Maternal and Neonatal Outcomes in Twin Pregnancies Complicated With Gestational
Diabetes Mellitus Compared to Twin Pregnancies Without Gestational Diabetes Mellitus:
A Population-based Retrospective Cohort Study of Nova Scotia Births

by

Norma Elizabeth Campbell

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is broadly defined as diabetes that is first diagnosed during pregnancy. It can lead to complications in singleton pregnancies for both mother and baby, such as excessively high birthweight and consequentially the need for Caesarean section, shoulder dystocia, birth trauma, gestational hypertension, and neonatal hypoglycemia. Women carrying twins have increased risk of adverse maternal and fetal outcomes such as growth restriction, discordant growth, pre-eclampsia and preterm delivery, but few studies have examined the outcomes of GDM among twin pregnancies.

Objectives: This study investigated twin pregnancies, comparing women affected by GDM to those unaffected with respect to: (1) maternal outcomes including hypertensive disorders of pregnancy, placental abruption, preterm delivery, mode of delivery and antepartum length of stay and (2) neonatal outcomes of perinatal death, hypoglycemia, birthweight discordance, small for gestational age (SGA), large for gestational age (LGA), neonatal intensive care unit (NICU) admission, neonatal length of stay, respiratory distress and low Apgar score.

Methods: The retrospective cohort study was carried out using provincial data from the Nova Scotia Atlee Perinatal Database (NSAPD) between 1988 and 2013. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) for the association between GDM and each outcome were estimated from logistic regression models with generalized estimating equations to account for nonindependence between twins.

Results: 2374 women who delivered twins were included, 109 (4.6%) of whom had GDM. Outcomes with estimated aORs > 1.30 included hypertensive disorders of pregnancy (aOR 1.44, 95% CI 0.88-2.38), an antepartum length of stay > 48 hours (aOR 1.55, 95% CI 0.97-2.50) and Caesarean section (aOR 1.34, 95% CI 0.87-2.07). Neonates born to mothers with GDM had estimated aORs > 1.30 for the outcomes of hypoglycemia (aOR 3.07, 95% CI 1.82-5.19) and small for gestational age (aOR 1.46, 95% CI 0.99-2.15), while aORs < 0.77 were calculated for respiratory distress (aOR 0.70, 95% CI 0.41-1.22), and low Apgar score (aOR 0.53, 95% CI 0.23-1.23).

Conclusions: The results of this study confirmed some associations previously noted in the literature while finding differing results of other associations. The study suggested an association between GDM and a longer antepartum length of stay in women pregnant with twins, an outcome not previously examined. Further research is warranted, ideally with larger study numbers and information on maternal glucose control during pregnancy.

LIST OF ABBREVIATIONS USED

aOR	Adjusted Odds Ratio
BMI	Body Mass Index
CDA	Canadian Diabetes Association (renamed Diabetes Canada)
CI	Confidence Interval
GDM	Gestational Diabetes Mellitus
ICD	International Classification of Disease
IWK	Isaac Walton Killam Health Centre
LGA	Large for Gestational Age
NICU	Neonatal Intensive Care Unit
NSAPD	Nova Scotia Atlee Perinatal Database
OGCT	Oral Glucose Challenge Test
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
SGA	Small for Gestational Age
SD	Standard Deviation
RR	Risk Ratio

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Chapter 1 INTRODUCTION

Gestational diabetes mellitus (GDM) is broadly defined as diabetes that first is

diagnosed during pregnancy.[1,2] This diagnosis can lead to complications for both mother

and baby, particularly if left untreated.[1] The most common complication of GDM in

singleton pregnancies is macrosomia, defined as a neonate born with a high birthweight,

usually 4000 g or 4500 g.[3] Macrosomia can further lead to complications such as the need

for Caesarean section, shoulder dystocia, birth trauma, gestational hypertension, and

neonatal hypoglycemia.[1,3,4] The prevalence of GDM is higher in multiple pregnancies

such as twins.[5,6] Women carrying twins also have increased risk of adverse maternal and

fetal outcomes such as growth restriction, discordant growth, pre-eclampsia and preterm

delivery.[7] Gestational diabetes and pregnancies of multiple gestations independently

carry some similar risks, but also some opposite yet equally concerning risks. To date,

most studies have examined the outcomes of GDM and twin pregnancies separately and

have not considered the outcomes of GDM among twin pregnancies. Further, of the few

studies conducted to date on this topic, most have focused mainly on neonatal outcomes,

whereas an examination of maternal outcomes would contribute to the current

knowledge. Therefore, the current retrospective cohort study investigated the outcomes of

GDM in twin pregnancies as compared to women pregnant with twins without GDM in

the maternal outcomes of hypertensive disorders of pregnancy, preterm delivery, mode of

delivery, placental abruption and antepartum length of stay, and the neonatal outcomes of

perinatal death, hypoglycemia, birthweight discordance, small for gestational age (SGA),

large for gestational age (LGA), neonatal intensive care admission (NICU), length of

stay, respiratory distress and low Apgar. Research focused on GDM within women with twin pregnancy, a population that is already at higher risk of adverse maternal and neonatal outcomes, has the potential to provide insight that will help health professionals treat GDM in women pregnant with twins.

Chapter 2 BACKGROUND

2.1   Background

2.1.1 Definition of Diabetes

Diabetes is a "metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both".[1] Prolonged hyperglycemia is associated with both microvascular and macrovascular complications. In general terms, diabetes can be sub-classified as Type 1 Diabetes, which is primarily due to pancreatic beta-cell destruction resulting in total deficiency of insulin; Type 2 Diabetes, which is predominately due to insulin resistance; and GDM, which occurs during pregnancy.[1] In pregnancy, Type 1 and Type 2 are often referred to as pre-existing diabetes. According to Diabetes Canada (formerly Canadian Diabetes Association [CDA]), GDM is defined as diabetes diagnosed in pregnancy.[1] It can be further defined as "carbohydrate intolerance resulting in hyperglycemia of varying severity, with first onset or recognition during pregnancy".[2]

Over the years, many studies have examined the pathophysiology leading to the development of GDM. It has been determined that pregnancy-related hormones are insulin antagonists, and as such, cause a reduction in insulin sensitivity.[3,8,9] Given this increased insulin resistance during pregnancy, it is hard for a woman's body to produce all of the insulin it requires to properly metabolize the carbohydrates ingested.[4] Hyperglycemia occurs when glucose builds up in the bloodstream instead of entering cells as it should. Although the pathophysiology of GDM has been well described, the reason some pregnant women develop GDM while others do not is less clear.[3]

2.1.2 Risk Factors for Gestational Diabetes

It has been determined that some women are at higher risk of developing GDM than others. Those who are aged 35 or older, have a pre-pregnancy body mass index (BMI) of >30 kg/m^2, have been diagnosed with polycystic ovarian syndrome or acanthosis nigricans, use corticosteroids, are part of certain minority groups including Aboriginal, Hispanic, South Asian, or African decent, have had GDM in a previous pregnancy, have a family history of diabetes or have previously given birth to a macrosomic infant are at higher risk.[1,4,10]

2.1.3 Fetal Sex and Relation to Gestational Diabetes

There is evidence that carrying a male fetus increases a mother's risk of GDM due to an association with poorer maternal β-cell function and the sex of the fetus appears to impact maternal glucose control.[11,12] Giannubilo and colleagues[12] followed 327 women diagnosed with GDM, 170 of whom who were carrying male fetus to assess blood glucose control and other outcomes. They found that in women carrying a male, OGTT (oral glucose tolerance test) results were higher at several time points, including at one-hour, compared to women carrying a female fetus (mean 9.25, SD 1.2 vs. mean 8.87, SD 1.3, p=0.006). Women carrying a male also had an increased need for insulin during pregnancy (47.6% vs 33.3%, p=0.018).[12] Retnakaren and colleagues[11] reviewed a population-based administrative database in Ontario, Canada, from 2000-2012 and found that in twin gestations, the crude rate of GDM was 5.6% if both fetuses were female, 6.1% if one was male and 5.2% if both were male. Once they adjusted for covariates, neither male/male [adjusted odds ratio (aOR 0.92, 95% confidence interval {CI} 0.76-1.11)] nor male/female (aOR 1.02, 95% CI 0.86-1.22) carried a greater risk than

female/female twins. Therefore, they concluded that the impact of carrying twins increased maternal glucose more so than fetal sex.[11] To further examine this hypothesis, they conducted a follow up study in 2015 that prospectively observed a cohort of 1074 women (540 pregnant with males and 534 with females) to evaluate the relationship between fetal sex and maternal risk of GDM.[13] They found no significant difference between the two groups with respect to major clinical risk factors, but the OGCT (oral glucose challenge test) results were higher in women carrying a male fetus than those carrying a female fetus (mean 8.3 mmol/L versus 8.1 mmol/L, $p<.001$). The women pregnant with males also had higher glucose concentrations in OGTT and an overall a higher incidence of GDM (22.2% versus 18.7%, $p=0.022$). In adjusted analyses, they found that carrying a male fetus was an independent risk factor for GDM (aOR 1.39, 95% CI 1.01-1.90).[13] Jaskolka et al.[14] found in their systematic review and meta-analysis of 20 studies representing 2,402,643 women, a very small increased risk of GDM in women carrying a male fetus [relative risk (RR) 1.04, 95% CI 1.02-1.06].

2.1.4 Screening and Diagnosis of Gestational Diabetes

Currently in most provinces in Canada, the majority of pregnant women are screened for GDM at 24 to 28 weeks' gestation using a two-step approach initially set forth by the CDA 2013 Clinical Practice Guidelines that are published every five years.[1] The guidelines for screening and diagnosis of GDM remain unchanged in the 2018 guidelines. The guidelines are based on a thorough and systematic compilation of the most recent research data, including guidelines specific for GDM.[1] For the purpose of this proposed research project, changes to the guidelines for screening and diagnosis of GDM in Nova Scotia from the period 1988-2013 to after 2013 will be highlighted.

Since the late 1980's, universal screening has been a standard of care for pregnant women in Nova Scotia. Screening occurred at 24 to 28 weeks' gestation unless indications for an earlier screen were present. Until the early 2000's, the screen was conducted via a 50 g OGCT with a one-hour plasma glucose. If this value was greater than or equal to 7.8 mmol/L, a 100 g OGTT was performed with blood glucose tested in a fasting state, and at one, two, and three hour increments after the ingestion of 100 g glucose. If two or more values exceeded pre-determined cut-points, a diagnosis of GDM was made. These cut-points were defined as greater than or equal to 5.3 mmol/L fasting, 10.6 mmol/L at 1 hour, 9.2 mmol/L at 2 hours, and 8.1 mmol/L at 3 hours.[1] After the early 2000's, the 50 g OGCT and diagnostic values remained the same, but the OGTT was changed to 75 g. This system of screening and diagnosis remained in place until the release and implementation of the 2013 guidelines.

The 2013 guidelines for the preferred method for screening and diagnosis of GDM also involve a two-step approach. Slight changes to the cut-points for the glucose concentrations were made, and of the three blood draws, only one value must be exceeded for a diagnosis of GDM. First, a 50 g oral glucose challenge test is conducted. If the 1-hour OGCT meets or exceeds 7.8 mmol/L but is less than 11.0 mmol/L, a 75 g OGTT is conducted.[1] If the fasting value of the OGTT is greater or equal than 5.3 mmol/L, the 1-hour value greater than or equal to 10.6 mmol/L or the 2-hour value is greater than or equal to 9.0 mmol/L, a diagnosis of GDM is given.[1] Some other countries are currently using slight variations of this diagnostic test. Some areas of the United States for example, use a one-step 75 g OGTT. If the fasting value is greater than or equal

to 5.1 mmol/L, the 1-hour greater than or equal to 10.0 mmol/L, or the 2-hour greater than or equal to 8.5 mmol/L, a diagnosis of GDM is made.[1,4]

2.1.5 Rates and Trends of Gestational Diabetes

As the prevalence of diabetes continues to rise, rates of diabetes in pregnancy are also on the rise. This is a growing concern as they tend to have high rates of pregnancy complications.[1,15] Gestational diabetes has been reported in various populations to have an average incidence of 5%.[15,16,17] In Canada, reported incidence rates of diabetes in pregnancy are similar to those around the world. The Public Health Agency of Canada reported in 2011 that maternal diabetes affected 5.5% of deliveries, up from 4.1% in 2005.[18] More specifically, in 2006, 5.1% of pregnancies in Canada were estimated to be affected by diabetes, with nearly 88% of these developing during pregnancy (GDM). [18] A population-based cohort study of over 1 million pregnant women in Ontario from 1996 to 2010 revealed that the age-adjusted rate of GDM doubled during the study period (2.7-5.6%, p <0.001).[15] Rates of diabetes in pregnancy rose as age increased, with rates higher in women aged 30 years and older, and women greater than 40 years old had the highest rate of diabetes in pregnancy (13% of women >40 had GDM).[15] In Nova Scotia, diabetes affected 5.9% of pregnancies in 2013, up from 3.3% in 2005.[19] As previously noted, the literature to date is conflicted as to the rates of GDM in multiple pregnancies as compared to singleton pregnancies. According to Simões et al.,[20] a similar prevalence of GDM was found in twin and singleton pregnancies, but Okby[21] found the prevalence of GDM in twins to be 7.8% as opposed to 3.2% in singletons. In a 2016 meta-analysis conducted by McGrath et al.,[22] the prevalence of GDM in twin pregnancies ranged from 3.2 to 21.5% with a mean prevalence across studies of 8.7%.

2.1.6 Treatment of Gestational Diabetes

The 2013 and 2018 Diabetes Canada Clinical Practice Guidelines state women with diabetes during pregnancy should be evaluated and followed by a registered dietitian, engage in physical activity, self-monitor blood glucose, and be educated on glycemic control.[1] If glycemic targets are not reached within two weeks of lifestyle modification, pharmacological therapy such as insulin or oral agents should be added.[1] Unlike other pregnancy-associated illnesses, once diagnosed, GDM is relatively easy to treat, thus lowering risks of maternal and fetal complications.[23] Treatment in Nova Scotia follows the Canadian guidelines, with women being referred to a Diabetes Management Centre for collaborative care during pregnancy.[24] Unfortunately, the blood glucose targets and associated treatment guidelines are, for the most part, based on the results of studies carried out on women with singleton pregnancies, and the applicability to twin gestation pregnancies is uncertain.[25,26]

2.1.7 Complications and Outcomes Associated with Gestational Diabetes

The diagnosis of GDM can lead to complications for both the mother and the infant, particularly if left untreated.[1,4] The most common potential adverse outcomes in singleton pregnancies include higher rates of birthweight for gestational age greater than the 90th percentile, stillbirth, miscarriage, preterm birth, Caesarean section, fetal macrosomia, shoulder dystocia, birth trauma, and maternal hypertension, as well as an increased maternal risk of developing Type 2 diabetes later in life.[1,2,3,21,27,28,29] Additional neonatal complications of jaundice, respiratory distress syndrome, polycythemia, and hypocalcemia have also been reported.[1,2,3,30] Excessive fetal growth and macrosomia remain the most common and most important perinatal concerns in GDM.[3,31]

2.1.8 Twin Types and Rates of Twins

Two biological processes determine zygosity in twin gestation. Dizygotic twins originate from the fertilization of two oocytes, creating dichorionic, diamniotic placentas.[32] This twin type typically carries the lowest risk of complications.[32] Monozygotic twins originate from fertilization of one egg that subsequently splits to form two embryos. Depending on the timing of this split, the placenta might have one or two chorion, and one or two amniotic sacs.[32,33] Monochorionic babies have a high rate of complications, including a high risk of twin to twin transfusion syndrome. This syndrome causes blood flow between the babies to become unbalanced.[28] Monochorionic twins also typically have a larger weight discrepancy due to placental blood vessel connection[7] and, therefore, can be associated with increased morbidity and mortality.[34] An ultrasound performed in the first trimester is usually able to determine amnionicity and chorionicity.[35] Dizygotic twins are fraternal, while monozygotic twins are identical.

As previously noted, the incidence of diabetes in pregnancy, specifically GDM, is increasing worldwide.[1,22] Likewise, around the world, rates of multiple pregnancy are on the rise.[22,35] In 2009, 3.3% of live births in the United States were twins.[22] In Canada, between 2001 and 2010, the rate of multiple births had increased from 2.8% to 3.2% of total births.[36] In Nova Scotia specifically, between 2006 and 2010, Vital Statistics recorded 44,785 total births, with 1470 of them being multiples (3.3%).[36] As expected, the Atlee Perinatal Database captured similar numbers in Nova Scotia, with 43,582 deliveries from 2006 to 2010, and 1436 of them being multiple deliveries (approximately 3.3%).[19] This increase in pregnancies yielding multiple gestations is due to a few factors. Typically, monozygotic twin rates remain stable around the world, as identical twins are

related to family history and previous history of twins.[37,38] Conversely, dizygotic twin rates are variable depending on geographic location, maternal age, and use of assisted reproductive therapies.[37] Around the world, more and more women are choosing to delay motherhood to pursue career goals and other life foci; therefore, the women's age at their first pregnancy has continuously increased.[37,39] As maternal age increases, so does the risk of infertility and, therefore, more women are utilising assisted reproductive therapy. Assisted reproductive techniques routinely result in pregnancies of multiple gestation as they often stimulate excess follicles or transfer multiple embryos.[39]

2.1.9 Complications Associated with Twin Pregnancies and the Relationship to Gestational Diabetes

Multiple gestation pregnancies are associated with many adverse conditions and outcomes affecting both the mother and the neonate such as spontaneous preterm delivery, preterm rupture of membranes, growth restriction, discordant growth and pre-eclampsia.[7,35,37] The perinatal morbidity and mortality reported in twin gestations is two to three times higher than in singleton pregnancies.[40,41] González González[31] notes that perinatal morbidity in twins is higher than singletons, partly due to the increased risks of maternal hypertensive disorders, low birthweight and prematurity. Just as women possess certain risk factors for developing GDM, a similar set of risk factors including older maternal age, obesity, polycystic ovarian syndrome, and the use of assisted reproductive therapies, might pre-dispose women to conceiving twins.[5,42,43]

Compared to singleton pregnancies, the prevalence of GDM is higher in multiple pregnancies, perhaps due to shared risk factors,[5,6] and women pregnant with twins could have up to a two-fold increased risk of developing GDM.[5] A large population-based

study conducted by Lai et al.[44] showed an increased risk of GDM in twin pregnancies, and that this risk remained even after controlling for maternal characteristics [odds ratio (OR) 1.15, 95% CI 1.03-1.27]. Because multiple pregnancies have larger placental mass (and therefore higher levels of anti-insulin hormones), usually occur in mothers of advanced maternal age, and can result in increased weight gain, this is not entirely surprising.[8,45,46] Although risk factors and some outcomes overlap between GDM and twin pregnancies, a common outcome in each condition, abnormal fetal growth, is typically opposite when GDM and twin gestations are examined independently. GDM in singletons can lead to a large for gestational age or macrosomic infant, while multiple pregnancies often lead to small for gestational age infants.

2.2 Existing Studies

2.2.1 Overview

To date, most studies examining outcomes of GDM and twin pregnancies have looked at each exposure independently. That is, the majority of research has been conducted on outcomes of GDM in singleton pregnancies, or outcomes of twin pregnancies not complicated by GDM. Some studies, however, have looked at the outcomes associated with GDM in women pregnant with twins. These main studies are summarized in Table 2.1. Unfortunately, many of these studies have small sample sizes, focus mainly on neonatal outcomes, and have produced conflicting results.[31,43,46,47] Cho et al.[43] studied only 33 twin pregnancies affected by GDM matched with 66 twin pregnancies without GDM on chorionicity, maternal age, parity, BMI and gestational age at delivery. Moses et al.[47] also had a small sample of 28 women with twin pregnancies and GDM, and only 20 glucose tolerant women with twin pregnancies obtained from the

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same database. Also, one of the larger studies that compared outcomes of diabetes in singleton and twin births included pre-existing diabetes and GDM.[44] As Dinham and colleagues[42] note, "it is uncertain how much GDM exacerbates the underlying maternal or fetal risks associated with a twin pregnancy". Nearly 30 years ago, Techobroutsky et al.[48] reported that babies born to Type 1 diabetic women had a high frequency of fetal malformations, but this study was of small sample size and the findings are not directly applicable to GDM. Since that time, studies have further examined GDM in singleton pregnancies, but few in multiple gestations.

A handful of the studies reviewed opted to match women pregnant with twins affected by GDM with twin pregnancies without GDM to adjust for any imbalances in the baseline characteristics between the groups.[20,43,47] The studies that employed matching techniques tended to be the studies with smaller sample sizes. Small sample size and subsequently reduced power could possibly explain some of the conflicting results. While some studies have found no difference in certain outcomes,[20,31,43] some even found positive associations between GDM and twin pregnancies, in that GDM improved birthweight in twins who otherwise would be at risk for being small for gestational age.[5,27,46]

Although several studies looked at some aspect of how GDM impacts maternal health during pregnancy or delivery, in the studies conducted on the topic of GDM in women pregnant with twins, only a small number of maternal outcomes have been examined. The most common maternal outcomes researched to date include hypertensive conditions,[20,31,42,44] mode of delivery,[20,31,42,46,49] and pre-term delivery.[20,21,31,44,47,49,50] Other maternal outcomes in the literature include placental abruption,[21] post-partum

hemorrhage,[21,49] and wound infection,[21] but these were examined in very few of the studies reviewed. The most common neonatal outcomes in the studies completed to date include respiratory distress,[20,42,43,46] perinatal death,[20,27,42,46] low Apgar score,[20,27,46,49,51] and small or large for gestational age.[20,31,33,49,51] Neonatal outcomes assessed to a much lesser extent included NICU admission,[5,46,51] hypoglycemia post-birth,[5,42,43,49] congenital anomalies,[27,42] and birthweight discordance.[7,33]

The findings of specific maternal and neonatal outcomes associated with GDM among twin pregnancies in other studies are summarized in greater detail in the following sections.

2.2.2 Hypertensive Disorders of Pregnancy

Simões et al.[20] conducted a matched cohort study of 105 twin pregnancies with GDM and 315 twin pregnancies without GDM over about a 10-year span in Portugal. The pregnancies were matched on gestational age, year of delivery and chorionicity. They defined hypertensive disorders as including pre-eclampsia, pregnancy induced hypertension and chronic hypertension, and while the percentage of diabetic mothers who were diagnosed with a hypertensive condition was higher than non-diabetic mothers, it was not significantly so (27.6% vs. 18.4%).[20] Because they included chronic hypertension, this result should be interpreted with caution, as chronic hypertension, defined as hypertension diagnosed prior to pregnancy, can often precede a diagnosis of GDM.

González González and colleagues[31] also assessed the impact of GDM on hypertensive outcomes in twin pregnancy. Over a 4-year period in Spain, they conducted a retrospective, multi-center cohort study. The authors included 534 pregnant women

carrying twins, 257 with GDM and 277 without. The exposed group was selected via medical record review, and the unexposed group was selected from the medical records of the next twin pregnancy. They found that the odds of hypertensive conditions was higher in women with GDM (OR 1.88, 95% CI 1.04-3.47), but, when they adjusted for maternal BMI, the strength of the association was attenuated (aOR 1.46, 95% CI 0.76-2.79).[31] This finding indicates that perhaps hypertensive conditions are found more frequently in women with GDM due to the fact that many of these women fall into a higher BMI range.

Lai, Johnson, Dover and Kaul[44] in Alberta also examined pre-eclampsia as an outcome of diabetes in pregnancy. In their research, they looked at a large cohort of singleton and twin births, with no diabetes, pre-existing diabetes and GDM, and further sub-analyzed these groups. They examined 336,400 live births and 2196 stillbirths, which included 5552 twin pregnancies and 405 of those twin pregnancies having GDM. They found that in twin pregnancies, GDM was associated with a higher odds of pre-eclampsia compared to twin pregnancies without GDM (OR 1.66, 95% CI 1.17-2.37) and this association persisted with adjustment for age, First Nations status, parity and pre-existing hypertension (aOR 1.54, 95% CI 1.07-2.21).[44]

Dinham and colleagues[42] conducted a 12-year retrospective cohort in Australia comprising 982 women pregnant with twins, 86 of whom were diagnosed with GDM. They conducted their analysis on two different time periods, as the screening criteria for GDM in their population changed. At the Royal Hospital for Women, a clinic for twin pregnancies was developed in 2009. After that time, it was recommended that all women with a twin pregnancy have screening for GDM twice during pregnancy, with a 75 g

OGTT at 14-16 weeks' gestation and again at 26-28 weeks' gestation. Prior to that time, women pregnant with twins were screened the same as women pregnant with singletons. These new criteria increased the rates of GDM from 4.4% to 14.7%. Therefore, epoch 1 (January 2002-December 2010) had only 25 women pregnant with twins having GDM, and epoch 2 (January 2010-December 2013) had 61. Overall, hypertensive disorders including gestational hypertension or pre-eclampsia were found in a significantly higher percentage of mothers with GDM (19.8% vs. 11.6%, p= .0003). This was fairly consistent between the two time periods.[42]

In a long-term retrospective study comparing pregnant women carrying twins with GDM to those without GDM in Israel, Okby et al.[21] included 4428 twin pregnancies, with 341 affected by GDM in their cohort. Unadjusted analysis showed that a higher percentage of women with GDM had mild pre-eclampsia (OR 2.2, 95% CI 1.54-3.15), and more women with GDM had severe pre-eclampsia, although this was not statistically significant (OR 1.4, 95% CI 0.84-2.38).[21] The authors did not, however, adjust for any potential confounders, as this was not the main focus of their study.

In a very large retrospective cohort of 16,562 women with GDM, 2137 with pre-existing diabetes and 258,857 women with no diabetes, Foeller et al.[46] found that gestational hypertension and pre-eclampsia were twice as likely (15.9% vs. 8.5%, p <.0001) in women with GDM compared to women with no GDM or pre-existing diabetes. This outcome, however, was reported as a maternal characteristic, and was not assessed as an outcome. In the 2011-2015 retrospective cohort, Ooi et al.[52] compared twin pregnancies with GDM to twin pregnancies without GDM and found that the risk of hypertension was higher in women with GDM (OR 2.45, 95% CI 1.13, 5.23). In 2016-

2017, Sheehan and colleagues[53] also examined GDM in both single and twin pregnancies, with a small cohort comprised of only 233 twin pregnancies, 39 of which had a diagnosis of GDM. Hypertensive disorders of pregnancy were examined as a secondary outcome. From the frequencies reported by the authors (GDM, 10.3%; without GDM, 10.3%), the OR showed no association (OR 0.99, 95% CI 0.28-2.94). The retrospective cohort by Hiersch et al.[54] in Ontario, Canada from 2012-2016 found that 11.7% of twin pregnancies with GDM had hypertension, while only 8.7% of twin pregnancies without GDM had hypertension (aRR 1.41, 95% CI 1.00-1.98).

2.2.3 Mode of Delivery

When examining the pregnancy characteristics of their study population, Simões et al.[20] found that the percentage of Caesarean section deliveries was not significantly higher in women with GDM and twin pregnancy versus those without (72.4% compared to 68.6%).[15]

González González[31] examined the mode of delivery more closely in their study and found no significant differences between women pregnant with twins with GDM as compared to those without, and also did not find significant differences in the reasons for Caesarean section to be performed (elective versus emergency). They adjusted for maternal age, maternal pre-pregnancy BMI, nulliparity, pre-existing hypertension, obstetric complications and other medical complications. In this adjustment, GDM was not found to impact the mode of delivery (OR 0.92, 95% CI 0.62-1.37).[31] It is not clear what obstetric and other medical complications were included in this adjustment, as these variables could potentially be mediators and not confounders, and therefore, the possibility of over adjustment is present.

Okby et al.[21] found that although twin pregnancies with GDM had higher odds of Caesarean delivery (OR 1.50, 95% CI 1.33-1.81), when examining factors associated with Caesarean delivery including age, fertility treatment and hypertensive disorders, GDM was not found to be an independent risk factor (aOR 1.17, 95% CI 0.92-1.49).

In the study conducted on 107 glucose intolerant women and 509 women with no glucose intolerance by Poulain et al.,[49] Caesarean section rate was one of the main outcomes assessed in relation to GDM after adjustment for maternal age and BMI using a multivariable analysis. They concluded that in well-controlled GDM in women pregnant with twins, the odds of Caesarean section were lower in the GDM group (aOR 0.67, 95% CI 0.46-0.98) than in women pregnant with twins but not affected by GDM.[49] However, in this study, they defined GDM as a combined group of those with two OGTT screening values out of range and those with mild gestational hyperglycemia (only having one screening value out of range). When they re-ran the analysis with only the mothers with GDM defined as two screening values out of range, they found a similar result (aOR 0.74, 95% CI 0.49-1.11).

Lai and colleagues[44] found that in twin pregnancies, GDM was associated with a higher rate of Caesarean section deliveries as compared to those uncomplicated by GDM, even when they adjusted for confounding variables (aOR 1.57, 95% CI 1.25-1.96). Moses et al.,[47] also out of Australia, found that women with GDM were more likely to have an elective Caesarean section, but found no difference in emergency Caesarean section rates. This study, however, was conducted on only 28 women with GDM and 29 without. Similarly, Hiersch and colleagues[54] found in twin pregnancies, Caesarean section rates were higher in pregnancies complicated by GDM. In women with GDM pregnant with

twins, 70.2% delivered via Caesarean section versus 59.3% of twin pregnancies without GDM (aRR 1.11, 95% CI 1.02-1.21).[54]

A number of studies reported only the percent of women who delivered by Caesarean section and did not adjust for potential confounders. Foeller et al.[46] reported the frequency of delivery by Caesarean section was significantly different between mothers with GDM and those without GDM who were pregnant with twins, but the difference in frequency was small (80.3% versus 74.6%, p <.0001). Dinham et al.[42] also found a small difference in Caesarean section rates in a much smaller cohort (66.6% in women with no GDM, and 73.3% in women with GDM, p=0.2). In an Australian cohort study by Ooi et al.,[52] Caesarean section was recorded for 47.9% of non-GDM twins and 54.6% of GDM twins. In Australia, Sheehan et al.[53] found that both twins and GDM independently were strong predictors of Caesarean section, but within twins, GDM did not have a strong impact. Among women pregnant with twins, 73.7% of those without GDM delivered by Caesarean section, while a similar amount of those with GDM also had a Caesarean section (76.9%).[53]

2.2.4 Preterm Delivery

In the retrospective cohort in Israel examining 4428 twin pregnancies, 341 with GDM, Okby et al. [21] did not find a difference in the mean gestational age at delivery between the groups (35.6 weeks in the GDM group and 35.4 in the group without, p=0.29).[21] They also found no difference in the percentage of deliveries before 34 weeks in their study population (16.6% with GDM and 18.1% without, p=0.49). Of babies born to mothers with GDM, 56.3% were born at 35-37 weeks' gestation, with 58.1% of those born to mothers without GDM being born within this gestational age range.[21]

In Canada, Lai et al.[44] found GDM was associated with increased risk of preterm delivery in singletons for both induced labour < 37 weeks (aOR 2.00, 95% CI 1.81-2.20) and spontaneous labour < 37 weeks' gestation (aOR 1.71, 95% CI 1.61-1.81). The same finding was not true of twin pregnancies with preterm labour induced < 37 weeks (aOR 1.18, 95% CI 0.82-1.71) and spontaneous labour (aOR 1.14, 95% CI 0.92-1.42) when adjusted for maternal age, First Nations status, parity and pre-existing hypertension.[44]

Foeller and colleagues[46] found that births < 37 weeks in twins were similar between women with GDM as compared to those without (aOR 1.01, 95% CI 0.97-1.04) but fewer babies with GDM were born before 32 weeks (aOR 0.72, 95% CI 0.68-0.76) in the analysis adjusted for maternal characteristics, prenatal care adequacy and history of preterm delivery.

González González et al.[31] found that rates of prematurity (birth < 37 weeks) were high in both groups (62.6% of women with GDM and 50.1% of women with no GDM, OR 1.63, 95% CI 1.14-2.34). However, after adjusting for potential confounders, the presence of GDM was not associated with preterm delivery (aOR 1.08, 95% CI 0.72-1.61).[31] Similarly, in a very small study, Bhuling et al.[23] found no significant difference in preterm premature rupture of membranes between women with and women without GDM. On the other hand, a very large cohort study conducted in the United States by Luo et al.[27] with 14,298,367 singleton pregnancies and 422,068 twin pregnancies, found a small increased risk of preterm birth in women with diabetes and twin pregnancy, compared to twins with normoglycemia, controlling for several maternal and neonatal characteristics (aRR 1.27, 95% CI 1.22-1.31) but they were not able to differentiate between GDM and pre-existing diabetes in this population. Ooi et al.[52] also found a

similar number of preterm births in twins with and without GDM, reporting 63.6% and 59.8%, respectively, and Hiersch et al.[54] reported a weak association with 56.4% of women pregnant with twins with GDM delivering before 37 weeks' gestation and 48.6% pregnant with twins and no GDM having a preterm delivery (aRR 1.21. 95% CI 1.08-1.37).

In Australia, Dinham and colleagues[42] also conducted a retrospective cohort in a small population of women carrying twins (86 women with GDM and 982 without GDM). When they assessed prematurity of < 37 weeks' gestation, they found no difference (71.5% versus 64.6%, p= 0.08). This finding is a combined analysis of the two study epochs, where the screening and diagnostic criteria changed, as previously described.[42] In France, Poulain et al.[49] conducted a single center retrospective study of 177 twin pregnancies complicated with glucose intolerance versus 509 twin pregnancies without. They found that no difference between glucose intolerance in pregnancy compared to age and BMI matched controls in terms of birth < 37 weeks (61.6% vs 57.6%). They did however, exclude any women who gave birth < 28 weeks' gestation or who had other complications such as twin to twin transfusion syndrome or monochorionic pregnancy.[49]

In 2016, McGrath et al.[22] conducted a meta-analysis of studies investigating GDM in twin pregnancies as compared to twin pregnancies without GDM. Thirteen observational (retrospective and prospective) studies were included. Overall, they found that GDM in twin pregnancies did not impact gestational age at birth as compared to twins born to mothers who were not diagnosed as having GDM (standardized mean difference -0.11 weeks; 95% CI -0.27-0.05).[22]

2.2.5 Placental Abruption

The only study reviewed to date on the association between GDM in women pregnant with twins and placental abruption was by Okby and colleagues.[21] They found no difference between the groups, with 1.2% of GDM pregnancies and 1.5% of non-GDM pregnancies having placental abruption (aOR 0.8, 95% CI 0.41-1.6).[21]

2.2.6 Hypoglycemia

Often, babies born to mothers who have GDM are prone to low blood sugar after birth.[1] Of the studies that examined this outcome, only one found it to be associated with GDM in twin pregnancies. Dinham et al.[42] found that 11.1% of twin pregnancies with GDM had babies born with hypoglycemia, but only 1.1% of babies born to mothers without GDM had hypoglycemia after birth (p=.0001). No significant difference has been observed in other studies that examined twin pregnancies;[5,43,49,52,53,54] interestingly, Rauh-Hain[5] found a slightly higher percentage of hypoglycemia in the group with no GDM (7.6% in the GDM group, and 8.3% in the no GDM group, p=0.14). This study was designed to examine the risk of developing GDM in twin pregnancies, but also looked at some maternal and neonatal outcomes. The study included only 22 women with GDM, so this result should be interpreted with caution.[5]

2.2.7 Neonatal Intensive Care Unit (NICU) Admission

In some centers, admission to NICU is standard of care for twins. Presumably, because of this, only a small number of studies looked at NICU admission as an outcome. Of the studies, four found a significant association between GDM and admission to NICU,[23,46,51,54] and five were borderline significant.[5,44,52–54] Foeller and his colleagues[46] found that when adjusted for maternal characteristics, prenatal care, history of preterm

delivery and delivery mode, NICU admission was still significantly higher in babies born to mothers with GDM versus those without (aOR 1.22, 95% CI 1.18-1.26). Tward et al.[51] found similar results. Their study looked at four groups of mothers: those who had a negative result in the OGCT, those who had a negative result in the OGTT, those who tested positive for GDM via the International Association for Diabetes in Pregnancy Study Group guidelines, and those who tested positive for GDM via the Canadian Diabetes Association guidelines. They found that in the group that tested positive for GDM via the CDA guidelines versus the GDM negative group, NICU admission was significantly higher.[51]

Buhling et al.[23] also found a significant association between the percent of twins born to mothers without GDM and twins born to mothers with GDM that were admitted to NICU (31% vs. 100%, p=0.028). Given the very small sample size of this study however, results should be interpreted with caution as only three twin GDM births were included. Hiersch et al.[54] found a small difference between groups, with 53.8% of GDM twins being admitted and 46.3% of non-GDM twins being admitted (aRR 1.12, 95% CI 1.00-1.23).

When comparing GDM vs. non-GDM twin pregnancies, Lai et al.[44] found a very small percent difference in NICU admission (49.9% vs. 49.2%, respectively). The adjusted analysis echoed this finding (aOR 1.04, 95% CI 0.85-1.26)[44]. Sheehan et al.[53] also found that 54.5% of twins were admitted to the NICU, while 61.5% of twins born to mothers with GDM were admitted. It is unclear if this is significant. Ooi et al.[52] reported 53.6% of non-GDM twins were admitted to NICU, while 74.2% with GDM were. Rauh-Hain et al.[5] found that 37% of babies born to mothers without GDM were admitted to

NICU, whereas 52% of those born to mothers with GDM were admitted (p=0.05), although this was not a primary outcome of the study.

2.2.8 Respiratory Distress

In the study by Simões et al.,[20] respiratory distress was diagnosed by clinical signs and symptoms. They found a significant increase in the prevalence of respiratory distress at birth in babies born to mothers with GDM. In this group, 14.3% of babies had respiratory distress, where 7% of babies in the non-GDM group showed clinical signs of distress leading to a diagnosis (OR 2.20, 95% CI 1.3-3.7).[20] An adjusted odds ratio was not reported as confounding was stated to be considered by matching the exposed group to the unexposed group on gestational age and chorionicity.

In their retrospective cohort, Foeller and his colleagues[46] found that in the twin GDM neonates, assisted ventilation lasting less than one hour and surfactant administration were lower than in the non-GDM group (aOR 0.83, 95% CI 0.79-0.87) but prolonged ventilation lasting more than 6 hours was greater (aOR 1.30, 95% CI 1.21-1.39).

Cho et al.[43] in Korea conducted a 4-year retrospective analysis on twin pregnancies in which 33 women were diagnosed with GDM, and matched in a 1:2 ratio to 66 twin pregnancies without GDM. The criteria used to match the two groups included chorionicity, maternal age, parity, BMI and gestational age at delivery. They diagnosed respiratory distress as 'requiring mechanical ventilation' and found that while 22.7% of babies born to mothers with GDM required a ventilator, only 15.2% of babies born to mothers without GDM did, a non-significant difference.[43] With similar findings to Cho et al., Hiersch et al.[54] found that 20.0% of babies born to mothers with GDM had some

form of respiratory morbidity, while 18.9% of non-GDM twins did (aRR 0.93, 95% CI 0.75-1.16). Dinham and colleagues[42] found that 19.8% of babies born to mothers with GDM had respiratory distress, but only 15.5% of babies born to mothers without GDM did, a non-significant difference.

2.2.9 Low Apgar Score

In a small study of 28 GDM women and 29 glucose tolerant women carrying twins conducted by Moses et al.[47] in Australia, a significant difference in the mean 5 minute Apgar was determined to exist. The mean Apgar score for babies in the glucose tolerant group was lower (mean 8.9, SD 0.7) than the group of babies born to GDM women (mean 9.2, SD 0.7) (p <.05).[47]

Simões et al.[20] and Ooi et al.[52] found no significant difference in the Apgar score of the GDM groups versus the non-GDM groups. Luo et al.[27] found that babies born to mothers with diabetes had a 26% reduced risk of an Apgar score less than 4 at 5 minutes in an adjusted analysis (aRR 0.74, 95% CI 0.58-0.96). Foeller et al.[46] also found fewer neonates in the GDM group had 5 minute Apgar scores less than 4 (aOR 0.8, 95% CI 0.68-0.94). Poulain and colleagues[49] defined low Apgar as less than 7 at 5 minutes and found that 0.8% of babies born to mothers with GDM had a low Apgar score, while 0.6% of babies born to mothers without GDM had an Apgar score less than 7 at 5 minutes, a difference that was not significant. When Tward and colleagues[51] in Canada assessed the difference in Apgar scores less than 7 at 5 minutes across their four study groups (those who had a negative result in the glucose challenge test, those who had a negative result in the oral glucose tolerance test, those who tested positive for GDM via the International

Association for Diabetes in Pregnancy Study Group guidelines and those who tested positive for GDM via the CDA guidelines), they found no significant differences.

2.2.10 Perinatal Death

Simões et al.[20] found one case of fetal death in the GDM group and three fetal deaths in the group without GDM, as well as three early neonatal deaths (defined as death less than 7 days post-birth) in the GDM group, and one in the non-GDM group after very preterm birth, but these were not significant differences. Dinham and colleagues[42] also found no significant difference when comparing the overall rates of stillbirth and neonatal death between the groups, although interestingly, the percentage was higher in the group with mothers who had a diagnosis of GDM. Foeller et al.[46] examined neonatal death within 27 days of birth and adjusted for maternal characteristics (prenatal care, history of preterm delivery and also delivery mode). Interestingly, twin gestations born to mothers with GDM showed a trend toward lower risk of neonatal death (aOR 0.84, 95% CI 0.68-1.02). Likewise, Luo and colleagues[27] in an adjusted analysis found a lower incidence of neonatal death in babies born to mothers with diabetes than in those without (aRR 0.76, 95% CI 0.63-0.92), but they did not differentiate between pre-existing diabetes and GDM.

2.2.11 Small for Gestational Age and Large for Gestational Age

In an observational, retrospective study with 106 twin pregnancies affected with GDM and 166 twin pregnancies without, Guillén et al.[34] found that GDM did not significantly influence the rate of any weight outcomes. They defined large for gestational age as either twin being > 90th percentile, macrosomia as either twin being > 95th percentile, small for gestational age as either twin being < 10th percentile, and

severely small for gestational age as either twin being $< 5^{th}$ percentile for gestational age.[34] They adjusted for possible confounders of maternal age, pre-pregnancy BMI, hypertension, pre-eclampsia, smoking, chorionicity, mode of conception, malformations, delivery < 34 weeks' gestation and parity. While the mean weight was higher in babies born to mothers with GDM, when they adjusted for gestational age, no significant difference was observed.[34]Also in a small retrospective cohort, Ooi et al.[52] found similar results with 25.3% of non-GDM twins being $< 10^{th}$ percentile and 23.3% of GDM twins being $< 10^{th}$ percentile, a result that was not a significant difference. They also found no difference in LGA babies with very small percentages of twins in both groups measuring $> 90^{th}$ percentile (2.0% of non-GDM twins and 0.5% of GDM twins).[52]

Lai et al.[44] compared twin pregnancies between women with GDM and those without and found less SGA babies born to mothers with GDM, although this was not found to be significant. Hiersch et al.[54] echoed this result. There were, however, a higher number of LGA babies born to mothers with GDM in the studies by Lai et al.[44] and Hiersch et al.,[54] even in the adjusted analysis (aOR 1.63, 95% CI 1.28-2.08, and aOR 2.53, 95% CI 1.55-4.23, respectively).

Tward el al.[51] compared outcomes across four groups of women: those who had a negative result in the OGCT, those who had a negative result in the OGTT, those who tested positive for GDM via the International Association for Diabetes in Pregnancy Study Group guidelines, and those who tested positive for GDM via the Canadian Diabetes Association guidelines. They found that the group of babies born to mothers diagnosed with GDM via the CDA criteria had a significantly lower mean weight (223 g, SD 650 g, p <.001), but were also born at a significantly earlier gestational age than

babies in the other three groups.[51] When birthweight for gestational age percentiles were examined, the association between higher weight percentiles and the degree of glucose intolerance was significant. That is to say, women who had GDM diagnosed by CDA criteria, had a larger percentage of babies born > 80th percentile, even when adjusted for potential confounding variables of maternal age, chorionicity and chronic hypertension.[51]

Poulain et al.[49] found a similar result in that the overall mean weight of babies in the glucose intolerant group was slightly higher; however, in conducting a multivariable analysis for macrosomia, no relationship between glucose intolerance and birthweight was observed (OR 1.56, 95% CI 0.71-3.44).

González González et al.[31] found that the percentage of newborns with birthweight for gestational age greater than the 90th percentile was not significantly higher in the GDM group than in the non-GDM group (p=0.15), but the percent of newborns with birthweight for gestational age greater than the 95th percentile was (p=0.002). Fewer small for gestational age babies (< 10th percentile) were in the group with GDM than in the group without GDM, but after they adjusted for inter-twin correlation and potential confounders such as maternal BMI, the presence of hypertension and other complications, the presence of GDM did not significantly influence birthweight (aOR 0.66, 95% CI 0.42-1.05).[31]

In their 12-year retrospective cohort, Dinaham et al.[42] defined large for gestational age as > 90th percentile, and small for gestational age as < 10th percentile using twin bodyweight centile charts. They found no significant difference in the rates of either LGA (p=0.50) or SGA (p=0.50).[42] Luo et al.[27] also defined large for gestational age and small for gestational age as > 90th and < 10th respectively, and in an adjusted analysis, found

that when compared to women with no diabetes (pre-existing or gestational), babies born to mothers with diabetes had a lower risk of being small for gestational age (aOR 0.81, 95% CI 0.78-0.84) and a higher risk of being large for gestational age (aOR 1.38, 95% CI 1.10-1.73).[27] These findings were echoed by Foeller et al.[46] who found similar adjusted odds ratios for LGA and SGA using twin growth curve charts. Simões et al.[20] found no significant differences in the rates of LGA and SGA between the GDM group and non-GDM group.

In the meta-analysis of 13 observational studies conducted by McGrath et al.,[22] the analysis found a lower mean birthweight between twin neonates born to mothers with GDM versus those without (standardized mean difference -1.49; 95% CI -2.96- -0.67) but no difference in the incidence of large or small gestational age neonates. A high rate of heterogeneity between the studies suggests that these results should be interpreted with caution.

2.2.12 Birthweight Discordance

In a study by Klein and colleagues,[7] the main outcome was birthweight discrepancy between twins. They examined birthweight discrepancy in grams in pairs of twins of 43 mothers with and 157 mothers without GDM. The influence of maternal age, BMI, parity, smoking, chorionicity, gestational age at delivery and diagnosis of GDM on weight discrepancy was evaluated.[7] In the multivariate model, only diagnosis of GDM was negatively associated with weight discrepancy (coefficient -0.16, p=0.02).[7] In unadjusted comparisons of rates, Simões et al.[20] found no difference in birthweight discordance of greater than 25%, and Guillén et al.[34] found no difference in the percentage of discordance greater than 20%.

2.2.13 Congenital Anomalies

When Foeller and colleagues[46] conducted a logistic regression analysis controlling for maternal characteristics, prenatal care, history of preterm delivery an delivery mode, they found that a significantly higher odds of congenital anomalies in the twins born to mothers affected with GDM as compared to twins born to mothers without (aOR 1.41, 95% CI 1.09-1.82). In their large cohort study, Luo et al.[27] found a slightly increased risk of congenital anomalies in the twins born to mothers with GDM as compared to twins born to unaffected mothers (RR 1.55, 95% CI 1.43-1.67).

Simões et al.[20] examined major malformations in 105 GDM exposed participants and 315 matched comparison group participants. They found that in the group of neonates born to mothers with GDM and twin pregnancy, the rate of major malformations was higher than the group from mothers having a twin pregnancy unaffected by GDM (3.3% vs. 2.4%), but not significantly so. The groups were matched on gestational age, chorionicity and year of birth. Cho et al.[43] found similar results when they compared rates of congenital anomalies between twins born to 33 women with GDM matched to 66 women without GDM. In the group with GDM, the rate was higher, but not significantly so (4.5% vs. 2.3%). Conversely, Dinham and colleagues[42] and Ooi and colleagues[52] found a slightly higher rate of congenital anomalies in the group of twin neonates born to mothers without GDM compared to twins born to mothers with GDM, but it was not significantly different in either study.

2.2.14 Summary and Key Gaps in Knowledge

The results of existing studies on GDM and twin pregnancies are quite heterogeneous, perhaps due to different designs and methods, as well as varying degrees

of confounder adjustment. Few existing studies have examined placental abruption, hypoglycemia and birthweight discordance in relation to GDM among twin pregnancies. Further, we did not find any studies that examined both neonatal length of stay and maternal length of stay in this population but doing so would add to the existing knowledge and provide information that will have clinical implications. Before we know if tailored diagnosis and treatment guidelines are required for multiple gestation pregnancies affected by GDM, we first need more information.[46]

Table 2.1   Summary of main studies examining the association between twin pregnancy and gestational diabetes

Lead Author	Study type	Years and location	Subjects	Outcomes of interest	Results of interest
Buhling[23]	Prospective cohort	1994-1997 Germany	89 women pregnant with twins, 3 with GDM, 86 without. Matched 1:2 with singleton pregnancy on age, BMI, parity, gestational age, ethnicity.	To determine incidence of hypertension and GDM in twin pregnancies vs. singletons and assess GDM outcomes. Sub analyzed twins with and without GDM.	Pts with twins did not have higher rate of GDM. Higher rate of NICU admission in twins with GDM (100% vs. 31%, p=0.028). Frequencies and p-values reported.
Cho[43]	Retrospective cohort	1998-2002 Korea	33 twin pregnancies with GDM matched 1:2 with 66 twin pregnancies without GDM matched on maternal age, gestational age, parity, BMI, chorionicity	Respiratory distress, hyperbilirubinemia, hypoglycemia, Apgar, congenital anomalies.	No statistical differences found in outcomes between the two groups. Only frequencies and p-values reported.
Rauh-Hain[5]	Retrospective cohort	1998-2006 USA	22 women with GDM and twin pregnancy, 511 with no GDM but twin pregnancy, also compared to singletons.	Primary exposure was twin versus singleton pregnancy with the outcome of developing GDM. Also did examine NICU admission, respiratory distress, and neonatal hypoglycemia in twin pregnancies with and without GDM.	Twin pregnancy was associated with a two-fold risk of developing GDM (OR 2.2, 95% CI 1.4-3.6). Higher rate of NICU admission (37% vs. 50%, p 0.05) and higher rates of respiratory distress (7% vs. 27%, p 0.001)
Klein[7]	Prospective cohort	2007-2008 Austria	200 twin pregnancies- 43 with GDM and 157 without *only included women on insulin	Twin weight discrepancy, twin to twin transfusion syndrome, pre-eclampsia	Mean weight discrepancy was 285g. Univariate analysis showed GDM, chorionicity and gest age at delivery were significantly associated with weight discrepancy. In multivariate model, only GDM was associated. Means and SDs reported.
Simões[20]	Prospective cohort	1999-2010 Portugal	105 GDM twin pregnancies and 315 controls (twin pregnancies with no GDM), matched on gestational age, chorionicity and year of birth.	Birthweight, centile, Apgar, respiratory distress	Pregravid obesity seems to predispose women to GDM during twin pregnancy (OR 3.5, 95% CI 1.7-7.0) GDM group had more respiratory distress (OR 2.2, 95% CI 1.3-3.7).
González González[31]	Retrospective cohort	2004-2008 Spain	534 women, 257 pregnant with twins and GDM, 277 with twins and no GDM, unclear matching criteria.	Hypertensive complications, preterm delivery, mode of delivery, LGA/SGA/macrosomia, Apgar, NICU admission, perinatal mortality	Rate of hypertensive complications was significantly higher with GDM. The regression showed that only BMI had significant predictive value on the appearance of hypertension, while the presence of GDM lost its significance when adjusting by this parameter. When adjusting for BMI, obstetric complications was higher with GDM. Prematurity was high in both groups, higher with GDM but not significant when adjusted for confounders. Risk of SGA was reduced by nearly half in GDM group.

Lead Author	Study type	Years and location	Subjects	Outcomes of interest	Results of interest
Guillén[34]	Retrospective cohort	1999-2011 Spain	106 women with GDM and twins and 166 with no GDM, matched on maternal age and year of delivery	Neonatal bodyweight, macrosomia, weight discrepancy	Women with GDM delivered at greater gestational age even when adjusted for chorionicity. C-section rate similar in both groups, no difference in LGA/SGA/macrosomia, mean birthweight sig higher in newborns bon to moms with GDM, but when adjusted for gest age, there was no diff between the groups. Frequencies and p-values reported.
Okby[21]	Retrospective cohort	1988-2010 Israel	341 with GDM and twin pregnancy, 4087 with no GDM but twin pregnancy	Preterm delivery, preeclampsia, anemia, amniotic fluid abnormalities, placental abruption, intrauterine growth restriction, induction of labour, vacuum extraction, C-section, post-partum hemorrhage, blood transfusion, wound infection	GDM not independent risk factor for c-section when controlled for other variables Rate of low Apgar and perinatal mortality were actually lower in comparison group.
Lai[44]	Retrospective cohort	2005-2011 Canada	327,198 singleton births and 5552 twin pregnancies, 405 with GDM *also included pre-diabetes, but analyzed separately.	Prevalence of pre-diabetes and GDM were main outcomes, but also assessed preeclampsia, still birth, C-section, preterm delivery, shoulder dystocia, macrosomia, SGA/LGA	GDM in twins was associated with increased risk of pre-eclampsia (aOR 1.54) and c-section (aOR 1.57), and LGA (aOR 1.63)
Poulain[49]	Retrospective cohort	1997-2010 France	177 women with GDM and twin pregnancy and 509 with no GDM but twin pregnancy. Matched on age and BMI *also included mild gestational hyperglycemia	Two main outcomes were rate of c-section and rate of LGA. Secondary outcomes included: preterm labour, gestational hypertension, preeclampsia, HELLP, onset of labour, mode of delivery, post-partum hemorrhage, prematurity, birthweight, Apgar, respiratory distress, neonatal hypoglycemia, hyperbilirubinemia, NICU admission, congenital anomalies.	Complications of pregnancy and mode of delivery were similar between the two groups. The only risk for macrosomia was history of macrosomia in a previous pregnancy (OR 5.9, 95% CI 1.8-19.2)
Tward[51]	Retrospective cohort	2003-2014 Canada	GCT negative group-1021 OGTT negative group-184 GDM-IADPSG- 99 GDM-CDA- 89 Analyzed sep.	Fetal growth was primary outcome, secondary outcomes included: NICU admission, Apgar, bodyweight	A continuous relationship was found between the degree of glucose intolerance and fetal growth.
Foeller[46]	Retrospective cohort	2006-2009 USA	277,556 neonates were included. 16,562 twin pregnancies with GDM, 2137 with pre-diabetes, 258,857 twin pregnancies with no diabetes.	Preterm delivery, LGA/SGA, congenital abnormalities, Apgar, neonatal death, ventilation use, NICU admission, prematurity, pregnancy weight gain, mode of delivery, hypertension	GDM significantly reduced SGA and very SGA compared to controls (AOR .84 (.81-.87)) and (AOR .85 (.81-.89)). GDM exerted a positive impact on Apgar scores, delivery prior to 32 weeks and neonatal death. GDM did however, increase the risk of NICU admission and prolonged ventilation >6 hours.

Lead Author	Study type	Years and location	Subjects	Outcomes of interest	Results of interest
Dinham[42]	Retrospective cohort	2002-2013 Australia	86 women with GDM and twin pregnancy, 896 women with twin pregnancy but no GDM, 2 epochs due to screening protocol change.	Examined incidence and risk of GDM, as well as composite adverse pregnancy outcome (preterm birth, weight in 10th or 90th centile, birth trauma, death, pre-eclampsia, gestational hypertension) bodyweight, respiratory distress, neonatal hypoglycemia, hypertensive disorders, mode of birth, induction, prematurity (<37 weeks), congenital anomaly, perinatal death or neonatal death	Women with a monochorionic pregnancy with 4x more likely to have adverse composite pregnancy outcome (OR 3.8, 95% CI 2.8-5.3). Women with GDM showed a trend toward more adverse pregnancy outcomes (79.9% vs 73.1% P.06). after adjusting for maternal and pregnancy risk factors, women with GDM were almost 1.6x more likely to have adverse pregnancy outcomes (aOR 1.8, 95% CI 1.02-2.47)
Moses[47]	Retrospective cohort	1990-1999 New Zealand	28 women pregnant with twins and GDM and 29 women pregnant with twins and no GDM	Gestational age at delivery, mode of delivery, birthweight and Apgar	No significant differences in outcomes except for a higher rate of elective c-section. Frequencies and p-values reported.
Luo[27]	Retrospective cohort	1998-2001 USA	14,876 births with GDM and 407,192 births without GDM (from twin pregnancies) also compared to singletons but separately.	Primary outcomes were macrosomia (>90th percentile), congenital anomalies, Apgar, neonatal death	GDM was associated with a similar increased risk in twins and singletons, as was macrosomia, but reduced rates of Apgar.
Ooi[52]	Retrospective cohort	2011-2015 Australia	410 twin births, 99 with GDM, 2639 singletons with GDM	Comparted twins with and without GDM, also compared to singletons. Premature births, mode of delivery, hypertension, Apgar, LGA, SGA, NICU, anomalies, hypoglycemia	Higher NICU admit, higher premature births, more hypoglycemia
Sheehan[53]	Retrospective cohort	2016-2017 Australia	194 twins, 39 with GDM, 11915 singletons, 1379 with GDM	Comparted twins with and without GDM, also compared to singletons. LGA, mode of delivery, respiratory distress, NICU, hypertension, preterm	Twin pregnancies with GDM had higher adverse outcomes in all except macrosomia.
Hiersch[54]	Retrospective cohort	2012-2016 Canada	3575 twins, 326 GDM, 250,211 singles, 16,731 GDM.	Compared twins with and without GDM, also compared to singletons. hypertension, mode of delivery, preterm delivery	GDM was associated with LGA, even in twins

Chapter 3 OBJECTIVES

The current study investigated the maternal and fetal outcomes of GDM in twin pregnancies as compared to twin pregnancies without GDM in Nova Scotia between the years of 1988 and 2013. Specifically, the two main objectives were:

1. In women pregnant with twins, to examine the association between GDM and the maternal outcomes of hypertensive disorders of pregnancy, placental abruption, preterm delivery, mode of delivery, and antepartum length of stay.

2. In twin neonates, to examine the association between GDM and the neonatal outcomes of fetal and perinatal death, hypoglycemia, birthweight discordance, small for gestational age, large for gestational age, neonatal intensive care admission, neonatal length of stay, respiratory distress, congenital anomalies, and low Apgar score.

Chapter 4 METHODOLOGY

4.1 Overview of Study Design and Ethics

Using data from the Nova Scotia Atlee Perinatal Database between the years of 1988-2013, a retrospective cohort of Nova Scotian residents who delivered twin neonates was formed. The project received ethics approval from the Data Access Committee of the Reproductive Care Program (RCP) and approval from the Isaac Walton Killam (IWK) Health Centre Research Ethics Board.

4.2 Data Sources

The NSAPD, housed at the IWK Health Centre in Halifax, Nova Scotia, is a population-based database with information compiled from prenatal records and hospital charts using standardized collection forms by trained personnel. It was used to build a cohort of Nova Scotia women who delivered twins with GDM, as well as those without, from 1988 to 2013. The comprehensive, quality database is administered by the Reproductive Care Program of Nova Scotia. The database includes information on live and stillbirths of > 500 g or > 20 weeks' gestation in Nova Scotia. In twin pregnancy, if a fetus is lost at < 20 weeks, but the co-twin is born at 20 weeks or more, the information on both neonates is retained. The database also includes Nova Scotia mothers who gave birth in New Brunswick since 1988. Data on mothers who gave birth at home has been captured since 2009 but this is a very small percentage of births, and in Nova Scotia, homebirths are not permitted in the case of multiple gestations. In Nova Scotia, there are on average, 8000 deliveries per year. The NSAPD has a very low percentage of missing values for most variables. Labour, delivery and infant variables have almost no missing

values. The personnel who work to manage the NSAPD ensure continuous development and maintenance of data collection and reporting systems, linkages, and assurance of data quality and security, as well as validation studies to maintain and ensure reliability of the data. For each individual in the NSAPD, demographic variables, information on tests and procedures undertaken, delivery data, maternal and newborn diagnoses, and reports of morbidity and mortality are available. The data in the NSAPD allowed calculation of the prevalence of twin pregnancies and prevalence of GDM in Nova Scotia. As well, it provided information on maternal and neonatal variables related to the two objectives previously stated, and variables considered as possible confounders.

4.3 Inclusion/Exclusion Criteria

The NSAPD includes information on all births to Nova Scotia residents as well as those who deliver in New Brunswick. All women who were residents of Nova Scotia were included even if they gave birth in New Brunswick. Only twin births in which one or both neonates were born > 20 weeks' gestation between January 1, 1988 and December 31, 2013 were included. Births were excluded if the mother had a pre-existing diagnosis of diabetes as this carries a higher risk of adverse outcomes. Monochorionic twin types were excluded as they have a higher rate of complications and make up a very small percentage of twin births. To maintain more homogeneity in the cohort, only dichorionic twin types were included. Conjoined twins were also excluded.

4.4 Variables

4.4.1 Independent Variable: Gestational Diabetes

The change in screening and diagnosis of GDM was fairly subtle from the mid-1980's to 2013. Therefore, the rates in Nova Scotia increased as the prevalence of GDM

has been increasing worldwide. Upon adoption of the 2013 guidelines, the rate of

diagnosis of GDM has risen considerably, and hence the cut-off date of 2013 for this

study. Just as the screening and diagnosis of GDM is inconsistent around the world, the

classification has also been controversial and has changed over time. Until approximately

2003, coding in the NSAPD used the White Classification of diabetes in pregnancy. This

system was developed in 1965 by Priscilla White and classified diabetes based on age at

diagnosis, complications, and treatment. Gestational diabetes was Class A, which was

further sub-divided into treated with diet and lifestyle and treated with medications and/or

insulin. More commonly, diabetes is categorized into four types based on etiology: Type

1, Type 2, GDM and 'other'. Type 1 diabetes generally refers to total beta-cell

destruction resulting in total deficiency of insulin, Type 2 is predominantly due to insulin

resistance, gestational is first diagnosed in pregnancy, and 'other' refers to diabetes

caused by medical disorders or drug use.[1] The International Classification of Diseases

(ICD) is the international standard for reporting of diseases and health conditions.[55] The

ICD codes for diabetes are derived from the common categorizations. After 2003, GDM

was coded in the NSAPD using the ICD codes, as well as a NSAPD specific code.

Although the codes have changed overtime, GDM has always been captured and,

therefore, did not affect the variable. The mother's Prenatal Record is the usual source for

a code of GDM in the NSAPD. Exact laboratory values are not recorded, but a diagnosis

of GDM is recorded if present. If it is not captured on the Prenatal Record, a diagnosis of

GDM is recorded at the time of delivery on hospital forms of the mother and would then

be entered into the NSAPD.

4.4.2 Dependent Variables: Maternal

The maternal outcome variables of interest are described below.

Hypertensive disorders of pregnancy for this study included a diagnosis of pregnancy-induced hypertension with or without significant proteinuria. When hypertensive disorders were being examined, women with chronic (pre-existing) hypertension were excluded.

Placental abruption was defined as any partial and complete separation of the placenta. Due to low numbers, this was not able to be examined.

Preterm delivery was defined as birth earlier than 37 completed weeks' gestation (less than 259 days but >20 weeks) and was further categorized as obstetrically indicated (including induced or surgically delivered prior to the onset of labour for medical or obstetrical conditions placing the mother or fetus at risk) or spontaneous (including spontaneous preterm labour).

Mode of delivery was obtained for each twin. Any woman who delivered via Caesarean section for one or both twins was defined as Caesarean section. It was further categorized as Caesarean section in labour or Caesarean section after the onset of labour.

Antepartum length of stay was obtained from the NSAPD as the difference between the admission date/time and date/time of delivery. This difference was then categorized as greater or less than 48 hours.

4.4.3 Dependent Variables: Neonatal

The neonatal outcome variables of interest are described below.

Fetal and perinatal death included stillbirth, neonates born unresponsive of greater than 500 g or 20 weeks' gestation, and neonates who died less than 28 days after birth. Due to low numbers, this was not able to be examined.

Hypoglycemia post-birth in the neonate was defined as a blood sugar value of $<$ 1.67mmol/L.

Birthweight discordance was defined as a greater than 25% difference in birthweight between twins.

Large for gestational age was derived from infant birthweight obtained from the NSAPD. The database provides the birthweight as a continuous variable in grams. Neonates with a birthweight $> 90^{th}$ percentile for gestational age and sex (based on Canadian singleton growth reference curves as they currently provide the best predictors of adverse outcomes in twins, and are thus recommended by obstetrical associations as the preferred method for evaluating growth abnormalities in twins)[56] were defined as large for gestational age.

Small for gestational age was derived from infant birthweight obtained from the NSAPD and was defined as neonates with a birthweight $< 10^{th}$ percentile for gestational age and sex (based on singleton growth curves).[56]

Neonatal Intensive Care Unit admission was defined as admission to NICU lasting longer than 24 hours.

Respiratory Distress Syndrome was defined as any form of distress including mild, moderate, or severe, or transient tachypnea of the newborn.

Apgar score at 5 minutes was extracted from the database as a continuous variable (a score of 0 to 10) and was dichotomized as greater than or equal to 7 or less than 7.

Congenital anomalies was defined as the presence of any major anomalies. Congenital anomalies was excluded from all other neonatal analysis.

Neonatal length of stay was obtained from birth date/time and discharge date/time and was categorized as greater than 10 days or less than and including 10 days.

4.4.4 Covariates

Characteristics of the cohort including important covariates of maternal socioeconomic status, health concerns, and pertinent medical history were obtained from the NSAPD.

Maternal age was obtained from the database as a continuous variable and categorized as < 25, 25-29, 30-34, and ≥ 35 years old.

Smoking status was categorized as no smoking during pregnancy or smoking during pregnancy (at the time of the first prenatal visit, smoking at 20 weeks' gestation, and/or smoking at the time of delivery).

Previous births (parity) was obtained from the database as a numerical value measuring the number of pregnancies excluding the present one which resulted in the delivery of an infant 500 g or more, or with a gestational age of greater than 20 weeks. This was then categorized as 0 or ≥ 1.

Marital status was dichotomized into no partner (single, separated, widowed, and divorced) or partner (married and common-law).

Neighborhood income quintile was derived from postal code linked to Canadian census data used as an approximation of income level.

Drug use was extracted from the NSAPD and dichotomized to drug abuse or no drug abuse.

4.4.5 Effect Modifiers

The following variables were extracted from the NSAPD and explored as confounders or effect modifiers to examine the possibility that they modify the relationship between GDM and the aforementioned outcomes of interest.

Pre-pregnancy weight that is recorded on the prenatal form is either self-reported pre-pregnancy weight or weight measured at the first prenatal visit. Maternal height has been recorded in the NSAPD only since 2003, and BMI could not be calculated across the entire span of this study. Therefore, pre-pregnancy weight was represented in categories using cutpoints (54.4 kg, 68.0 kg, and 76.7 kg) that have been identified from analyses of 77,297 deliveries recorded in the NSAPD between 2003 and 2016. These weight cutpoints are the ones that best discriminate between the four World Health Organizations BMI categories (< 18.5 kg/m^2, $18.5-< 25$ kg/m^2, $25-< 30$ kg/m^2, and ≥ 30 kg/m^2).

Fetal sex was obtained as presented in the NSAPD. The female sex was given a value of 0 and the male sex given 1. Infants born with an ambiguous sex were excluded.

Year of birth was obtained from the database as birth date and split into epochs as 1988-1992, 1993-1997, 1998-2002, 2003-2007, and 2008-2013.

Other maternal variables extracted from the NSAPD to fully describe the characteristics of the cohort included: history of GDM, previous delivery of a macrosomic infant (> 4080 g), previously pregnant with multiple gestations, previous spontaneous abortion, previous delivery of a stillborn baby, previous preterm delivery, and previous delivery by Caesarean section.

4.5 Statistical Analysis

4.5.1 Software

All analyses were completed using SAS statistical software 9.4 (SAS Institute Inc., Cary, NC).

4.5.2 Analysis

Initially, the characteristics of women who had GDM versus those without GDM were described using frequencies and compared using X^2 or Fisher's exact test as appropriate. Any outcome that affected fewer than 5 individuals in either women with or without GDM was not examined in association with GDM. Logistic regression was used to obtain unadjusted odds ratios of each outcome associated with having GDM compared with not having GDM, as well as 95% confidence intervals. Potential confounding variables and covariates were identified from the literature. Any factors with a p-value of <0.1 on univariate analysis were included in the final multivariable model. Logistic regression was then used to obtain the adjusted odds ratios to assess the association between GDM and maternal and neonatal outcomes. To adjust for the non-independence of twins, generalized estimating equations were used for all neonatal outcomes except for

birthweight discordance, for which the unit of analysis was the twin pair, to account for repeated observations.

In the NSAPD, the extent of missing data was nearly 0% for labour, delivery, and infant factors. Pre-pregnancy weight was missing in about 20% of the records in the NSAPD. Primary analyses were done on a complete case basis (women with missing values were excluded from the analysis). Pre-pregnancy weight, fetal sex and year of birth were explored as possible effect modifiers by including an interaction term and testing for significance.

Because a previous Caesarean section puts a mother at an increased likelihood of repeat Caesarean section regardless of other factors, a sub-analysis of women who had not had a previous Caesarean section was also carried out.

4.5.3 Sample Size and Minimally Detectable Effect Size

The size for the study was pre-determined by the number of twin births in the NSAPD. As noted, there are approximately 8000 deliveries per year in Nova Scotia. Given the study duration of 26 years (1988-2013) and using the incidence rate of multiple births of 3% and GDM of 5%, this was estimated to yield approximately 3000 multiple deliveries (approximately 6000 babies, assuming most are twins). Because the study population was limited to dichorionic twins, this twin type makes up approximately 70% of twin births and, therefore, this cohort yielded approximately 2100 twin births. Of the 2100 twin births, approximately 105 mothers were estimated to have a diagnosis of GDM. Prior to the start of the study, a sample size calculation was performed for hypertensive disorders of pregnancy with a level of significance (α) of 0.05 and a power (1-β) of 80%, as an example. The calculation was completed using OpenEpi software.[57]

Prevalence estimates for hypertensive conditions in pregnancy in the unexposed group was extracted from the literature.[20] The prevalence of hypertension in the women with no GDM was estimated at 19%. A minimal effect size (odds ratio) of 1.88 or larger was estimated to be detectable. Given the sample size available and the desired effect size, 1888 unexposed mothers and 95 exposed were estimated to be required, within the numbers of the study group. The ability to detect similar effect sizes for most variables was anticipated, except for those with very low prevalence for which small odds ratios would not be detectable.

Chapter 5 RESULTS

5.1 Description of Cohort

A total of 258,245 births were recorded in the NSAPD during the study period of

1988 to 2013. Of these births, 6738 were neonates who were twins. After removing

mothers who had pre-existing diabetes as well as babies who were of a twin type that did

not meet the eligibility criteria (monochorionic, conjoined or undetermined), and one

baby coded as a twin but who did not have co-twin data, 4748 neonates were included.

This yielded a dataset of 2374 women. The incidence of GDM was 4.6% (109 women) as

shown in Figure 5.1. The characteristics of the study population are presented in Table

5.1. Compared with women without GDM, women with GDM were older (p <0.0001),

had a higher pre-pregnancy weight (p<0.0001), had at least one previous pregnancy

(p=0.0920), and a higher proportion had a previous Caesarean section (p=0.0671).

Women with and without GDM were not different (p>0.10) in respect to smoking, drug

use, baby sex, previously given birth to a high or low weight baby, and socioeconomic

variables such as marital status, urban vs. rural dwelling, and neighbourhood income

quintile. Year of birth, maternal age, parity and pre-pregnancy weight were included in

the final logistic regression model. Although previous Caesarean section had a p-value of

<0.10, it was not included in the model as it was assessed only as a potential effect

modifier of the association between GDM and Caesarean section in the present

pregnancy.

5.2 Maternal Outcomes

Results for the association between GDM and maternal outcomes are shown in

Table 5.2. The odds of maternal outcomes were higher in women with GDM during

pregnancy than in those without, but most 95% CIs did not exclude the null (no association). A higher proportion of women with GDM had hypertension of pregnancy (aOR 1.44, 95% CI 0.88-2.38), delivered via Caesarean section (aOR 1.34, 95% CI 0.87-2.07), and had an antepartum length of stay longer than 48 hours (aOR 1.55, 95% CI 0.97-2.50). Relative to women without GDM, women with GDM did not have higher odds of a medically indicated preterm delivery (aOR 1.05, 95% CI 0.63-1.74), but had lower odds of spontaneous preterm delivery (aOR 0.51, 95% CI 0.28-0.91).

5.2.1 Maternal Outcomes by Pre-pregnancy Weight

The adjusted odds ratios for maternal outcomes stratified by pre-pregnancy weight (< 76.7 kg and ≥ 76.7 kg) are presented in Table 5.3. None of the associations between GDM and the maternal outcomes assessed were modified by pre-pregnancy weight (all p interactions >0.10). Compared to women who did not have GDM, women with GDM had elevated odds of hypertension, Caesarean section, and longer antepartum length of stay in both strata of maternal pre-pregnancy weight. The associations were not statistically significant, however, and due to low numbers, the 95% confidence intervals were wide. Among the women with a higher pre-pregnancy weight, estimated aORs were > 1.50 for the associations between GDM and hypertension of pregnancy (aOR 1.66, 95% CI 0.84-3.31), Caesarean section in labour (aOR 2.09, 95% CI 0.97-4.52), and antepartum length of stay (aOR 1.89, 95% CI 0.97-3.70).

5.2.2 Maternal Outcomes by Year of Birth

None of the associations between GDM and maternal outcomes among twin pregnancies were significantly heterogeneous by year of birth (Table 5.4). Estimated

aORs >1.50 were found in women who delivered between 2003 and 2013 for hypertension (aOR 1.66, 95% CI 0.88-3.15) and longer antepartum length of stay (aOR 2.06, 95% CI 1.11-3.82). Point estimates of < 1.00 were found among women with GDM compared to women without GDM from the first to the second epoch (1988-2002, 2003-2013) in spontaneous preterm delivery (aOR 0.68, 95% CI 0.32-1.44 vs. aOR 0.34, 95% CI 0.13-0.88).

5.2.3 *Maternal Outcomes by Fetal Sex*

The results of the association between GDM and maternal outcomes by fetal sex are presented in Table 5.5. When stratified by at least one of the twins being male versus both twins being female, women who were carrying a male fetus, an increased odds was found between GDM and hypertensive disorders of pregnancy, but not significantly so, (aOR 2.05, 95% CI 0.83-5.07 vs. aOR 1.19, 95% CI 0.66-2.14; p-value for interaction = 0.32) and a longer antepartum length of stay (aOR 2.41, 95% CI 1.03-5.66 vs. aOR 1.29, 95% CI 0.73-2.29; p-value for interaction = 0.23). Unfortunately, due to low numbers, preterm delivery could not be examined.

5.3 Neonatal Outcomes

Table 5.6 shows the results of the association between GDM and neonatal outcomes. Neonates born to mothers with GDM had a statistically significant threefold greater odds of experiencing hypoglycemia after birth (aOR 3.07, 95% CI 1.82-5.19). Point estimates > 1.00 were found for birthweight discordance (aOR 1.32, 95% CI 0.71-2.43), large for gestational age (aOR 1.19, 95% CI 0.47-2.98), small for gestational age (aOR 1.46, 95% CI 0.99-2.15), and congenital anomalies (aOR 1.20, 95% CI 0.56-2.60),

though none were significant. Compared to neonates born to mothers without GDM, those born to mothers with GDM had aOR (95%CI) of 0.70 (0.41-1.22) for respiratory distress syndrome, 0.53 (0.23-1.23) for 5-minute Apgar score and 0.87 (0.54-1.41) for a neonatal length of stay longer than 10 days.

5.3.1 Neonatal Outcomes by Pre-pregnancy Weight

The associations between GDM and neonatal outcomes among twin pregnancies by pre-pregnancy weight status are shown in Table 5.7. The association between GDM and no GDM and neonatal hypoglycemia was weaker in neonates born to mothers with a pre-pregnancy weight of < 76.7kg (aOR 1.88, 95% CI 0.86-4.10) than those born to mothers with a pre-pregnancy weight of ≥ 76.7kg (aOR 4.77, 95% CI 2.33-9.77). However, these odds ratios were not statistically different from one another (p-interaction 0.08). The odds ratios for small for gestational age were 1.52 (95% CI 0.81-2.85) in the lower pre-pregnancy weight strata and 1.22 (95% CI 0.54-2.77) in the higher weight strata. The odds of respiratory distress syndrome was < 1.00 in neonates exposed to GDM in both strata, more so in the higher pre-pregnancy weight group (aOR 0.40, 95% CI 0.12-1.33). Odds of neonatal length of stay greater than 10 days was < 1.00 in neonates in the lower weight strata (aOR 0.61, 95% CI 0.29-1.32) but > 1.00 in neonates in the higher weight strata (aOR 1.15, 95% CI 0.57-2.32). Other neonatal outcomes including birthweight discordance, large for gestational age, neonatal intensive care stay, Apgar score and congenital anomalies could not be examined due to low numbers.

5.3.2 Neonatal Outcomes by Year of Birth

The associations between GDM and neonatal outcomes were not heterogeneous by year of birth (Table 5.8). For example, neonates born to mothers with GDM in both epochs had a nearly threefold increase in the odds of having hypoglycemia after birth (aOR 2.71, 95% CI 1.00-7.35) and (aOR 3.13, 95% CI 1.69-5.81) for each epoch, respectively. Neonatal length of stay greater than 10 days had an odds ratio close to 1.0 for the earlier epoch, but a decreased odds in the later (aOR 0.71, 95% CI 0.35-1.41).

5.3.3 Neonatal Outcomes by Fetal Sex

Table 5.9 presents the results of the associations between GDM and neonatal outcomes by fetal sex. No heterogeneity by sex was observed. In both the male and female strata, odds of hypoglycemia after birth were higher in the presence of GDM than without GDM (aOR 2.50, 95% CI 1.30-2.83 and aOR 3.67, 95% CI 1.91-7.06), but this difference was not statistically significant (p interaction 0.35). There was also an increased odds of birthweight discordance between twins in the GDM group as compared to the group unaffected by GDM, more so in the twin pairs with one or more male fetuses (aOR 1.39, 95% CI 0.63-3.06).

5.4 Additional Analysis

5.4.1 Caesarean Section in Women with a Previous Caesarean Section

Because a previous Caesarean section puts a mother at an increased likelihood of subsequent Caesarean section regardless of other factors, a sub-analysis of women who had not had a previous Caesarean section was carried out. Women pregnant with twins who had GDM had an odds ratio > 1.00 of having a Caesarean section in both the crude

and adjusted analysis (OR 1.27, 95% CI 0.81-2.02 and aOR 1.21, 95% CI 0.75-1.97), though not significantly so. The odds ratio for the association between GDM and requiring a Caesarean section after labour started was 1.67 (95% CI 0.96-2.91) in the adjusted analysis. The aOR for requiring a Caesarean section in the absence of labour was 0.84, (95% CI 0.45-1.56).

5.4.2 Confounding of the Association Between GDM and SGA

In the initial analysis of the small for gestational age variable, the difference between the crude and adjusted odds ratios was quite large (OR 1.16, 95% CI 0.80-2.72 and aOR 1.46, 95% CI 0.99-2.15). To examine which confounder made the largest impact, each one was removed individually, and the adjusted odds ratio was recalculated. Pre-pregnancy weight was found to be the most impactful confounder that resulted in an 8.9% change (without weight in the model, aOR 1.33, 95% CI 0.91-1.96).

5.4.3 Birthweight Discordance as a Continuous Variable

Birthweight discordance was further analysed as a continuous variable. A log transformation of the variable was applied to ensure a reasonably normal distribution, and a linear regression was run. The adjusted mean difference, back-transformed from the log, in discordance between the twins affected by GDM and those who were not, was 1.2 g (95% CI -0.1, 2.4). This result was consistent with the results of the logistic regression on the dichotomized variable (p=0.34).

5.4.4 Respiratory Distress and Apgar Score by Mode of Delivery

Because the odds ratios associated with the association between GDM and two outcomes (respiratory distress syndrome and Apgar score) were less than 1.0 indicating a

possible protective effect of GDM, additional exploratory analysis was conducted on these variables by mode of delivery. This analysis yielded an unadjusted odds ratio of 1.11 (95% CI 0.66-1.88) between GDM and respiratory distress syndrome within those with a Caesarean section and 0.19 (95% CI 0.03-1.41) within those with a vaginal delivery (p interaction 0.0952). Therefore, the prevalence of respiratory distress syndrome could possibly be influenced by babies delivered vaginally. Repeating the same methods on the outcome variable of 5-minute Apgar score, the unadjusted odds ratio for vaginal delivery was 0.35 (95% CI 0.08-1.44) and for Caesarean section, 0.44 (95% CI 0.29-1.72) (p interaction 0.41). This indicated that the prevalence of a low Apgar score cannot be explained by mode of delivery.

5.4.5 Inclusion of Stillborn Infants in Analyses of Neonatal Outcomes

The final additional exploratory analysis was a sensitivity analysis to observe the impact of stillbirth on the weight outcomes of birthweight discordance, small for gestational age and large for gestational age. When stillborn neonates were included in the model for the noted outcomes, the odds ratios remained largely unchanged.

```
┌─────────────────────────────┐
│ All deliveries between January 1, 1988 and │
│ December 31, 2013 to Nova Scotia │
│ residents │
│ │
│ (n= 258,245) │
└─────────────────────────────┘
```

Excluded due to:
- Not being twins (n= 251,507)
- Mother having pre-existing diabetes (n=50)
- Monochorionic or conjoined twins (n= 1662)
- Twin type undetermined (n= 277)
- No co-twin in dataset (n= 1)

Neonatal study cohort

(n= 4748)

Maternal study cohort
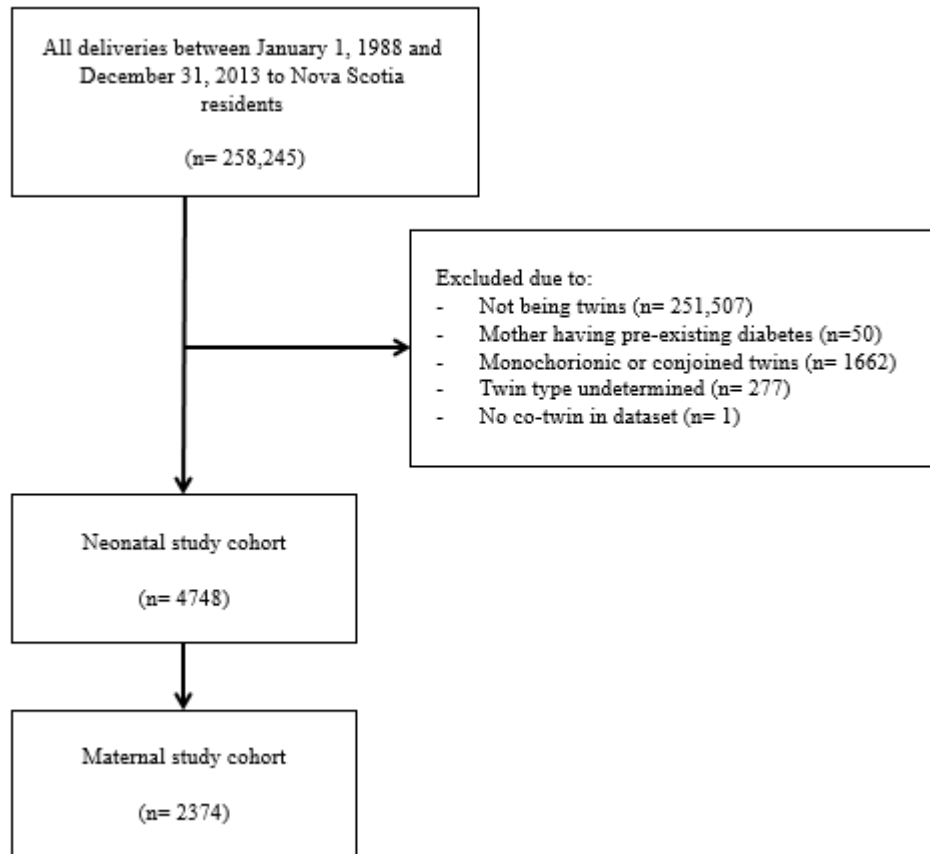
(n= 2374)

Figure 5.1   Flow diagram showing cohort inclusion.

Table 5.1　　Characteristics of the study population by gestational diabetes status

Characteristic	Overall N (%)		GDM (yes) N (row %)		GDM (no) N (row %)		p-value
N	2374		109		2265		
Age (years)							<0.0001
<25	428	(18.0%)	8	(1.9%)	420	(98.1%)	
25-29	716	(30.2%)	27	(3.8%)	689	(96.2%)	
30-34	808	(34.0%)	40	(5.0%)	768	(95.1%)	
≥35	422	(17.8%)	34	(8.0%)	388	(92.0%)	
Missing	0						
Parity							0.0926
0	1015	(42.8%)	38	(3.7%)	977	(96.3%)	
≥1	1359	(57.2%)	71	(5.2%)	1288	(94.8%)	
Missing	0						
Pre-pregnancy weight (kg)							<0.0001
<54.4-67.9	1040	(43.8%)	31	(3.0%)	1009	(97.0%)	
68.0-76.7	370	(15.6%)	21	(5.7%)	349	(94.3%)	
≥76.8	597	(25.2%)	45	(7.5%)	552	(92.5%)	
Missing	367						
Smoker							0.3584
No	1742	(73.4%)	84	(4.8%)	1658	(95.2%)	
Yes	582	(24.5%)	22	(3.8%)	560	(96.2%)	
Missing	50						
Partner							0.1549
Yes	1725	(72.7%)	86	(5.0%)	1639	(95.0%)	
No	521	(22.0%)	18	(3.5%)	503	(96.6%)	
Missing	128						
Neighborhood income quintile							0.5564
1 (low)	437	(18.4%)	17	(3.9%)	420	(96.1%)	
2	493	(20.8%)	24	(4.9%)	469	(95.1%)	
3	528	(22.2%)	22	(4.2%)	506	(95.8%)	
4	473	(20.0%)	20	(4.2%)	453	(95.8%)	
5 (high)	411	(17.3%)	25	(6.1%)	386	(93.9%)	
Missing	32						
Rural							0.5240
Yes	726	(30.6%)	30	(4.1%)	696	(95.9%)	
No	1644	(69.3%)	79	(4.8%)	1565	(95.2%)	
Missing	4						
Drug use							0.6228
Yes	23	(1.0%)	0	(0%)	23	(100%)	
No	2351	(99.0%)	109	(4.6%)	2242	(95.4%)	
Missing	0						
Year of birth							0.0277
1988-1992	415	(17.5%)	10	(2.4%)	405	(97.6%)	
1993-1997	392	(16.5%)	19	(4.9%)	373	(95.2%)	
1998-2002	428	(18.0%)	14	(3.3%)	414	(96.7%)	
2003-2007	479	(20.2%)	31	(6.5%)	448	(93.5%)	
≥2008	660	(27.8%)	35	(5.3%)	625	(94.7%)	
Missing	0						
Baby sex							0.4294

Characteristic	Overall N (%)		GDM (yes) N (row %)		GDM (no) N (row %)		p-value
Male/male	698	(29.0%)	28	(4.1%)	661	(96.0%)	
Male/female	969	(40.8%)	51	(5.3%)	918	(94.7%)	
Female/female	715	(30.1%)	30	(4.2%)	685	(95.8%)	
Missing	1						
Previous high birthweight baby							0.6795
Yes	189	(14.0%)	11	(5.8%)	178	(94.2%)	
No	1118	(82.3%)	57	(5.1%)	1061	(95.0%)	
Missing	52						
Previous low birthweight baby							0.7945
Yes	81	(6.0%)	a				
No	1210	(89.0%)					
Missing	68						
Previous Caesarean section							0.0671
Yes	279	(20.5%)	21	(7.5%)	258	(92.5%)	
No	1073	(79.0%)	49	(4.6%)	1024	(95.4%)	
Missing	7						
Breastfeeding							0.1041
Yes	1435	(60.5%)	59	(4.1%)	1376	(95.9%)	
No	872	(36.7%)	49	(5.6%)	823	(94.4%)	
Missing	67						

[a] Data suppressed due to cell size <5.

Table 5.2 Association between gestational diabetes and maternal outcomes among twin pregnancies

Outcome GDM status	N with outcome (%)	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Hypertension of pregnancy			
GDM (no)	358 (19.0)	1.00	1.00
GDM (yes)	24 (24.7)	1.40 (0.87-2.25)	1.44 (0.88-2.38)
Medically indicated preterm delivery			
GDM (no)	362 (19.0)	1.00	1.00
GDM (yes)	24 (24.7)	1.31 (0.69-1.85)	1.05 (0.63-1.74)
Not medically indicated preterm delivery			
GDM (no)	557 (29.2)	1.00	1.00
GDM (yes)	15 (15.5)	0.46 (0.26-0.82)	0.51 (0.28-0.91)
Caesarean section			
GDM (no)	1002 (52.5)	1.00	1.00
GDM (yes)	60 (61.9)	1.47 (0.97-2.24)	1.34 (0.87-2.07)
Caesarean section in labour			
GDM (no)	449 (23.5)	1.00	1.00
GDM (yes)	26 (26.8)	1.42 (0.85-2.38)	1.57 (0.92-2.68)
Caesarean section no labour			
GDM (no)	553 (29.0)	1.00	1.00
GDM (yes)	34 (35.1)	1.51 (0.94-2.43)	1.18 (0.72-1.93)
Antepartum length of stay > 48 hours			
GDM (no)	441 (23.1)	1.00	1.00
GDM (yes)	27 (27.8)	1.29 (0.81-2.03)	1.55 (0.97-2.50)

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Excluding women with missing values for confounders.
[b] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.

Table 5.3   Association between gestational diabetes and maternal outcomes among twin pregnancies, by maternal pre-pregnancy weight status

Outcome / GDM status	Pre-pregnancy weight <76.7 kg		Pre-pregnancy weight ≥ 76.7 kg		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypertension of pregnancy					
GDM (no)	17.2%	1.00	23.8%	1.00	0.61
GDM (yes)	19.2%	1.28 (0.62-2.64)	31.1%	1.66 (0.84-3.31)	
Medically indicated preterm delivery					
GDM (no)	17.5%	1.00	22.6%	1.00	0.97
GDM (yes)	23.1%	1.05 (0.52-2.09)	26.7%	1.07 (0.51-2.23)	
Not medically indicated preterm delivery					
GDM (no)	29.9%	1.00	27.5%	1.00	0.46
GDM (yes)	13.5%	0.41 (0.18-0.93)	17.8%	0.63 (0.27-1.44)	
Caesarean section					
GDM (no)	50.1%	1.00	41.3%	1.00	0.89
GDM (yes)	42.3%	1.31 (0.74-2.30)	33.3%	1.39 (0.72-2.69)	
Caesarean section in labour					
GDM (no)	23.8%	1.00	22.8%	1.00	0.29
GDM (yes)	21.2%	1.16 (0.55-2.48)	33.3%	2.09 (0.97-4.52)	
Caesarean section no labour					
GDM (no)	26.1%	1.00	35.9%	1.00	0.54
GDM (yes)	36.5%	1.38 (0.73-2.64)	33.3%	1.01 (0.47-2.16)	
Antepartum length of stay longer than 48 hours					
GDM (no)	22.6%	1.00	24.3%	1.00	0.41
GDM (yes)	23.1%	1.27 (0.64-2.50)	33.3%	1.89 (0.97-3.70)	

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.

Table 5.4   Association between gestational diabetes and maternal outcomes among twin pregnancies, by year of birth

Outcome GDM status	Year of birth 1988-2002		Year of birth 2003-2013		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypertension of pregnancy					
GDM (no)	20.2%	1.00	17.7%	1.00	0.53
GDM (yes)	23.7%	1.20 (0.55-2.64)	25.4%	1.66 (0.88-3.15)	
Medically indicated preterm delivery*					
GDM (no)					
GDM (yes)					
Not medically indicated preterm delivery					
GDM (no)	33.1%	1.00	24.4%	1.00	0.26
GDM (yes)	26.3%	0.68 (0.32-1.44)	8.5%	0.34 (0.13-0.88)	
Caesarean section					
GDM (no)	51.9%	1.00	42.3%	1.00	0.81
GDM (yes)	44.7%	1.28 (0.66-2.49)	33.9%	1.43 (0.81-2.53)	
Caesarean section in labour					
GDM (no)	27.7%	1.00	18.5%	1.00	0.54
GDM (yes)	42.1%	1.84 (0.89-3.77)	17.0%	1.31 (0.59-2.91)	
Caesarean section no labour					
GDM (no)	20.5%	1.00	39.2%	1.00	0.23
GDM (yes)	13.2%	0.69 (0.25-1.90)	49.2%	1.42 (0.78-2.58)	
Antepartum length of stay longer than 48 hours					
GDM (no)	28.0%	1.00	17.1%	1.00	0.18
GDM (yes)	29.0%	1.08 (0.52-2.23)	27.1%	2.06 (1.11-3.82)	

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.

[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.

*Unable to assess due to low numbers.

Table 5.5   Association between gestational diabetes and maternal outcomes among twin pregnancies, by fetal sex

Outcome GDM status	One or both twins are male		Both twins are female		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypertension of pregnancy					
GDM (no)	18.9%	1.00	19.7%	1.00	0.32
GDM (yes)	33.3%	2.05 (0.83-5.07)	21.9%	1.19 (0.66-2.14)	
Medically indicated preterm delivery*					
GDM (no)					
GDM (yes)					
Not medically indicated preterm delivery*					
GDM (no)					
GDM (yes)					
Caesarean section					
GDM (no)	50.4%	1.00	46.3%	1.00	0.81
GDM (yes)	37.5%	1.50 (0.64-3.49)	38.4%	1.29 (0.78-2.12)	
Caesarean section in labour					
GDM (no)	20.5%	1.00	24.9%	1.00	0.79
GDM (yes)	33.3%	1.79 (0.66-4.82)	24.7%	1.53 (0.82-2.86)	
Caesarean section no labour					
GDM (no)	29.1%	1.00	28.9%	1.00	0.95
GDM (yes)	29.2%	1.23 (0.45-3.41)	37.0%	1.19 (0.68-2.07)	
Antepartum length of stay longer than 48 hours					
GDM (no)	22.4%	1.00	23.4%	1.00	0.23
GDM (yes)	41.7%	2.41 (1.03-5.66)	23.3%	1.29 (0.73-2.29)	

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.
*Unable to examine due to low numbers.

Table 5.6   Association between gestational diabetes and neonatal outcomes among twin pregnancies

Outcome GDM status	N with outcome (%)	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Hypoglycemia			
GDM (no)	185 (5.2)	1.00	1.00
GDM (yes)	27 (14.9)	3.15 (1.91-5.21)	3.07 (1.82-5.19)
Birthweight discordance			
GDM (no)	198 (11.0)	1.00	1.00
GDM (yes)	13 (14.0)	1.32 (0.72-2.41)	1.32 (0.71-2.43)
Large for gestational age			
GDM (no)	134 (3.8)	1.00	1.00
GDM (yes)	8 (4.4)	1.13 (0.47-2.72)	1.19 (0.47-2.98)
Small for gestational age			
GDM (no)	898 (25.3)	1.00	1.00
GDM (yes)	51 (28.2)	1.16 (0.80-1.69)	1.46 (0.99-2.15)
Neonatal intensive care stay >24 hours			
GDM (no)	340 (9.6)	1.00	1.00
GDM (yes)	12 (6.6)	0.74 (0.35-1.57)	0.99 (0.46-2.14)
Respiratory distress syndrome			
GDM (no)	515 (14.5)	1.00	1.00
GDM (yes)	20 (11.1)	0.72 (0.42-1.25)	0.70 (0.41-1.22)
5-minute Apgar score ≤7			
GDM (no)	217 (6.1)	1.00	1.00
GDM (yes)	6 (3.3)	0.53 (0.23-1.20)	0.53 (0.23-1.23)
Congenital anomalies			
GDM (no)	221 (5.8)	1.00	1.00
GDM (yes)	12 (6.2)	1.07 (0.50-2.30)	1.20 (0.56-2.60)
Neonatal length of stay >10 days			
GDM (no)	957 (26.9)	1.00	1.00
GDM (yes)	38 (21.0)	0.73 (0.45-1.18)	0.87 (0.54-1.41)

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.

[a] Excluding neonates with missing values for confounders.

[b] Adjusted for year of birth, maternal age, parity and pre-pregnancy weight.

Table 5.7   Association between gestational diabetes and neonatal outcomes among twin pregnancies, by maternal pre-pregnancy weight status

Outcome GDM status	Pre-pregnancy weight < 76.7 kg		Pre-pregnancy weight ≥ 76.7 kg		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypoglycemia					
GDM (no)	5.2%	1.00	5.2%	1.00	0.08
GDM (yes)	10.5%	1.88 (0.86-4.10)	19.8%	4.77 (2.33-9.77)	
*Birthweight discordance					
GDM (no)					
GDM (yes)					
*Large for gestational age					
GDM (no)					
GDM (yes)					
Small for gestational age					
GDM (no)	27.8%	1.00	19.4%	1.00	0.67
GDM (yes)	32.6%	1.52 (0.81-2.85)	23.3%	1.22 (0.54-2.77)	
*Neonatal intensive care >24 hours					
GDM (no)					
GDM (yes)					
Respiratory distress syndrome					
GDM (no)	13.4%	1.00	17.0%	1.00	0.48
GDM (yes)	8.4%	0.71 (0.25-1.98)	14.0%	0.40 (0.12-1.33)	
*5-minute Apgar score ≤7					
GDM (no)					
GDM (yes)					
*Congenital anomalies					
GDM (no)					
GDM (yes)					
Neonatal length of stay >10 days					
GDM (no)	27.4%	1.00	25.3%	1.00	0.23
GDM (yes)	16.8%	0.61 (0.29-1.32)	25.6%	1.15 (0.57-2.32)	

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.
*Unable to examine due to low numbers.

Table 5.8   Association between gestational diabetes and neonatal outcomes among twin pregnancies, by year of birth

Outcome GDM status	Year of birth 1988-2002		Year of birth 2003-2013		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypoglycemia					
GDM (no)	3.2%	1.00	7.5%	1.00	
GDM (yes)	8.9%	2.71 (1.00-7.35)	22.1%	3.13 (1.69-5.81)	0.81
*Birthweight discordance					
GDM (no)					
GDM (yes)					
*Large for gestational age					
GDM (no)					
GDM (yes)					
Small for gestational age					
GDM (no)	28.8%	1.00	22.0%	1.00	
GDM (yes)	31.7%	1.34 (0.72-2.49)	25.4%	1.50 (0.92-2.43)	0.78
*Neonatal intensive care >24 hours					
GDM (no)					
GDM (yes)					
Respiratory distress syndrome					
GDM (no)	12.6%	1.00	17.3%	1.00	
GDM (yes)	7.6%	0.48 (0.17-1.37)	16.4%	0.83 (0.43-1.60)	0.38
*5-minute Apgar score ≤7					
GDM (no)					
GDM (yes)					
Congenital anomalies					
GDM (no)	6.3%	1.00	6.4%	1.00	
GDM (yes)	8.1%	1.28 (0.44-3.77)	6.8%	1.16 (0.40-3.37)	0.90
Neonatal length of stay >10 days					
GDM (no)	29.1%	1.00	25.0%	1.00	
GDM (yes)	27.9%	1.05 (0.53-2.08)	20.5%	0.71 (0.35-1.41)	0.42

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.
*Unable to examine due to low numbers.

Table 5.9   Association between gestational diabetes and neonatal outcomes among twin pregnancies, by fetal sex

Outcome GDM status	Male		Female		p-value interaction
	% with outcome	Adjusted OR[a] (95% CI)	% with outcome	Adjusted OR[a] (95% CI)	
Hypoglycemia					
GDM (no)	6.1%	1.00	4.4%	1.00	
GDM (yes)	14.3%	2.50 (1.30-4.83)	15.6%	3.67 (1.91-7.06)	0.35
Birthweight discordance					
GDM (no)	11.6%	1.00	10.4%	1.00	
GDM (yes)	16.0%	1.39 (0.63-3.06)	11.6%	1.13 (0.43-2.95)	0.75
*Large for gestational age					
GDM (no)					
GDM (yes)					
Small for gestational age					
GDM (no)	25.2%	1.00	25.5%	1.00	
GDM (yes)	28.6%	1.55 (0.94-2.57)	27.8%	1.31 (0.78-2.21)	0.63
*Neonatal intensive care >24 hours					
GDM (no)					
GDM (yes)					
Respiratory distress syndrome					
GDM (no)	16.0%	1.00	13.0%	1.00	
GDM (yes)	9.9%	0.55 (0.29-1.06)	12.2%	0.88 (0.47-1.67)	0.19
*5-minute Apgar score ≤7					
GDM (no)					
GDM (yes)					
*Congenital anomalies					
GDM (no)					
GDM (yes)					
Neonatal length of stay >10 days					
GDM (no)	26.9%	1.00	26.9%	1.00	
GDM (yes)	18.7%	0.74 (0.42-1.30)	23.3%	0.97 (0.57-1.65)	0.30

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.
[a] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.
*Unable to examine due to low numbers.

Table 5.10   Association between gestational diabetes and Caesarean section in women with no previous Caesarean section

Outcome GDM status	N with outcome (%)	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Caesarean section			
GDM (no)	825 (48.5)	1.00	1.00
GDM (yes)	42 (54.6)	1.27 (0.81-2.02)	1.21 (0.75-1.97)
Caesarean section in labour			
GDM (no)	411 (24.2)	1.00	1.00
GDM (yes)	25 (32.5)	1.52 (0.90-2.58)	1.67 (0.96-2.91)
Caesarean section no labour			
GDM (no)	414 (24.3)	1.00	1.00
GDM (yes)	17 (22.1)	1.03 (0.57-1.86)	0.84 (0.45-1.56)

CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio.

[a] Excluding women with missing values for confounders.

[b] Adjusted for year of birth, maternal age, parity, and pre-pregnancy weight.

Chapter 6 DISCUSSION

6.1 Summary of Main Results

Of the 2374 mothers in the study, 109 (4.6%) had GDM. This rate of GDM in twin pregnancies is similar to those reported in the literature.[15,16,17,20,21]

The aim of this thesis was to examine the association between GDM and maternal and neonatal outcomes in women pregnant with twins and their neonates between 1988 and 2013 in Nova Scotia, Canada. Covariates available in the NSAPD were examined by GDM status. Mothers who had GDM were very similar to those without regarding smoking and drug use, marital status, income and medical history regarding previous pregnancies, but mothers with GDM were older, had a higher pre-pregnancy weight, differed in year of delivery, were more likely to have had a previous pregnancy, and were more likely to have had a previous Caesarean section. These differences are consistent with reported risks for GDM[1,4,10] and with differences between mothers with GDM and those without GDM pregnant with twins in previous studies. Age,[21,31,46,52,53] pre-pregnancy weight[20,31,47,53] and parity[23,53] were the most common heterogenous characteristics previously reported. Gestational diabetes tended to increase the risk (aORs > 1.30) of Caesarean section, gestational hypertension and an antepartum length of stay longer than 48 hours in the mother, and neonatal hypoglycemia, small for gestational age and birthweight discordance in the babies. The GDM group showed a lower proportion of respiratory distress syndrome and low Apgar score than the group without GDM (aOR < 0.77). Logistic regression was used to examine both maternal and neonatal outcomes and generalized estimating equations were used to account for the non-independence of twins. Compared to the unadjusted ORs, adjustment for year of birth, maternal age, parity and

pre-pregnancy weight caused little change for the maternal outcomes of hypertension and mode of delivery, and neonatal outcomes of hypoglycemia, birthweight discordance, large for gestational age, respiratory distress, and low Apgar. Adjustment for these potential confounders, however, did change the ORs for preterm delivery, Caesarean section without labour, and antepartum length of stay. Stratified analysis was completed in order to better understand the impact of maternal pre-pregnancy weight, year of birth and fetal sex on the relationship between GDM and maternal and fetal outcomes. There were no significant interactions between these variables and GDM for most of the maternal and neonatal outcomes investigated, with the exception of not medically indicated preterm delivery and neonatal hypoglycemia.

The results of the current study support some, but not all, previous research examining the association of GDM and maternal and neonatal outcomes. Major methodological differences between studies likely contribute to some of the inconsistencies in the current literature. For example, the existing studies are heterogeneous with respect to design (prospective, retrospective, matched cohorts), comparison groups, size, confounding variables and definition of variables such as respiratory distress, weight centiles, and low Apgar. In the following sections, for each outcome examined, a more detailed summary of the results from the present study will be presented and put into context with what has been published in the literature.

6.2 Maternal Outcomes

6.2.1 Hypertensive Disorders of Pregnancy

For our study, gestational hypertension was defined as pregnancy-induced hypertension with or without significant proteinuria. Women with GDM had an estimated 1.4 fold higher odds of having gestational hypertension in pregnancy compared to women without GDM after adjusting for year of birth, maternal age, parity and pre-pregnancy weight (aOR 1.44, 95% CI 0.88-2.38). In the stratified analysis for maternal pre-pregnancy weight, the aOR in the stratum of lower pre-pregnancy weight (< 76.7 kg) was 1.28 (95% CI 0.62-2.64), and in the higher pre-pregnancy weight stratum (≥ 76.7 kg), 1.66 (95% CI 0.84-3.31, p interaction 0.61). Although not significant, the point estimates indicate that potentially, women who are heavier pre-pregnancy could be more susceptible to gestational hypertension when they have GDM. Given the known relationship of overweight and obesity on hypertension even in the absence of pregnancy and diabetes, this increased risk is plausible.[58,59] When stratified by year of birth, a non-significant difference was found between epochs, 1988-2002 and 2003-2013 respectively, (aOR 1.20, 95% CI 0.55-2.64 versus aOR 1.66, 95% CI 0.88-3.15, p interaction 0.53). When stratified by fetal sex, women with GDM who were carrying a male fetus had a twofold increased risk of gestational hypertension based on the odds ratio (aOR 2.01, 95% CI 0.83-5.07), while the risk was closer to the null in women carrying two female fetuses (aOR 1.19, 95% CI 0.66-2.14, p interaction 0.32). There has been evidence that carrying a male fetus increases the risk of several adverse outcomes, although the mechanism for this remains largely unclear.[11,12]

Several studies have examined the association of GDM and the outcome of maternal hypertension in women pregnant with twins and found results similar to those in the present study.[20,21,31,42,46,52,53,54] Hiersch and colleagues,[54] also in Canada, conducted a cohort study of both singleton and twin pregnancies but analyzed each type separately. Their twin cohort was slightly larger than our study, with 3575 mothers with no GDM and 326 mothers with GDM. Although the study years crossed the previously mentioned change in GDM diagnostic criteria of 2013, the researchers did not account for this, as treatment protocols had not changed. They found the risk of gestational hypertension in the GDM group to also be 1.40 fold greater (aRR 1.41, 95% CI 1.00-1.98), when adjusted for maternal age, parity, smoking, race, maternal BMI, and pre-existing hypertension. Researchers in Spain also found that the odds of hypertension was higher in women pregnant with twins and who were diagnosed with GDM (OR 1.88, 95% CI 1.04-3.47), and, when adjusted for maternal BMI, the risk estimate was attenuated (aOR 1.46, 95% CI 0.76-2.79).[31] The authors echo our hypothesis, stating that perhaps gestational hypertension is more due to increased maternal BMI and less due to GDM.[31] In a study with a similar number of twin pregnancies to the present study, 105 twin pregnancies were matched to 315 controls on gestational age, chronicity and year of delivery.[20] The two groups were notably similar in mean maternal age and parity, but the GDM group had higher pre-pregnancy BMI. The odds ratio was 1.69 (95% CI 1.00-2.82) from the reported frequencies, but they included chronic, pre-existing hypertension in their outcome, which has the possibility to falsely increase the odds, as it precedes the diagnosis of GDM.

Dinham and colleagues[42] showed some analyses by year of birth as there was a change in screening protocol during the study period, but they only reported differences in outcomes by GDM in both time periods combined. They reported that 19.8% of the 86 women with GDM and only 11.6% of the 896 women without GDM had gestational hypertension (p 0.0003) from which the calculated unadjusted odds ratio was 1.88 (95% CI 1.04-3.27), similar to the present study. Lai et al.[44] conducted a sub-analysis of mothers pregnant with twins with GDM compared to those pregnant with twins without GDM and found that after adjustment for age, First Nations status, parity and pre-existing hypertension, the adjusted odds ratio was 1.54 (95% CI 1.07-2.21). Foeller and colleagues[46] also reported similar frequencies in the description of their cohort, and in small studies by Ooi[52] and Sheehan[53], results echoed those of both the previously mentioned studies, as well as the present study.

6.2.2 Preterm Delivery

Preterm delivery was defined as birth at or before 37 completed weeks' gestation and was assessed as medically indicated (delivery prior to the onset of labour) and not medically indicated (spontaneous preterm delivery). On initial analysis, women pregnant with twins with GDM appeared to have a higher risk of medically indicated preterm delivery (OR 1.31, 95% CI 0.69-1.85), but, this risk approached the null when adjusted for maternal age, parity, pre-pregnancy BMI and year of birth (aOR 1.05, 95% CI 0.63-1.74). Conversely, women with GDM had a 49% lower risk of spontaneous preterm delivery (aOR 0.51, 95% CI 0.28-0.91), suggesting that women pregnant with twins who have GDM were less likely to go into labour before 37 weeks of pregnancy without medical intervention. This supports previous research that found that in women pregnant

with singletons with GDM, elective preterm delivery is often suggested between 37-40 weeks' gestation to lessen possible risk to mother and baby.[60] When medically indicated preterm delivery was stratified by pre-pregnancy weight, no difference was observed between strata in the present study. Spontaneous preterm delivery was similar across both strata of pre-pregnancy weight (aOR 0.41, 95% CI 0.18-0.93, aOR 0.63, 95% CI 0.27-1.44, p interaction 0.46).

Overall, most studies that examined preterm delivery in twin pregnancies also found slightly increased risk in women with GDM, with a few finding slightly stronger associations. One study, after adjusting for maternal age, pre-pregnancy BMI, nulliparity, hypertension, obstetric complications and other medical complications, found that the odds ratio for preterm birth (< 37 weeks) was close to the null at 1.08 (95% CI 0.72-1.61) ,[31] similarly to our results. In a study that matched cases and controls on maternal age and BMI, frequencies of births < 37 weeks were similar in the neonates born to mothers with and without GDM (OR 1.18, 95% CI 0.93-1.51) .[49] Their exposure variable of GDM also included women with 'mild gestational hyperglycemia', defined as women who had one glucose value out of range on the two-step O'Sullivan test (OGTT), rather than the two values required for a diagnosis of GDM in the present study, which could potentially mean there was heterogeneity of glucose values within the glucose intolerant group, which might weaken the differences between groups.[49] In a very small study in Germany, researchers found no significant difference in preterm premature rupture of membranes between mothers with and without GDM, but their study included only three mothers with GDM.[23] Luo and colleagues[27] conducted a large cohort study in the United States and found a small increase in risk of preterm birth in women associated with diabetes

(aRR 1.27, 95% CI: 1.22-1.31), but included women with pre-existing diabetes in their exposure group which can increase the risk of many negative pregnancy outcomes to a greater extent than GDM. In another Canadian study, Hiersch et al.[54] found a similar risk of preterm birth < 37 weeks among women with GDM and without, even after adjusting for the confounders of age, smoking status, parity, pre-existing hypertension, race, maternal BMI and use of assisted reproductive technology (aRR 1.21, 95% CI 1.08-1.37). Both Ooi et al.[52] and Dinham et al.[42] reported slight, but not significant, higher rate of preterm birth between women with GDM than in those without GDM.

6.2.3 Mode of Delivery

Caesarean section was assessed overall, and then further as Caesarean section in labour and Caesarean section prior to labour starting. An odds ratio of > 1.30 was found for the overall risk of Caesarean section in women with GDM (aOR 1.34, 95% CI 0.87-2.07), which was largely accounted for by Caesarean deliveries conducted after labour had started, meaning the Caesarean section delivery was not pre-planned. The association was nearly twofold in mothers with pre-pregnancy weight ≥ 76.7 kg as opposed to women weighing < 76.7 kg in whom the association was null, suggesting that pre-pregnancy weight might impact the effect of GDM on mode of delivery (aOR 2.09, 95% CI 0.97-4.52, vs. aOR 1.16, 95% CI 0.55-2.48, p interaction 0.29). Further, the association between GDM and elective Caesarean section (no labour) was higher in more recent years (aOR 0.69, 95% CI 0.25-1.90 vs. aOR 1.42, 95% CI 0.78-2.58, p interaction 0.23). This is not surprising given the increasing Caesarean section rates in Canada over the years.[61] One study reviewed examined mode of delivery by in labour or prior to labour; most other studies only looked at all forms of Caesarean section in comparison to

vaginal delivery. Most studies found a trend toward a higher rate of Caesarean section in women with GDM, reiterating our results. In one study that did differentiate between the two types of Caesarean section (emergency – done in labour, and elective – no labour), a very small reduced risk of overall vaginal delivery was observed in women with GDM (aOR 0.92, 95% CI 0.62-1.37) when adjusted for maternal age, pre-pregnancy BMI, nulliparity, pre-existing hypertension, obstetrical complications and medical complications, meaning no more than 8% increased risk of Caesarean section.[31] The complications adjusted for as confounders were not clearly outlined, however, and there is the possibility of them being mediators and not confounders of the relationship between GDM and mode of delivery; therefore, the odds ratio should be interpreted with caution.[31] Unadjusted odds ratios calculated from the frequencies presented for Caesarean section as emergency or elective were 1.31 (95% CI 0.93-1.85) in the elective group, and 0.83 (95% CI 0.52-1.32) in the emergency group.[31] Lai et al.[44] found a one and half fold increased risk of Caesarean section in women with GDM even when they adjusted for maternal age, First Nations status, and pre-existing hypertension (aOR 1.57, 95% CI 1.25-1.96). A matched cohort in Portugal found a slightly higher risk of Caesarean section in women with GDM as compared to women without GDM (OR 1.20, 95% CI 0.74-2.00) but the groups were only matched on gestational age, chorionicity and year of delivery, and not on maternal pre-pregnancy weight or BMI, even though they noted that mothers with a higher pre-pregnancy weight were more likely to have GDM.[20] Okby et al.[21] also found a slightly increased odds of Caesarean delivery (aOR 1.17. 95% CI 0.92-1.49) when adjusted for maternal age, fertility treatment, and hypertensive disorders. Again however, they did not adjust for maternal pre-pregnancy weight or BMI, which in

our study, impacted the mode of delivery. Hiersch and colleagues[54] estimated a risk ratio close to the null, especially when adjusted for age, smoking status, nulliparity, race, pre-pregnancy BMI and reproductive technology (aRR 1.11, 95% CI 1.02-1.21). Foeller et al.[46] only looked at mode of delivery as part of the characteristics of their cohort, and not as an outcome variable, and found a significant difference in frequency of Caesarean section in mothers with GDM (80.3% vs. 74.6%, p <0.0001). This finding was echoed by Dinham and colleagues[42] who found 66.0% of women without GDM had a Caesarean section, while 73.3% with GDM did (p=0.02), as well as Ooi and Wong[52] (47.9% vs. 54.6%). Moses et al.[47] also found an increased percentage of Caesarean sections in mothers with GDM but this study was very small, including only 28 women with GDM and 29 without.

One study of women with diabetes and a matched group of women without diabetes found a lower risk of Caesarean section in diabetic mothers, and although their study included both gestational diabetic mothers, as well as those with mild gestational hyperglycemia, they did conduct a separate analysis including only those women with GDM.[49] They found a 26% lower risk of Caesarean section in the GDM twin mothers group (aOR 0.74, 95% CI 0.49-1.11), an opposing result to both the other studies and our present study.

As noted, an additional analysis of women who previously had a Caesarean section was carried out, as this puts a mother at high risk of requiring another Caesarean section regardless of other factors. In this group, we estimated that women who had GDM had 20% higher odds of having a Caesarean section overall (aOR 1.21, 95% CI 0.75-1.97), a finding that was similar to the overall Caesarean section risk in all mothers

with GDM and twin pregnancy (aOR 1.34, 95% CI 0.87-2.07). Sheehan et al.[53] also examined Caesarean section risk and also further analyzed Caesarean delivery as overall or repeat section. They found that the odds ratio for the overall risk of Caesarean section was 1.16 (95% CI 0.53-2.71), but they estimated a lower risk of repeat Caesarean section with an odds ratio of 0.77 (95% CI 0.26-2.33).

6.2.4 Antepartum Length of Stay Greater than 48 Hours

In obstetrics, a woman's length of stay in hospital typically only exceeds a few days if there are concerns, complications, or adverse maternal outcomes.[62] Therefore, a length of stay of greater than 48 hours is an outcome variable to not only assess potential costs to the healthcare system, but it also acts as a rough proxy for maternal health risks as a whole. The estimated increased adjusted odds ratio of a length of stay greater than 48 hours in women with GDM relative to women without GDM was found to be 1.55 (95% CI 0.97-2.50). When stratified by year of birth, the association was close to the null in the years 1988 to 2002 (aOR 1.08, 95% CI 0.52-2.23), but the risk was twofold in the 2003 to 2013 epoch (aOR 2.06, 95% CI 1.11-3.82, p interaction 0.18), signifying that perhaps care is more conservative now in women who have not only one, but two risks (i.e., both twinning and GDM) impacting their pregnancy. When stratified by fetal sex, women carrying a male fetus had nearly a 2.5 fold increased risk of a longer length of stay (aOR 2.41. 95% CI 1.03-5.66), further suggesting that carrying a male fetus increases a mother's risk of adverse pregnancy outcomes. No other studies on twin pregnancies complicated with GDM examined maternal length of stay.

6.3 Neonatal Outcomes

6.3.1 Neonatal Hypoglycemia

Neonates of women with GDM were threefold more likely to have a low blood sugar after birth (aOR 3.07, 95% CI 1.82-5.19). This association was more pronounced in mothers whose weight was higher than 76.7 kg before pregnancy (aOR 4.77, 95% CI 2.33-9.77 vs. 1.88, 95% CI 0.86-4.10, p interaction 0.08). The association between GDM and neonatal hypoglycemia was fairly similar across epochs (aOR 2.71, 95% CI 1.00-7.35 vs. aOR 3.13, 95% CI 1.69-5.81, p interaction 0.81), but a higher association was observed in female neonates than in male neonates (aOR 3.67, 95% CI 1.91-7.06 vs. aOR 2.50, 95% CI 1.30-4.83 p interaction 0.35). With all of these estimates, however, wide confidence intervals indicate imprecise estimates. Over 50 years ago, Jorgen Pedersen, formulated the hypothesis that increased maternal blood glucose levels increased fetal blood glucose levels leading to an increase in fetal insulin levels.[63] This increase in insulin levels causes a subsequent drop in blood glucose after birth. The finding that neonates born to GDM mothers have a higher risk of hypoglycemia after birth is, therefore, not surprising. This result was echoed by Dinham[42] who found 1.1% of twin neonates born to women with no GDM had hypoglycemia after birth, whereas 11.1% of twin neonates born to women with GDM did (p=0.0001). Interestingly, Poulain[49], Cho[43], Hiersch[54], Ooi[52] and Sheehan[53] all found no significant differences between the groups, and Rauh-Hain et al.[5] and colleagues found a very small decreased risk of hypoglycemia in the twin neonates born to mothers with GDM. However, most of these studies were small.

6.3.2 Birthweight Discordance

In twin pregnancy, high degrees of difference in growth between fetuses leads to poorer neonatal outcomes.[64] In the literature, common cut points for the absolute difference in birthweights range from $\geq$ 15% to $\geq$ 30%. For this study, birthweight discordance was defined as a $\geq$ 25% difference in weight between twins. In twins born to mothers with GDM, the odds of having a difference in birthweight of 25% or more was estimated to be 1.32 times that of twins born to mothers without GDM (95% CI 0.71-2.43). We were unable to stratify by pre-pregnancy weight or year of birth as effect modifiers due to low numbers. In male/male neonatal pairs, the odds ratio for having birthweight discordance was estimated to be 1.39 (95% CI 0.63-3.06), and in female/female neonatal pairs, it was 1.19 (95% CI 0.43-2.95, p interaction 0.75). The reason for this increased odds in twins with exposure to GDM is not clear but the impact of maternal hyperglycemia on fetal growth could be surmised to play a role.

Very few studies have examined birthweight discordance in relation to GDM. Klein and colleagues[7] specifically examined weight discrepancy between twins born to women diagnosed with GDM compared to those without in a prospective cohort of 200 women, 43 of those having GDM. They found that the mean weight difference between twins was significantly higher in the GDM group (304 g vs. 214 g, p 0.02). Guillén et al.[34] found that 20.6% of twins exposed to GDM had birthweight discordance, compared to 15.2% unexposed (p=0.32), but used $\geq$ 20% as their variable definition. As in our study, Simões et al.[20] also used 25% difference, but unlike our results, found a 30% lower risk of discordance in twins born to mothers with GDM when the odds was calculated from reported frequencies (OR 0.70, 95% CI 0.30-1.54).

6.3.3 Large for Gestational Age

In singleton pregnancies complicated by GDM, outcomes that are studied frequently include large for gestational age or macrosomic (high birthweight) neonates[1,2,3,4]. This is due to the aforementioned mechanism described by Pedersen, whereby the mothers high blood sugar levels cause high blood sugar and subsequent high insulin levels in the neonate, which can cause increased growth in utero.[63] This however, is presumed not to be the case in multiple gestation pregnancies, as twins and higher order multiples tend to be smaller neonates.[34] Typically, the definition of large for gestational age is $\geq 90^{th}$ percentile for gestational age and sex. This can be based on growth charts for singleton neonates, or less commonly, twin specific growth charts. We used $\geq 90^{th}$ percentile based on singleton growth charts for the present study and found a very small additional increased risk of being large for gestational age in twins exposed to GDM (aOR 1.19, 95% CI 0.47-2.98). These findings suggest that GDM might accelerate the growth of twin neonates, as it does singletons, but perhaps to a lesser extent. Further analysis of potential effect modification by pre-pregnancy weight, year of birth or fetal sex could not be carried out due to low numbers.

Guillén[34], Ooi[52], Simões[20], and Dinham[42] echoed the results of our present study, each finding little difference in the risk of large for gestational age between neonates born to mothers with and without GDM. Luo and colleagues[27] found in their large, retrospective cohort, an odds ratio just slightly greater than our findings (aRR 1.38, 95% CI 1.10-1.73) controlling for race, age, education, marital status, smoking, alcohol use, prenatal care and infant sex. Their study had comparable methods to ours, using the same diagnostic criteria for GDM and defining large for gestational age as $\geq 90^{th}$ percentile on

singleton growth charts. Foeller et al.[46] found a similar odds to that of Luo, also in a large

retrospective cohort (aOR 1.37, 95% CI 1.17-1.64) when controlling for race, age,

education level, marital status, smoking status, prenatal care adequacy, eclampsia

diagnosis, history of preterm delivery, maternal weight gain, chronic hypertension and

mode of delivery. This finding was based on large for gestational age as defined as $\geq 90^{th}$

percentile on a singleton growth chart. Interestingly, Luo et al.[27] also calculated an

adjusted risk ratio using the same analysis but using twin growth chart and found nearly

the same result (aRR 1.37, 95% CI 1.30-1.45). In their retrospective study, Poulain et al.[49]

found a similar adjusted odds ratio using only women diagnosed with GDM and

excluding the women in their study who had mild gestational hyperglycemia, as

described above (aOR 1.31, 95% CI 0.57-3.44). This adjusted odds ratio was calculated

by controlling for 'weight and size of the patient', parity and fetal sex.

6.3.4 Small for Gestational Age

A common outcome studied in relation to multiple gestation pregnancies is small

for gestational age neonates, as the fetuses are sharing space and nutrients in utero.[34]

Given that GDM increases the risk of large for gestational age or macrosomia in

singleton pregnancies, some researchers have hypothesized that GDM would protect

against small for gestational age births and complications associated with this[27,46].

Typically, the definition of small for gestational age is $\leq 10^{th}$ percentile for gestational

age and sex. As with LGA, this can be based on growth charts for singleton neonates, or

less commonly, twin specific growth charts. We used $\leq 10^{th}$ percentile based on singleton

growth charts for the present study. Somewhat unexpectedly, we found after applying the

logistic regression model to control for confounders, the odds ratio of small for

gestational age neonates being born to women with GDM was nearly 1.5 (aOR 1.46, 95%

CI 0.99-2.15). Due to the change in the odds ratio with adjustment for maternal age, pre-

pregnancy weight, parity and year of birth (OR 1.16, 95% CI 0.80-1.69), which

confounder made the most impact on the association was explored. Pre-pregnancy weight

was the strongest confounder, with its removal decreasing the aOR by 8.9%. Therefore,

we recognize pre-pregnancy weight as a negative confounder. We also found that when

stratified by pre-pregnancy weight, the odds ratio was higher among women with a pre-

pregnancy weight < 76.7 kg (aOR 1.52, 95% CI 0.81-2.85), compared to women who

weighed ≥ 76.7 kg (aOR 1.22, 95% CI 0.54-2.77, p interaction 0.67), though not

significant. Understanding that insulin resistance increases as weight increases, we can

hypothesize that women with a smaller pre-pregnancy weight could have better glucose

control and therefore the neonatal weight increase often observed in GDM might be

lessened. The association between SGA and GDM was similar to the original adjusted

odds when stratified by year of birth and fetal sex.

Of the studies previously conducted on neonatal outcomes of twin pregnancies

complicated by GDM, none found results similar to those of our study. All other studies

found the odds of a small for gestational age infant to be less in the neonates born to

mothers with GDM. Guillén et al.,[34] Ooi et al.,[52] Lai et al.,[44] Tward et al.,[51] Poulain et

al.,[49] González González et al.,[31] Dinham et al.,[42] Luo et al.,[27] Foeller et al.,[46] and Simões

et al.[20] all found odds ratios to be less than 1.0. However, it should be noted that many of

these studies only presented frequencies of SGA neonates, and therefore only crude odds

ratios could be calculated for comparative purposes. All of the above-mentioned results

were based on SGA being defined as less than 10th percentile, but some utilized growth charts for singleton neonates, while others used twin growth charts.

6.3.5 Neonatal Intensive Care Unit Admission for Longer than 24 Hours

Often, admission to a neonatal intensive care unit is standard of care for twins or higher order multiples, due to the higher risk of neonatal complications.[65] If no complications are present, the neonates are often discharged promptly. Examining NICU stays lasting longer than 24 hours, therefore, provided valuable information for clinical decision making. We observed no association between GDM and NICU admission of greater than 24 hours in twin neonates (aOR 0.99, 95% CI 0.46-2.14). Small cell sizes did not permit further exploration of pre-pregnancy weight, year of birth or fetal sex as effect modifiers. Only a handful of studies to date have assessed NICU admission, and of those reviewed, the length of stay is unclear. Lai and colleagues[44] also found no association (aOR 1.04, 95% CI 0.85-1.26), while Hiersch et al.[54] and Foeller et al.[46] found a slightly higher NICU admission frequency in twins born to mothers with GDM (aRR 1.12, 95% CI 1.00-1.23 and aRR 1.22, 95% CI 1.18-1.26, respectively).

6.3.6 Respiratory Distress Syndrome

Any form of respiratory distress syndrome (any severity including transient tachypnea of the newborn) was examined in neonates exposed to GDM and those who were not exposed. Gestational diabetes was associated with an estimated 30% reduction in odds of respiratory distress syndrome (aOR 0.70, 95% CI 0.41-1.22). This association was stronger in the higher pre-pregnancy weight group than the low pre-pregnancy weight group (aOR 0.40, 95% CI 0.12-7.33). When stratified by year of birth, the

estimated association was attenuated in the later epoch, 2003-2013 (aOR 0.48, 95% CI

0.17-1.37 vs aOR 0.83, 95% CI 0.43-1.60, p interaction 0.38) perhaps indicating a change

in clinical diagnosis, although this is not clear. Because respiratory distress syndrome can

be impacted by mode of delivery, a supplementary analysis was carried out. During

vaginal delivery, as a neonate descends through the birth canal, the lungs are squeezed

and fluids and phlegm are expelled, facilitating better breathing after delivery. This

process does not happen during a Caesarean section.[66] In neonates born to mothers with

GDM, 20.6% born by Caesarean section had respiratory distress syndrome, while only

4.9% of those born vaginally did (aOR 1.11, 95% CI 0.66-1.88 and aOR 0.19, 95% CI

0.03-1.41, respectively; p interaction 0.0952).

Foeller et al.[46] also found a similar association between GDM and respiratory

distress. In their study, respiratory distress was defined as assisted ventilation lasting one

hour or less (aOR 0.83, 95% CI 0.79-0.87) or surfactant administration (aOR 0.88, 95%

CI 0.80-0.98). However, they also separately assessed neonates requiring assisted

ventilation for more than 6 hours and found a positive association between GDM and this

more severe respiratory distress (aOR 1.30, 95% CI 1.21-1.39).[46] Simões[20] also found a

positive association between GDM neonates and respiratory distress syndrome, finding a

nearly twofold increased risk (OR 2.2, 95% CI 1.3-3.7).

6.3.7 Apgar Score of Less than 7 at 5 Minutes

The Apgar score is a well validated assessment tool for summarizing the clinical

status of a neonate after birth.[67] It is conducted at 1 minute and 5 minutes after delivery.

A 5-minute score of less than 7 is considered abnormal. We found neonates born to

mothers with GDM had a trend toward a lower risk of a 5-minute Apgar score < 7

compared to non-GDM neonates (aOR 0.53, 95% CI 0.23-1.23). We were unable to stratify this analysis by possible effect modifiers of pre-pregnancy weight, year of birth and fetal sex due to low numbers but were able to stratify by mode of delivery to examine this possible protective association further. The unadjusted odds ratio for a 5-minute Apgar score < 7 among women who had a Caesarean section was 0.44 (95% CI 0.29-1.72) and for vaginal delivery was 0.35 (95% CI 0.08-1.44), indicating that the possible negative association of GDM and Apgar cannot be explained by mode of delivery.

Other studies have reported a similar decreased risk of low Apgar in the presence of GDM. In a small Australian study, Moses et al.[47] found that the mean Apgar in twin neonates exposed to GDM was 9.2 while in the non-GDM group, it was 8.9 (p <0.05). Luo and colleagues[27] found a 25% lower risk (aRR 0.74, 95% CI 0.58-0.96) in GDM neonates, but their variable was a 5 minute Apgar score < 4. Foeller et al.[46] also used Apgar score < 4 in their study and found a 20% reduced risk (aOR 0.80, 95% CI 0.68-0.94). Simões[20], Poulain[49] and Tward[51] all reported non-significant differences in the percentages of low Apgar scores between infants born to women with GDM and those born to women unaffected by GDM.

6.3.8 Congenital Anomalies

In examining major congenital anomalies, the odds ratio was close to the null indicating no increased risk in the presence of GDM (aOR 1.20, 95% CI 0.56-2.60). We were unable to assess the impact of the potential effect of pre-pregnancy weight or fetal sex due to low numbers. When stratified by year of birth, the earlier stratum (1988-2002) showed a slightly stronger association than in the later years (1.28, 95% CI 0.44-3.77 vs. 1.16, 95% CI 0.40-3.37). One hypothesis for this finding is that women a higher

proportion of women in the earlier epoch diagnosed with GDM could have, in fact, been affected Type 2 diabetes that had not previously been diagnosed. In women with pre-existing diabetes, the risk of congenital anomalies is much higher as maternal hyperglycemia can lead to increased oxidative stress, epigenetic changes and, therefore, increased rates of fetal growth anomalies, neural tube defects, and other anomalies.[68] These adverse outcomes are not as commonly observed in GDM, as its onset is later in the second trimester, after which time the development of most anomalies has been completed.

In contrast to the present study, Foeller et al.[46] and Luo et al.[27] both found about 1.5 fold increased risk of congenital anomalies associated with GDM (aOR 1.71, 95% CI 1.09-1.82 and aRR 1.52, 95% CI 1.39-1.66), in larger cohorts than our present study.

6.3.9 Neonatal Length of Stay Greater than 10 Days

In the present study, the GDM-exposed neonates had an estimated 10% decreased odds of hospital stay as compared to the neonates who were not exposed (aOR 0.87, 95% CI 0.54-1.41). In the stratified analysis, this appears to be more driven by the lower pre-pregnancy weight stratum (aOR 0.61, 95% CI 0.29-1.32, aOR 1.15, 95% CI 0.57-2.32) and by the later epoch (aOR 0.71, 95% CI 0.35-1.41). No other studies examined this outcome and it would need to be confirmed in future studies with adequate sample size and statistical power.

6.4 Strengths and Limitations

6.3.10 Strengths

The strengths of this study include the use of the NSAPD as the data source. As described, the NSAPD is a large, highly comprehensive and quality database that is continuously checked and maintained to be reliable and complete. It is a clinical database and therefore, the variables are designed, defined and coded to be used for research and not only administrative purposes. It provided population-based information from all residents of Nova Scotia, including both rural and urban areas, as well as allowing many important maternal and neonatal variables to be assessed. Generalized estimating equations were used to account for the non-independence of twins, strengthening our results by allowing us to provide valid estimates of the association between GDM and neonatal outcomes at the baby-level as opposed to the maternal level, while accounting for the correlation between twin pairs. Unlike previous studies on the impact of GDM on twin pregnancies, we not only assessed the impact of confounding variables in our logistic regression model, but we also examined potential biologically plausible effect modifiers in further analyses. In order to have the largest possible dataset, the study examined pregnancies over a long period of time (1988-2013). Although changes in obstetric practice over the years would be expected, interaction terms between GDM and year of birth did not indicate effect modification. Additionally, we were able to examine the outcomes of antepartum length of stay greater than 48 hours, NICU admission greater than 10 days, and mode of delivery not only as vaginal versus Caesarean section, but also as spontaneous versus planned. These outcomes have not been previously reported on in previous studies, even though they are clinically relevant.

6.3.11 Limitations

Despite the strengths of the project, there are also some limitations that need to be mentioned. Firstly, although the NSAPD is very complete, some variables have missing values or were introduced later, such as height, as it was not added as a variable until 2003. For this reason, pre-pregnancy weight was used. Also, the database does not contain lab values, and therefore, GDM is a yes/no diagnosis. Because of this, we were unable to assess glucose intolerance of pregnancy or the degree of glycemia, nor were we able to assess glycemic control during pregnancy. Additionally, information on diabetes management (i.e., referral to and/or attendance at a diabetes management centre) was not available. However, women in all areas of Nova Scotia have access to a diabetes management centre and referral for counseling is standard of care. Because we were not able to assess the increased monitoring and care provided to women with GDM, we could not rule out this additional care as impacting outcomes due to ascertainment bias. However, because women pregnant with twins already receive additional care and surveillance, this impact is likely small. Small cell sizes in some analysis did not allow for concrete interpretation or reporting. Lastly, because Nova Scotia is a fairly homogeneous province, there is little representation of ethnic minority groups. Given that minority groups are at a higher risk of GDM, there is the possibility that the results of this study would not be generalizable to other populations.

6.4 Conclusion

Although the present study did not have many statistically significant findings, often being limited by low numbers and imprecise estimates, the results contribute to the current body of knowledge of the outcomes of GDM in twin pregnancies. The

statistically significant findings included the maternal outcome of spontaneous preterm delivery having a lower odds in the group of mothers with GDM, and the neonatal outcome of hypoglycemia having a greater odds in neonates exposed to GDM. Both of these findings add to existing literature as these outcomes, to our knowledge, have been included in only a few prior studies. The other outcomes that did not reach statistical significance still have clinical relevance and may contribute when evidence is pooled across studies. The odds ratios found in this research project were mostly similar to odds ratios found for the same outcomes in larger studies. It is possible that some of our results are due to chance, but given the similarities to prior studies, do show trends of clinical value. The null results demonstrate the need for further future research.

6.5 Future Directions

While this study showed a trend toward some adverse outcomes as well as suggestions of some protective factors, numbers were too low to allow for concrete interpretation. Future, larger studies should be undertaken to examine this topic further. The present study identified trends toward increased incidence of hypertensive conditions of pregnancy, hypoglycemia, birthweight discordance, and large for gestational age, which are outcomes that in previous studies on GDM in singleton pregnancies, have shown to be influenced by glycemic control.[3] Future research should consider data linkages with laboratory values if available, or a large, multicentre prospective cohort following women pregnant with twins, with and without a diagnosis of GDM, to enable the collection of data on outcome measures as well as blood sugar values throughout pregnancy.

6.6 Implications

This research project has provided further knowledge of GDM outcomes in women pregnant with twins. Our findings, while most were not statistically significant, when added to existing literature, suggest that women pregnant with twins and GDM do have greater odds of adverse outcomes and, therefore, would benefit from increased prenatal care. The combined risks of twins and GDM should be carefully considered by healthcare providers when planning maternal and neonatal care for this population group.

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