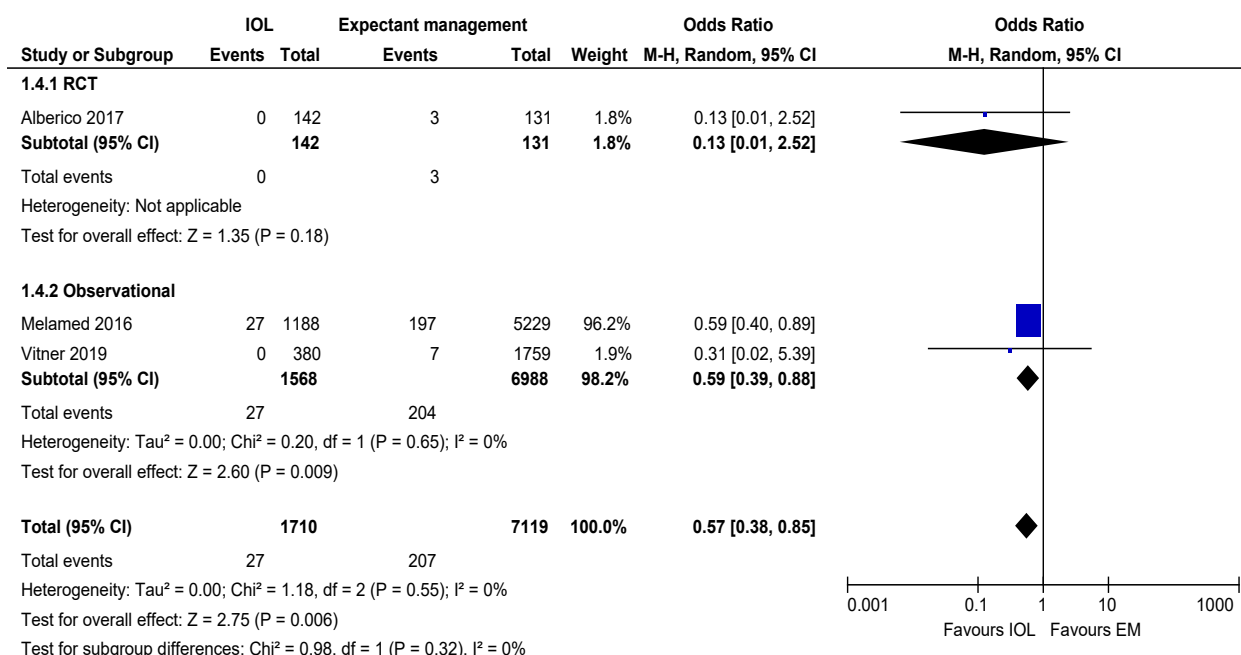


Figure. S3 Forest plot for severe perineal lacerations comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. One RCT (Alberico 2017) and one observational study (Vitner 2019) had no events recorded in induction group, and a fixed correction using 0.5 to each cell of the 2X2 tables was applied for individual study odds ratio calculation. IOL, induction of labour; EM, expectant management

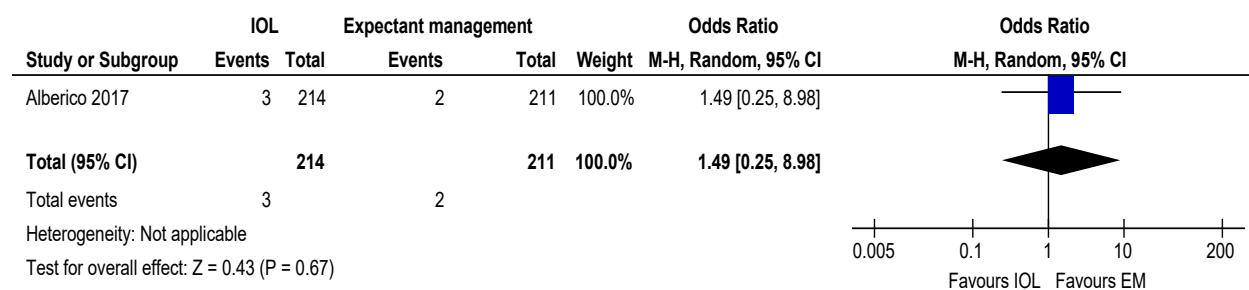


Figure. S4 Forest plot for ICU comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. IOL, induction of labour; EM, expectant management

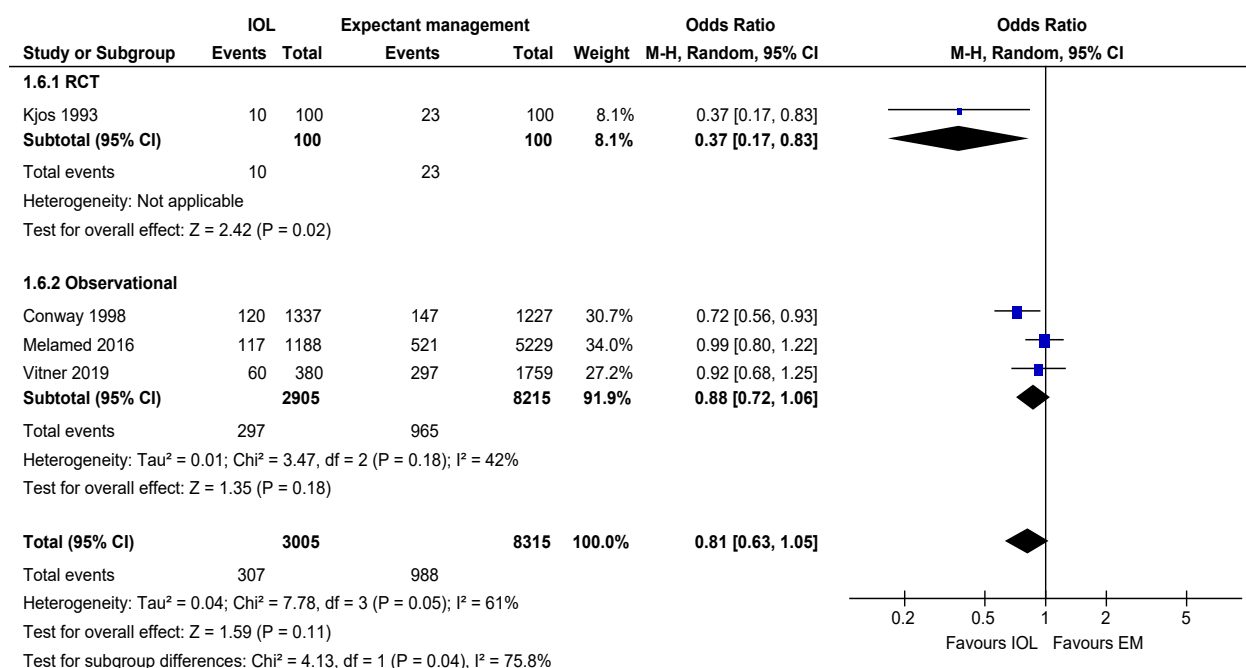


Figure. S5 Forest plot for LGA comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. IOL, induction of labour; EM, expectant management

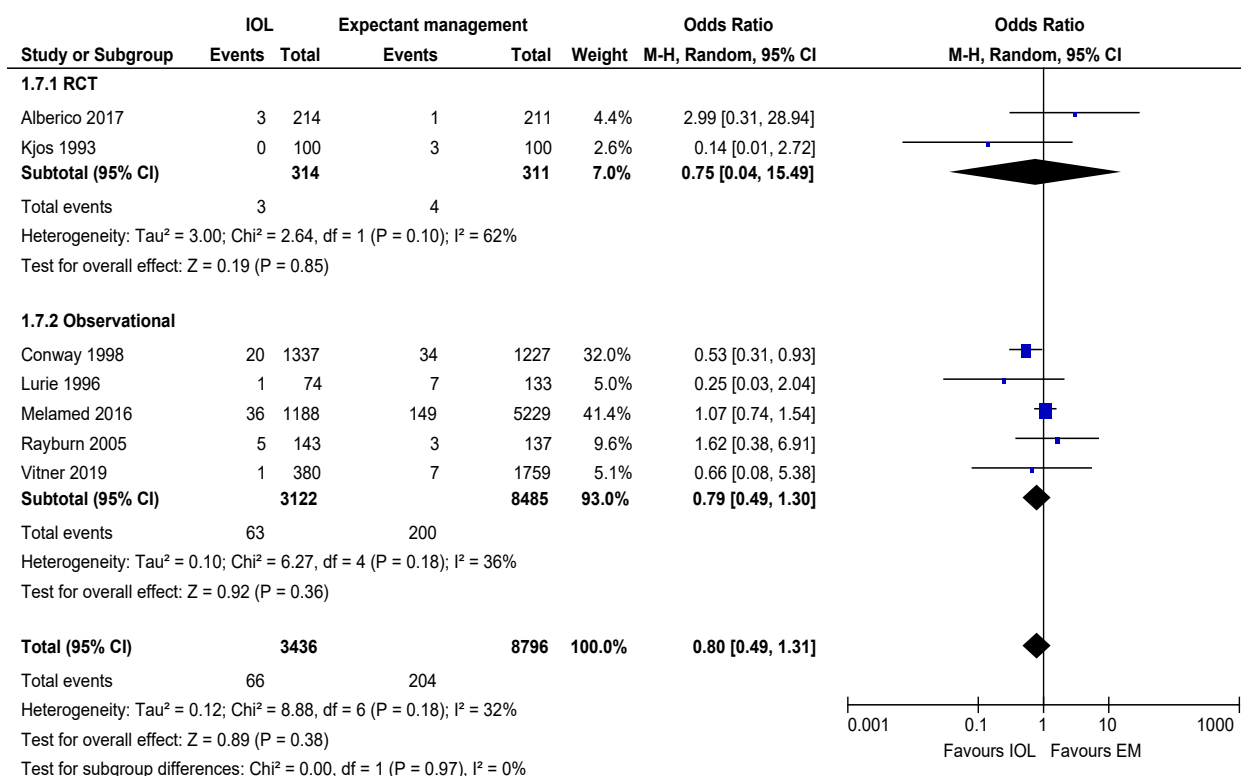


Figure. S6 Forest plot for shoulder dystocia comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. One RCT (Kjos 1993) had no events recorded in induction group and a fixed correction using 0.5 to each cell of the 2X2 tables was applied for individual study odds ratio calculation. IOL, induction of labour; EM, expectant management

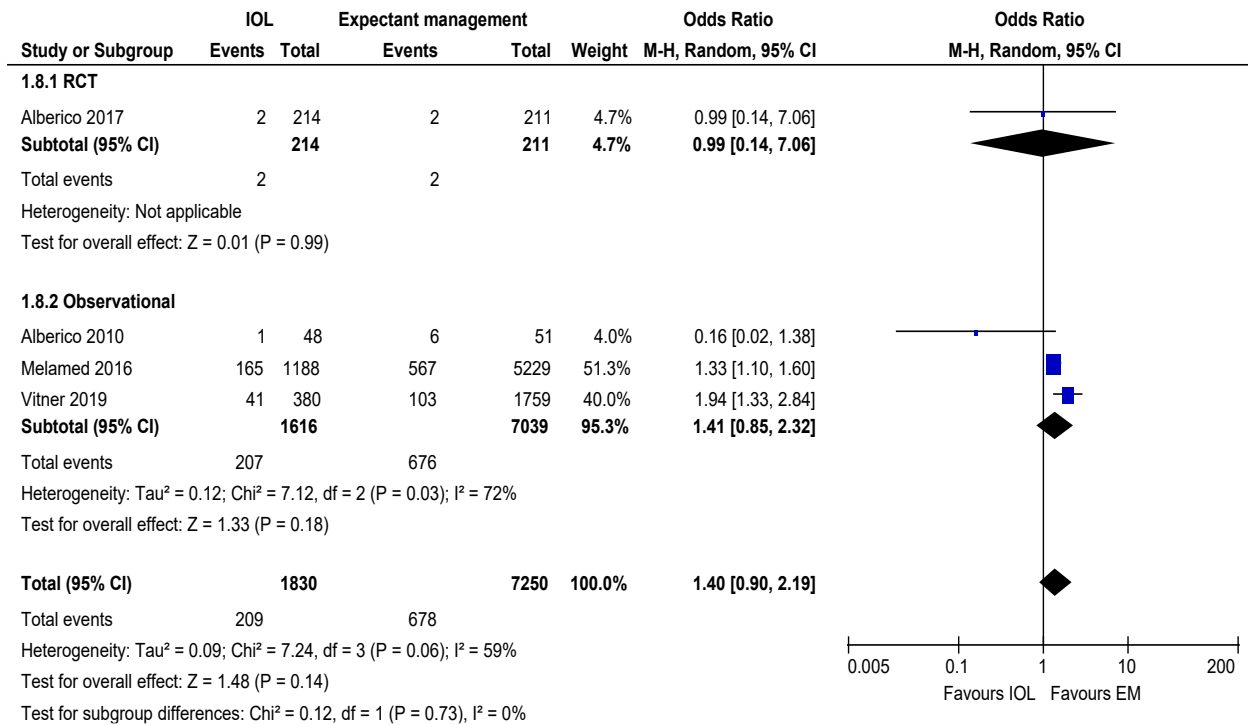


Figure. S7 Forest plot for NICU comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. IOL, induction of labour; EM, expectant management

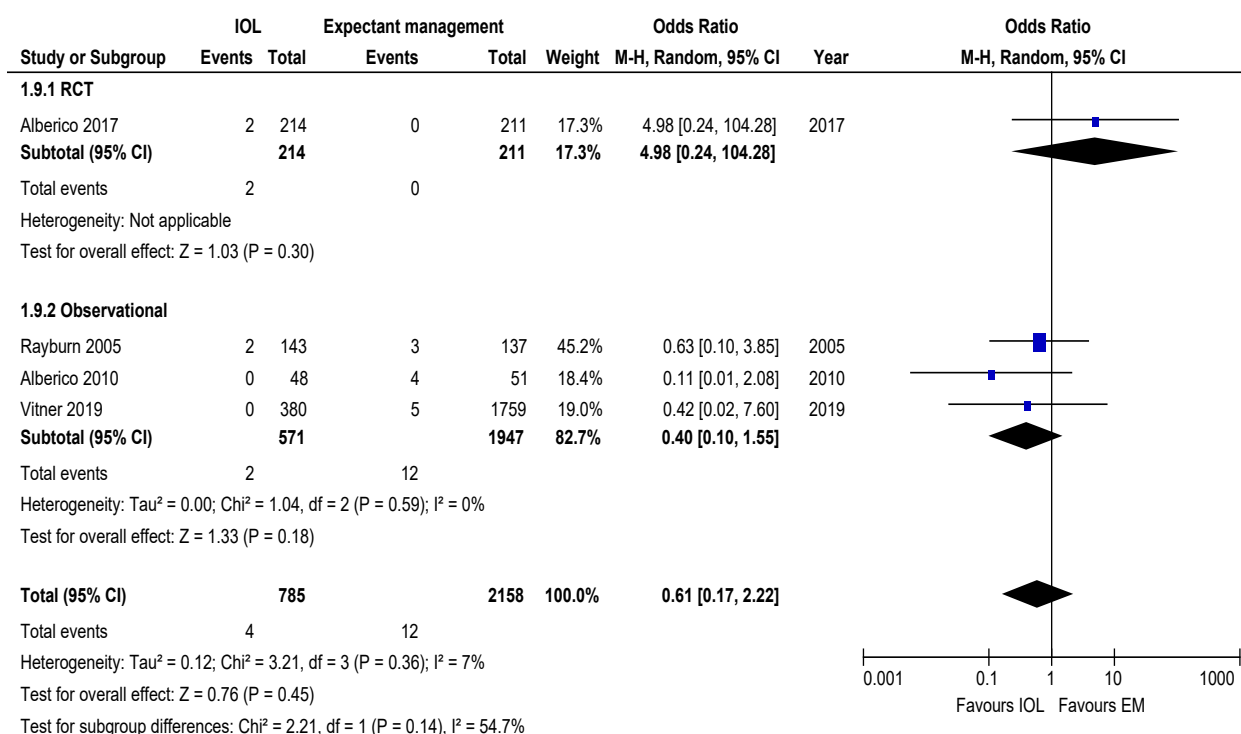


Figure.S8 Forest plot for 5-min Apgar score<7 comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. One RCT (Alberico 2017) and two observational studies (Alberico 2010; Vitner 2019) had no events recorded in one group, and a fixed correction using 0.5 to each cell of the 2X2 tables was applied for individual study odds ratio calculation. IOL, induction of labour; EM, expectant management

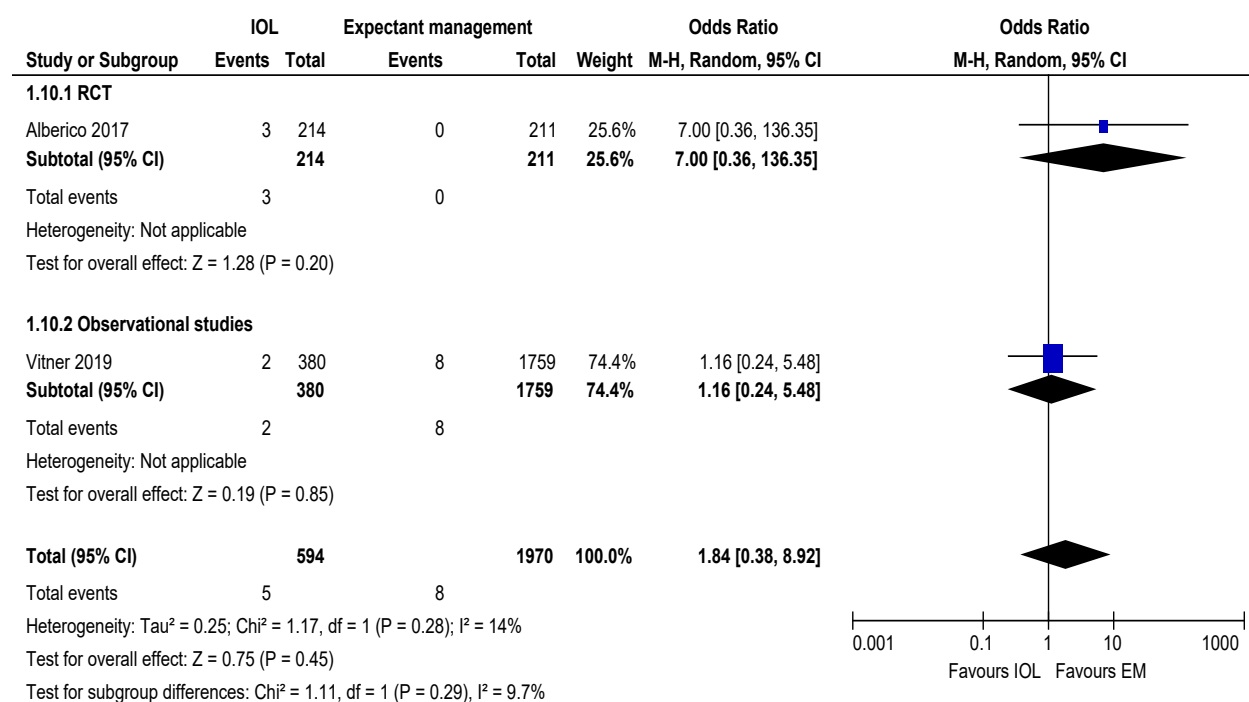


Figure. S9 Forest plot for neonatal acidemia comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. One RCT (Alberico 2017) had no events recorded in expectant management group and a fixed correction using 0.5 to each cell of the 2X2 tables was applied for individual study odds ratio calculation. IOL, induction of labour

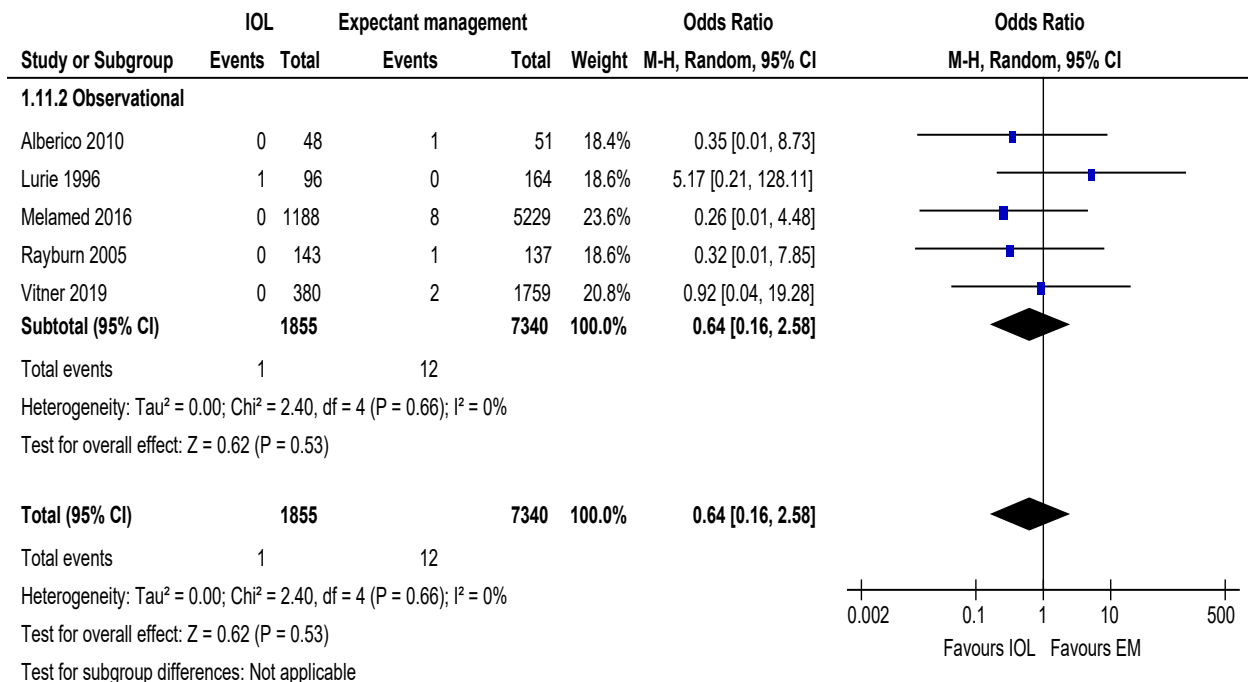


Fig. S10 Forest plot for perinatal mortality comparing induction with expectant management in women with GDM. Reference citations for studies can be found in Table 1. Four observational studies (Alberico 2010; Melamed 2016; Rayburn 2005; Vitner 2019) had no event recorded in induction group, and one study (Lurie 1996) had no event recorded in expectant management group. A fixed correction using 0.5 to each cell of the 2X2 tables was applied for individual study odds ratio calculation. IOL, induction of labour

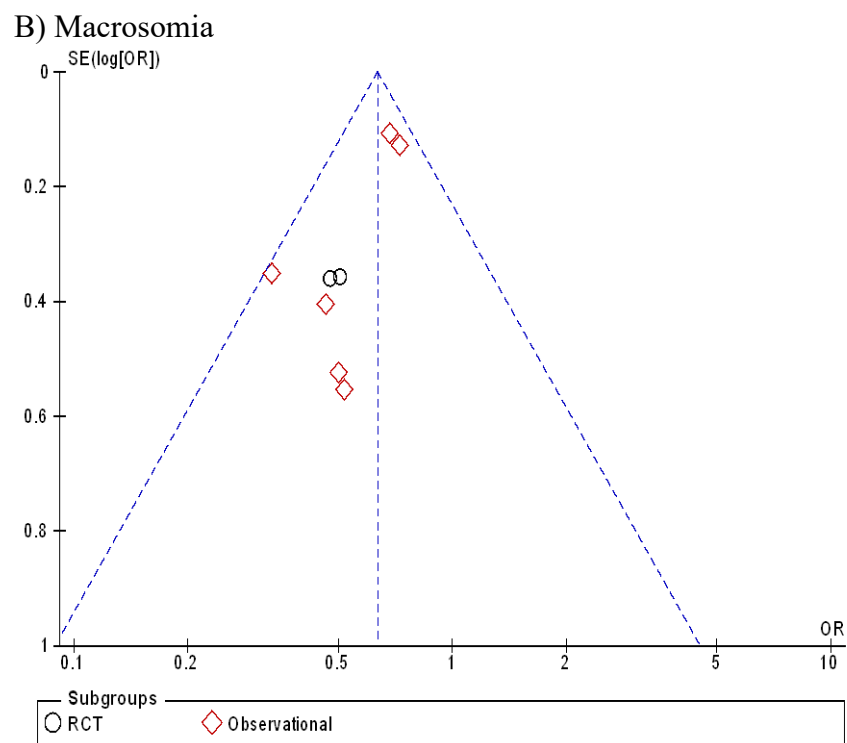
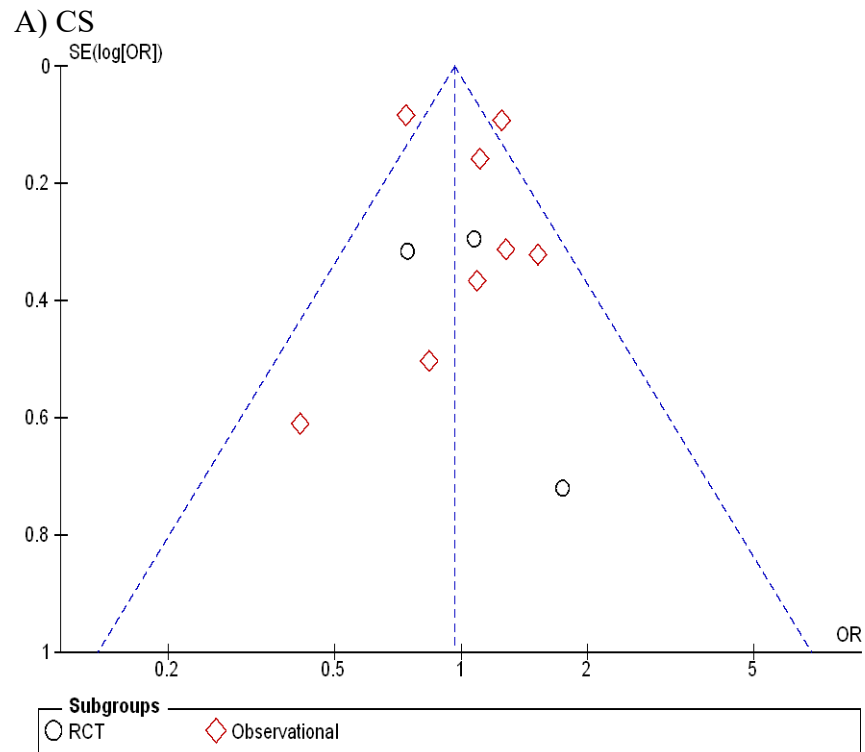
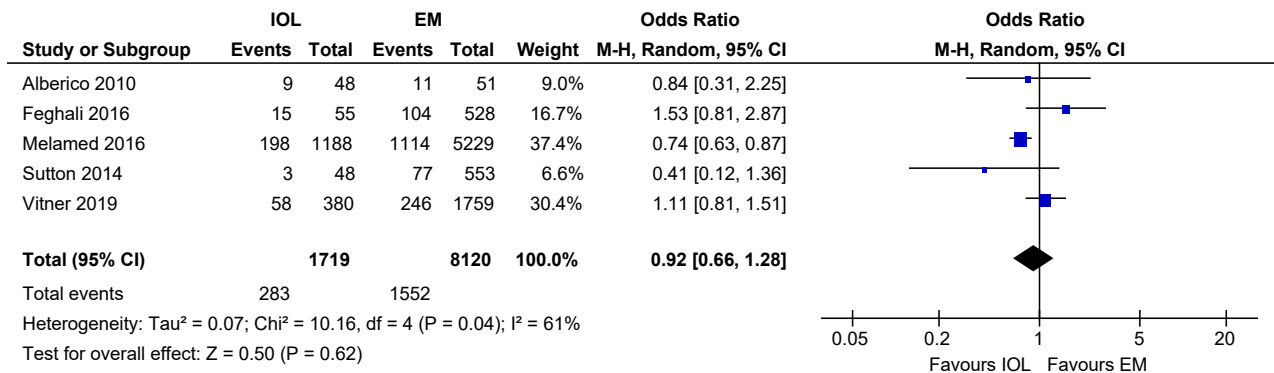


Figure. S11 Funnel plot to assess publication bias for primary outcomes A) CS B) Macrosomia

A) CS



B) Macrosomia

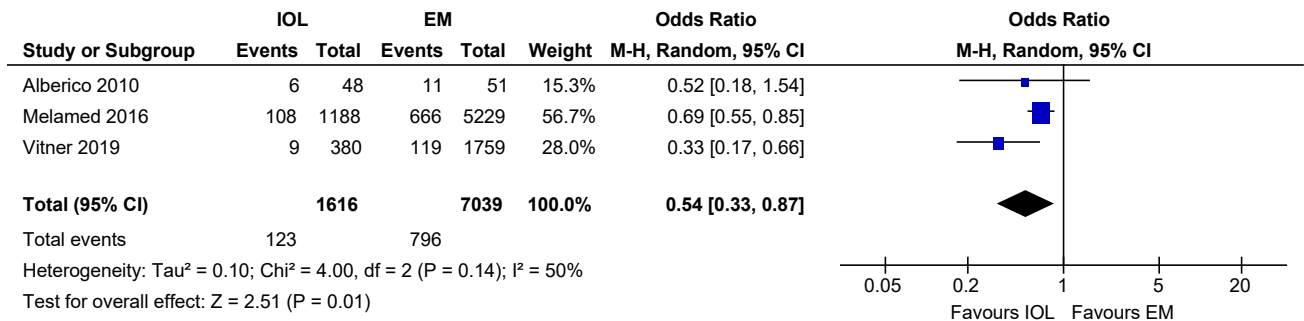
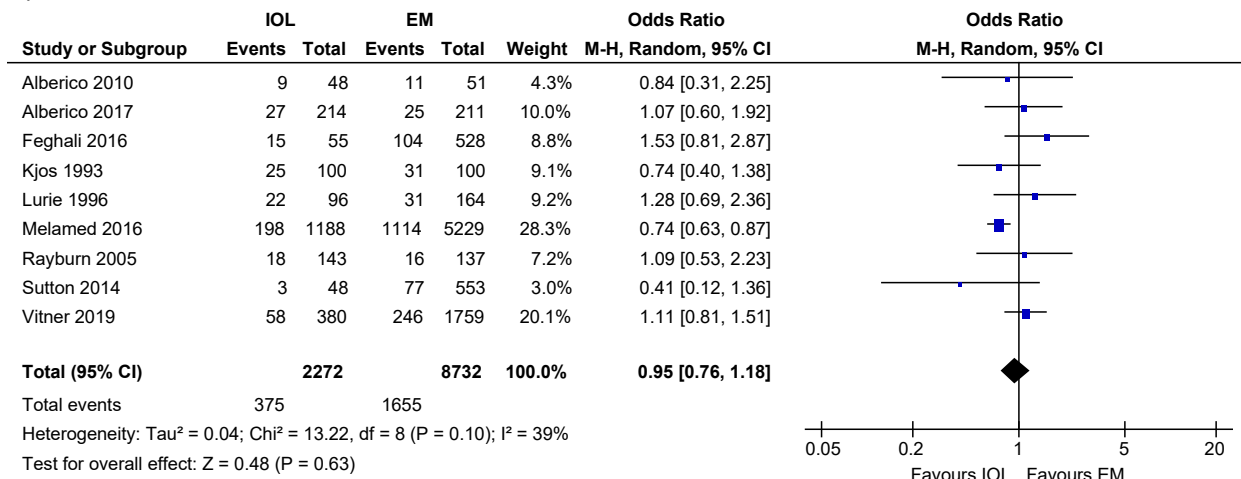


Figure. S12 Sensitivity analysis in high-quality studies A) CS B) Macrosomia

A) CS



B) Macrosomia

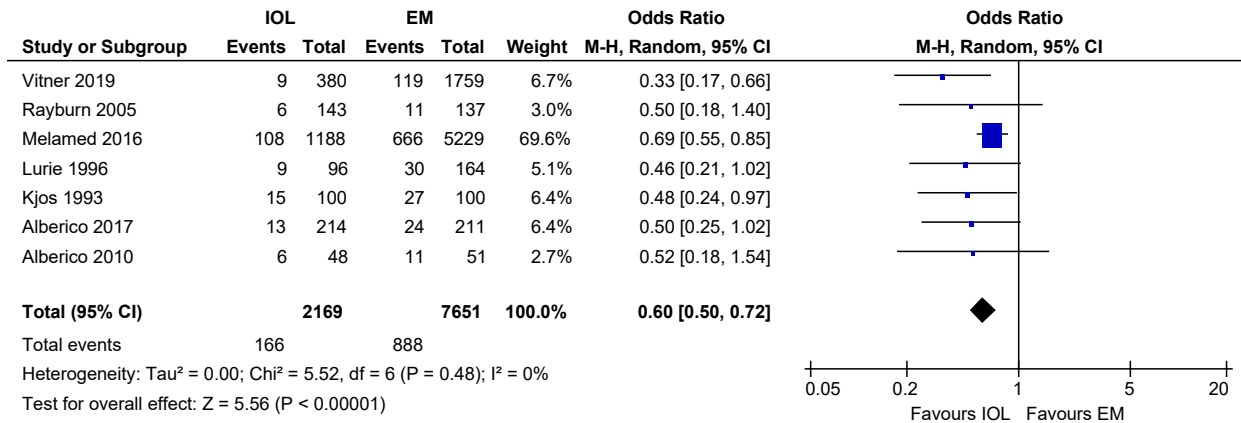


Figure. S13 Sensitivity analysis in studies with same gestational age at induction