RATES AND DETERMINANTS OF PRETERM BIRTH IN PREGNANCIES COMPLICATED BY DIABETES MELLITUS

by

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Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
July 2014

DEDICATION

To my Family – always believe in the impossible.

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Abstract

This population-based retrospective cohort study involving all singleton births between 1988 and 2009 in Nova Scotia estimated the rate of preterm birth less than 37 weeks and less than 34 weeks among pregnancies complicated by pre-gestational and gestational diabetes mellitus using the Nova Scotia Atlee Perinatal Database (NSAPD). The highest risk of preterm birth less than 37 weeks occurred in women with pre-gestational diabetes (22.0%) compared with gestational diabetes (8.1%) and non-diabetics (4.9%). After adjusting for potential confounders, there was a four-fold increased risk of preterm birth less than 37 weeks in pregnancies complicated by pre-gestational diabetes mellitus compared with non-diabetics (adjusted relative risk [aRR] 4.00, 95% confidence interval [CI] 3.19-5.02) and a nearly two-fold increased risk among women with gestational diabetes (aRR 1.63, 95% CI 1.43-1.85) compared with non-diabetics. Using multivariate regression analysis, determinants of preterm birth among pregnancies complicated by diabetes were identified.

List of Abbreviations and Symbols Used

<	Less than
≤	Less than or equal to
>	Greater than
≥	Greater than or equal to
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
BMI	Body mass index
CDA	Canadian Diabetes Association
CI	Confidence interval
cRR	Crude relative risk
DM	Diabetes Mellitus
g	Gram(s)
GA	Gestational age
GDM	Gestational diabetes mellitus
GH	Gestational hypertension
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA_{1C}	Glycosylated hemoglobin A_1 concentration
HELLP	Hemolysis, elevated liver enzymes, low platelets
Hr	Hour(s)
IADPSG	International Association of Diabetes and Pregnancy Study Group
ICD	International Classification of Diseases
IUGR	Intra-uterine growth restriction
IWK	IWK Health Centre in Halifax, Canada
LNMP	Last normal menstrual period
mmol/L	Millimoles per liter
N	Quantity
N/A	Not applicable
NDDG	National Diabetes Data Group

NSAPD	Nova Scotia Atlee Perinatal Database
OR	Odds ratio
P	P-value
PGDM	Pre-gestational diabetes mellitus
PTB	Preterm birth
RCP	Reproductive Care Program of Nova Scotia
RR	Relative risk
SA	Spontaneous abortion
SGA	Small for gestational age
SOGC	Society of Obstetricians and Gynaecologists of Canada
uRR	Unadjusted relative risk
WHO	World Health Organization
wks	Weeks
Wt(s)	Weight(s)

Acknowledgements

Completion of this thesis would not be possible without the love and support of numerous individuals to whom I am eternally grateful.

First, I would like to thank Dr. Linda Dodds for your patience and understanding with this research project. I was lucky to have you as an advisor.

To my committee members, Dr. B. Anthony Armson, Dr. Victoria Allen, and Dr. K.S. Joseph, thank you for the time you invested in reviewing this document, editing, and offering crucial suggestions.

I would like to thank the Reproductive Care Program for accepting my research request and for supplying the data. I was blessed to have access to the highest quality of clinical data that exists in the country.

Thank you to Dr. Colleen O'Connell and Deshayne Fell for retrieving the data set and for my training in SAS. Thanks to Dr. Colleen O'Connell and John Fahey for responding to my numerous email requests and questions.

I wish to acknowledge the Department of Community Health and Epidemiology and its professors for creating in me a love and passion for preventive medicine. It's hard to believe that it first began as two courses to fulfill my Maternal Fetal Medicine specialization. I also greatly appreciate the permission I received to allow my two week old son to attend classes with me so that I could complete my course work in a timely fashion. As well, Tina Bowdridge, you were essential in keeping me on track.

My babies, Pixel, Linux, Sirai, Kincaid, and Mika, thank you for stepping around my papers scattered around the living room floor and for understanding when I couldn't play every time you wanted. I did this for you. I believe that you will surpass anything that I have accomplished.

And lastly, to Carl Heller, the love of my life, you have been a constant throughout this graduate process. Thank you for your daily reminder to "just get it done" and for your support as I worked late into the night. I hope I can provide you an equal amount of support as you proceed down the path of higher education.

Chapter 1 Introduction

1.1 Definition and Characteristics of Diabetes Mellitus

Diabetes mellitus (DM) is a "clinical syndrome characterized by an absolute or relative deficiency of insulin action in responsive organs, thereby exposing all tissues to chronic hyperglycemia".[1] Diabetes mellitus is one of the most common diseases affecting pregnancies. It represents a heterogeneous disorder with regards to severity, etiology, and duration. During pregnancy, there are two major forms of diabetes mellitus: pre-gestational and gestational. Pre-gestational diabetes can be further subcategorized into type 1 and type 2 diabetes mellitus.

Type 1 diabetes mellitus is a disease characterized by an "absolute deficiency of insulin".[2] Immune-mediated, juvenile, type I, and insulin-dependent diabetes are other terms used to describe type 1 diabetes. It is an autoimmune disorder that develops in genetically predisposed individuals following an environmental trigger. Depending on the age of onset, there may be sudden or gradual loss of beta cells which are found in the pancreas. The disease is characterized by the abrupt onset of clinical symptoms such as polydipsia, polyuria, polyphagia, and weight loss. Exogeneous insulin is essential for survival. Incorrect management of type 1 diabetes resulting in hyperglycemia may lead to ketoacidosis, coma, and death. Prolonged, uncontrolled hyperglycemia eventually leads to malfunction and failure of target organs (for example, eyes, vasculature, nervous system, heart, and kidneys).[3]

Type 2 diabetes mellitus is known as "disorder of insulin resistance".[2] It is also known as late-onset, non-immune mediated, non-insulin dependent, type II, and adult-

onset diabetes. Historically, the majority of individuals (80%) with type 2 diabetes were older than age 40.[2] However, a rise in the prevalence of obesity has resulted in a parallel rise in this form of diabetes in younger populations.[2] Ketoacidosis rarely occurs in this form of diabetes. However, with the increase resistance to insulin during pregnancy, introduction of insulin may be required to prevent hyperglycemia.

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy".[4] Gestational diabetes may be managed by either diet or hypoglycemic agent, such as insulin. Its prevalence varies based on diagnostic criteria and race/ethnicity. In the United States, the prevalence of gestational diabetes is between 1.1% and 14.3%.[5] In Canada, its prevalence is as low as 3.8% among Caucasians[6] and as high as 11.5% percent among First Nations Canadian women.[7] There are implications for both the infant and the mother in pregnancies complicated by gestational diabetes. Pregnancies complicated by gestational diabetes are at high risk of a macrosomic fetus and its possible association with shoulder dystocia and operative delivery.[8] Women diagnosed with gestational diabetes have a 40% risk of developing type 2 diabetes mellitus in the following 20 years after delivery.[9]

1.2 Classification of Diabetes Mellitus

A uniform classification system for diabetes mellitus does not exist. Consequently, several classification systems are encountered in the epidemiologic and clinical literature. Some methods of classification are not commonly encountered and are mentioned here for historical reasons.

One classification system that has been widely applied to pregnant women with diabetes mellitus is the White classification. In 1965, Pricilla White developed a classification system for diabetes in pregnancy based on the age of onset of disease, its duration, and related complications. The White classification was established to prognosticate on pregnancy outcome. The classes ranged from A (least severe) to F (most severe).[10] The original grouping was constructed to classify pre-existing diabetes. Since then, the classification has undergone several significant modifications. It was modified in 1971 and again in 1991. Gestational diabetes is now included in Class A, which is sub-divided into pregnancies managed by diet-only and those requiring treatment with insulin.

In 1965, Pederson published a 'prognostically bad signs of pregnancy' classification. Pederson disagreed with White, believing that perinatal mortality was most associated with duration of diabetes. Pederson identified four signs which were associated with a poor perinatal outcome, including pyelonephritis, precoma, severe acidosis, and neglect of disease.[11]

Diabetes may also be classified based on etiopathogenicity. According to this classification system, there are four categories[12]:

- Type 1
- Type 2
- Other specified types (caused by medical disorders or drugs)
- Gestational diabetes

This classification does not provide prognostic value, but it is a simplified method that is often applied to research studies.

Because type 1 and type 2 diabetes mellitus are often diagnosed prior to pregnancy, they are often categorized together as pre-gestational or pre-existing diabetes mellitus.

International Classification of Diseases (ICD)-10 can also be used to classify diabetes mellitus.[13] Under this system, diabetes initially diagnosed in pregnancy (gestational) receives a 024.8 code. Codes 024.5-024.7 are used to classify pre-gestational diabetes mellitus.

The comparison of studies evaluating obstetrical and perinatal outcomes is limited by differences in definitions and diagnosis of diabetes. This is an important detail to consider when reviewing the literature about diabetes in pregnancy.

1.3 Diagnostic Criteria for Gestational Diabetes

O'Sullivan and Mahan were the first to realize the importance of diagnosing gestational diabetes. In 1964, they developed a set of criteria based on the analysis of whole blood from 752 consecutive pregnancies, which was validated against the risk of women developing type 2 diabetes seven years after having had a pregnancy complicated by gestational diabetes.[14] Because the original criteria were based on whole blood, while samples taken from patients currently are processed on venous or plasma samples, the criteria cut-offs have been adjusted to take this difference into consideration.[12] Both the America Diabetes Association (ADA) and the National Diabetes Data Group (NDDG) adopted this set of criteria. Coustan subsequently developed a new set of standards to adjust for analysis procedures.[12] Coustan's criteria form the basis of the American College of Obstetricians and Gynecologists (ACOG) guidelines (Table 1.1).

Selective screening versus universal testing is another issue of debate. In Canada, according to the Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines on gestational diabetes, health care providers may offer screening to women who have risk factors for the disease. The risk factors identified by the SOGC include maternal conditions (obesity or advanced maternal age), past obstetrical history (previous history of gestational diabetes or glucose intolerance; previous macrosomia >4000 g, previous unexplained stillbirth, previous unexplained neonatal hypoglycemia, hypocalcemia, or hyperbilirubinemia), family history (a family history of diabetes), and current obstetrical complications (suspected macrosomia, hydramnios, or repeated glycosuria in pregnancy).[8] However, such an approach may miss nearly 50% of women with the condition.[8] Therefore, the predominant practice has been to offer universal screening.[8]

Prior to the 2013 Canadian Diabetes Association Clinical Practice Guidelines, in Nova Scotia, all women were screened for gestational diabetes mellitus between 24 and 28 weeks gestation.[8] This was a two-phase approach. The initial step was a screening test consisting of a 50-gram glucose load, with plasma glucose concentration measured after 1 hour. A value >10.3 mmol/L is diagnostic of gestational diabetes. A value between 7.8 and 10.3 mmol/L resulted in the need for a diagnostic test. The recommended diagnostic test in Canada was the 75-gram two-hour oral glucose tolerance test.[6] Prior to early 2000s, the glucose tolerance test was 100-grams in Nova Scotia.[15] Table 1.1 lists the diagnostic criteria for gestational diabetes mellitus by various organizations.

The new International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria for diagnosing gestational diabetes mellitus are based on the findings

from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study.[16] The study was a large, multinational endeavor that revealed a continuous relationship between glucose levels and adverse perinatal outcomes. The study determined that it was beneficial to lower the diagnostic threshold for gestational diabetes mellitus.

1.4 Perinatal Morbidity Associated with Diabetes Mellitus

Prior to the discovery of insulin, pregnancies complicated by diabetes had a poor prognosis: high maternal, fetal, and neonatal morbidity and mortality.[1] During the pre-insulin era, the maternal mortality rate was 45% and the perinatal mortality rate was 60-70% in pregnancies complicated by type 1 diabetes.[1] In 1920, De Lee observed that preterm delivery occurred in 33% of diabetic pregnancies.[1] Following the discovery of insulin, there was a rapid reduction in maternal mortality to 2% and perinatal mortality gradually decreased over the decades to less than 5%. There have been significant advances made in the reduction of mortality, but the effect on morbidity, in particular preterm birth, remains unclear.

Diabetes in pregnancy continues to be associated with significant perinatal morbidity.[3,17,18] Complications include preterm birth, congenital anomalies, macrosomia, shoulder dystocia, birth trauma, need for operative vaginal delivery, and respiratory distress. Preterm delivery is one of the most significant complications related to diabetes mellitus. Electrolyte derangements, hyperbilirubinemia, temperature imbalance, and neonatal hypoglycemia are additional complications seen in infants of diabetic mothers.[3,8]

1.5 Preterm Birth: Incidence, Definition, and Classification

Preterm birth (PTB) is defined as delivery prior to 37 completed weeks or 259 days from the first day of the last normal menstrual period.[19] Preterm birth can be subdivided based on gestational age. Late preterm births (34^0 and 36^6 weeks gestation) represent the majority of births occurring prior to 37 weeks gestation.

Preterm birth is one of the most important global public health issues. The burden of disease persists even beyond the immediate peripartum period. Preterm birth is associated with neonatal mortality and morbidity, and long term physical and neurodevelopmental sequelae. Preterm birth is responsible for seventy percent of all neonatal deaths and nearly 50% of all cases of long term neurologic disability.[20,21] Care for the premature infant also results in significant stress upon the family, community and economy.

In 2005, the global incidence worldwide was estimated at 9.6%; with over 85% of preterm births occurring in under developed continents, such as Africa and Asia.[22] In Canada, the incidence was lower, at 7.9% for births occurring in hospital as reported by the Canadian Institute for Health Information for 2010-2011; a rate that has remained stable (8.1%) since 2006-2007.[23] The preterm birth rate in Nova Scotia appeared to peak in 2006 at 8.3%, and has since gradually decreased to 7.2% in 2011.[24]

Even though emerging data suggests that late preterm births are at risk of neonatal deaths and complications, the poorest long-term childhood outcomes and highest infant mortality still tend to occur in infants born before 34 weeks.[25,26]

Numerous studies have explored the heterogeneous etiology of preterm birth syndrome. [27-29] Based on similarities in etiology, PTB can be further classified as

follows: spontaneous (idiopathic) or medically indicated (iatrogenic).[22] Spontaneous PTB is defined as spontaneous onset of preterm labor, preterm premature rupture of membranes, and/or cervical incompetence resulting in birth prior to 37 completed weeks gestation. Medically indicated or iatrogenic PTB are deliveries that occur following induced labour and/or cesarean section for maternal or fetal indications (e.g., preeclampsia or fetal distress) before 37 weeks. Some researchers divide preterm birth into three categories, with preterm premature rupture of membranes as a separate class.

Data used to measure rates of preterm birth are obtained by different methods, including administrative databases, surveys, and prospective epidemiologic studies. Care must be taken when comparing the rates of preterm birth due to inconsistencies in defining preterm birth. For example, ICD does not have a lower limit for gestational age when collecting information about preterm birth.[30] Other methods use a gestational age and/or weight lower limit (i.e. 20 weeks and/or 500 grams). As well, many First-World nations benefit from improvements in technology, allowing the survival of extremely preterm infants, and re-defining the limits of viability.[30] Bias may be introduced by the re-classification of preterm birth to stillbirth for infants born along the lower limits of extreme prematurity who subsequently succumb to complications related to prematurity.[30] Determination of gestational age can also lead to variation in study rates; for example, the assignment of gestational age based on last normal menstrual period versus ultrasound measurement. Researchers must clearly define gestational age a priori and explain how any discrepancies that may be noted after the infant is born will be handled. These are key issues to consider when reviewing the literature.

1.6 Nova Scotia Atlee Perinatal Database

The province of Nova Scotia has a well-established population-based perinatal database called the Nova Scotia Atlee Perinatal Database (NSAPD). It is administered by the Reproductive Care Program (RCP) of Nova Scotia.[31]

Data was first collected in 1980. Initially, the database collected birth variables solely from deliveries occurring at the IWK Health Centre (i.e. within Halifax County). However, following 1987, the database expanded to include birth information from deliveries occurring in hospitals throughout Nova Scotia. It also includes data for some deliveries to Nova Scotia residents who have given birth outside of the province.

The NSAPD collects information on all births, live or stillborn, with a birth weight of 500 grams or more or a gestational age of 20 weeks or more. The database contains several hundred variables pertaining to maternal and neonatal outcomes, including patient demographics, maternal medical complications, labor and delivery, and neonatal morbidity and mortality. The NSAPD is not an administrative database. To ensure that all births are captured by RCP, they are matched with Nova Scotia's Vital Statistics.[32] The RCP maintains strict confidentiality with regards to information found in the NSAPD. Extraction of information from antenatal and medical charts is conducted by a trained health-information professional using standardized forms. Data extraction is performed at each local health care facility. Collected information is then forwarded to the NSAPD.

Information about births of Nova Scotia residents occurring at non-maternity facilities in New Brunswick is also collected.[24] Only after the approval of home births by midwives in 2009 has data from these births been included.[24]

Gestational age is determined by an algorithm that integrates the following three variables[24]:

- Last normal menstrual period (LNMP)
- First or second trimester ultrasound measurements (prior to 25 weeks gestation)
- Newborn physical examination

Gestational age is predominantly calculated by LNMP. If a discrepancy between LNMP and ultrasound occurs or if LNMP is unknown, then gestational age is reassigned by early ultrasound estimation. In the event that LNMP is discordant with infant physical examination and there is no available early ultrasound estimation, then gestational age is based on clinical newborn assessment.

Even though the variables collected are quite extensive, it is not an exhaustive list. As well, the NSAPD is not a static database; new indicators for collection are regularly assessed for inclusion. For example, collection of maternal body mass index data began in 2004.

The quality and reliability of the database are ensured by ongoing quality assurance reviews and periodic re-abstraction studies.[33,34] Continual validation studies ensures reduction in misclassification bias. The NSAPD has been used as the basis of many descriptive and epidemiologic studies, including several studies on gestational and pre-gestational diabetes.[35]

1.7 Thesis Project

As will be demonstrated, previous studies have attempted to explore the association between diabetes and preterm birth, though most were underpowered to

detect an association, or preterm birth was considered a secondary outcome. Using the rich data contained within the NSAPD, this study will examine the rates of preterm birth among pregnancies complicated by diabetes and will determine the risk factors associated with preterm birth.

Table 1.1 Diagnosis of gestational diabetes mellitus by organization.

Name of Organization	FPG (mmol/L)	Oral Glucose Tolerance Test (g)	1 hr Plasma Glucose (mmol/L)	2 hr Plasma Glucose (mmol/L)	3 hr Plasma Glucose (mmol/L)	Number of Abnormal Values Required for Diagnosis
CDA (1998)	≥ 5.3	75g	≥ 10.6	≥ 8.9	N/A	≥ 2
ADA* (1998)	≥ 5.8	100g	≥ 10.6	≥ 9.2	≥ 8.0	≥ 2
WHO (1999)	≥ 7.0	75 g	N/A	≥ 7.8	N/A	1
ACOG (2001)	≥ 5.3	100 g	≥ 10.0	≥ 8.6	≥ 7.8	≥ 2
IADPSG (2010)	≥ 5.1	75 g	≥ 10.0	≥ 8.5	N/A	1
CDA (2013)	≥ 5.3	75 g	≥ 10.6	≥ 9.0	N/A	1

Source: Coustan[12], SOGC[8], IADPSG[36], CDA[37]

*Used by Joslin Center

Chapter 2 Literature Review

2.1 Pre-gestational Diabetes Mellitus and Preterm Birth

2.1.1 Type 1 Diabetes Mellitus and Preterm Birth

Diverse classifications used in studying diabetes mellitus in pregnancy makes it difficult to effectively compare studies. The majority of publications exploring the relationship between pre-existing diabetes mellitus and preterm birth have focused on type 1 diabetes mellitus (Table 2.1). According to the literature, the incidence of preterm birth ranges from 9.6% to 45.6% among pregnancies complicated by type 1 diabetes mellitus in the absence of overt renal disease. [38-48] One of the largest studies examining this group of interest was conducted by Eidem.[46] Using linkage from the Medical Birth Registry of Norway and the Norwegian Childhood Diabetes Registry, Eidem identified 1307 pregnancies complicated by type 1 diabetes mellitus compared with 1 161 099 non-diabetic pregnancies. There was a statistically significant higher rate of preterm birth less than 37 weeks among type 1 diabetic pregnancies compared with non-diabetics (crude odds ratio [OR] 4.9, 95% confidence interval [CI] 4.3-5.5).[46] Even after controlling for parity, maternal age, year of delivery, sex of child, maternal educational level, European and other origin, and marital status, the preterm birth rate remained elevated (adjusted odds ratio [aOR] 5.0, 95% CI 4.4-5.7).[46]

2.1.2 Type 2 Diabetes Mellitus and Preterm Birth

According to the literature, the risk of preterm birth among pregnancies complicated by type 2 diabetes mellitus ranges from 3.7% to 27.3% [39,45,48,49] (shown in Table 2.1). Most studies directly comparing pre-gestational diabetes based on subtype suggest that the preterm birth rate does not differ between either group. The largest study was conducted by Zhu et al. in Japan and included 482 deliveries complicated by pre-gestational diabetes mellitus, of which 57.8% were type 2 diabetics.[39] There was no significant difference in preterm birth rate between women with type 1 and type 2 diabetes mellitus (18.5% vs 15.6%, $p>0.05$). However, a prospective cohort study originating from East Anglia noted a significant difference in the risk of preterm birth less than 37 weeks between type 1 and type 2 diabetes (37.1% vs 17.5%, $p<0.001$).[47] This difference in risk for preterm birth between the two groups was no longer significant at less than 34 weeks (3.7% vs 7.1%, $p=0.1$). The authors hypothesized that the lower risk of preterm birth less than 37 weeks among pregnancies with type 2 diabetes mellitus was likely due to better glycemic control.

2.2 Diabetic Complications in Pre-gestational Diabetic Pregnancies and Risk of Preterm Birth

Many researchers have evaluated the significance of diabetic-specific complications on the risk of preterm birth. Over a ten-year period, Reece identified 288 pregnancies complicated with type 1 diabetes, of whom, 103 women had microvascular disease (classified as White class D).[40] The preterm birth rate was not statistically different between type 1 diabetics with microvascular disease and those without

microvascular disease (18.4% vs 13%, p>0.05). Rosenn also studied the presence of microvascular disease (defined as presence of proliferative retinopathy or proteinuria > 500 mg/24 h) among women with insulin-dependent diabetes.[38] The author observed a statistically significantly higher risk of preterm birth at less than 34 weeks among women with microvascular disease compared with women without microvascular disease (18% vs 8%, p=0.04); no difference in preterm birth less than 37 weeks' gestation was seen between insulin-dependent diabetic women with or without microvascular disease (37% vs 29%, p=NS).[38] Ekbom noted a positive association between rising urinary albumin levels and risk of preterm delivery.[42] The risk of preterm birth rose to 91% in women with urinary albumin excretion levels >300 mg/24 h.[42] Care must be taken when comparing studies as definitions of diabetic-related complications, such as overt nephropathy, are not standardized.

2.3 Pre-gestational Diabetes Mellitus and Preterm Birth Subtype

Because of its heterogeneity, it is important to study preterm birth based on its subtypes. Most study findings suggest that the preponderance of preterm delivery less than 37 weeks is secondary to medical and obstetrical indications. However, in Rosenn's study population, spontaneous preterm birth was the most common subtype for preterm delivery, representing 54% of preterm births less than 37 weeks and 63% less than 34 weeks.[38] Rosenn found that preeclampsia and fetal distress were the most common indications for induced preterm birth.[38] The factors resulting in spontaneous and indicated preterm births among pregnancies complicated by diabetes require further investigation.

2.4 Determinants of Preterm Birth in Pre-gestational Diabetes

Determining risk factors leading to preterm birth is pertinent to optimally monitor and care for pregnant women with diabetes. There is a paucity of studies examining the determinants of preterm delivery in pregnancies complicated by pre-gestational diabetes mellitus. On multivariate analysis, Zhu determined that the following conditions were significant factors for preterm birth among 482 pregnancies complicated by pre-gestational diabetes: nephropathy, severe pre-eclampsia, intra-uterine growth restriction, and fetal distress.[39] Nephropathy was most significantly associated with preterm birth ($p=0.0015$). This is an important area of study that requires further investigation.

2.5 Gestational Diabetes Mellitus and Preterm Birth

Numerous studies have attempted to analyze the impact of gestational diabetes on the preterm birth rate (Table 2.2). Published papers that have been reviewed suggest that the incidence of preterm birth is between 3.7% and 17.4% among women with gestational diabetes mellitus.[50-63] However, reports are inconsistent regarding the difference in the preterm birth rate of gestational diabetes compared with non-diabetes. It is important to keep in mind that the risk of preterm birth in gestational diabetes pregnancies differs based on criteria, method of screening, and race/ethnicity of study population.

For example, a cohort study comprised of 90 gestational diabetic women from Uganda revealed an unusually low incidence of preterm birth (3.7%).[54] There were no preterm births noted among the non-diabetic comparison group during the study period.

A larger Turkish study examined the association between GDM and the incidence of PTB.[51] It included 128 women with GDM and 138 non-diabetic women. Both groups were matched on the following factors: age, parity, and pre-pregnancy body mass index (BMI). The PTB rate was significantly higher in the GDM group than in the non-diabetic group (15.6% vs 5.8%, p=0.009). Five of the 20 preterm deliveries in the GDM group were induced for preterm premature rupture of membranes compared with two of the six in the control group.

A small prospective study was conducted in Iran by Keshavarz to determine the incidence and perinatal outcomes in women with gestational diabetes.[55] All pregnant women who attended the urban centre for antenatal care between December 1999 and January 2001 were offered universal screening (using Carpenter and Coustan criteria). Sixty-three of 1310 singleton pregnancies (4.8%) were diagnosed with gestational diabetes.[55] The risk of preterm birth among pregnancies complicated by GDM compared with non-diabetic pregnancies was 6.5% and 4.3%, respectively, OR 1.6, 95% CI 0.5-4.4.

Xiong et al. conducted a population based study to determine the impact of GDM on the PTB rate.[52] The prevalence of GDM in northern and central Alberta averaged 2.5%, ranging from 2.2% and 2.8%, between 1991 and 1997. The PTB rate remained significantly higher in the GDM compared to the non-GDM group (10.4% vs 7.5%, $p<0.01$), even after adjusting for certain maternal characteristics (unadjusted OR 1.42, 95% CI 1.26-1.61; adjusted OR 1.13, 95% CI, 1.08-1.18).[52] Unfortunately, the researchers examined the overall prematurity rate in their population, and did not classify preterm delivery into indicated and spontaneous.

Fadl and associates conducted a large population based study using the Swedish Medical Birth Registry study to determine the maternal, perinatal, and neonatal outcomes of women with gestational diabetes compared with non-gestational diabetic women.[56] Between 1997 and 2003, there were 10 535 women with GDM compared with 1 249 772 non-GDM women. The incidence of preterm birth less than 37 weeks in GDM group compared with non-GDM group was 8.6% versus 5.0%. The authors noted a statistically significant risk of preterm birth less than 37 weeks among the study population (OR 1.78, 95% CI 1.66-1.90, $p<0.001$). The risk remained significant even after adjusting for maternal age, body mass index, parity, chronic hypertensive disorder, smoking habits, and ethnicity (OR 1.71, 95% CI 1.58-1.86, $p<0.001$).

Though many studies have been conducted, there are still gaps regarding the association between gestational diabetes and preterm birth. Many studies were small and inconsistencies in rates remain, though the two largest population-based studies did suggest an association between gestational diabetes and preterm birth. There are no well-designed studies addressing the possible cause for preterm labour (spontaneous versus medically indicated) in this group of diabetics.

2.6 Comparing Diabetes Mellitus by Subtype and Preterm Birth

Several international studies have compared the rates of preterm birth between pre-existing diabetes and gestational diabetes[64-69] (Table 2.3). Many of the researchers were able to separate pre-gestational diabetics into either type 1 or type 2 diabetes mellitus, or to provide an exact percentage of women in either sub-group. Preterm birth was not the primary objective of these studies, but was one of several maternal and

perinatal outcomes that were assessed. The studies were small, with the exception of the ones conducted in Australia[69] and Ontario[68]. All, except the smallest study by Sobande[66], found that the highest risk of preterm birth was associated with pregnancies complicated by type 1 diabetes. Interestingly, there were no preterm births that occurred in pregnancies complicated by type 1 diabetes mellitus in Sobande's study. The Ontario study revealed a statistically significant increased risk of preterm birth among gestational diabetic pregnancies (OR 1.43, 95% CI 1.27-1.61) that held true even after adjusting for potential confounders (aOR 1.41, 95% CI 1.24-1.60, $p<0.01$).[68] It is difficult to make a direct comparison in the findings from the Australian paper since it provided odds ratios for individually grouped gestational ages (20-27, 28-31, 32-36, and ≥37 weeks), rather than defining preterm birth as less than 37 weeks.[69]

None of the researchers examined potential determinants of preterm birth in the diabetic groups.

2.7 Proposed Mechanisms of Preterm Birth in Diabetes Mellitus

Several theories as to possible underlying pathophysiology of spontaneous preterm delivery among diabetic pregnancies have been proposed. These include genetic predisposition, biological/psychological stressors in the mother and/or fetus, inflammatory or infectious processes (e.g., urinary tract infections), and mechanical influences (e.g., hydramnios).[70] Suboptimal glycemic control may trigger the activation of parturition.[71] Another study suggests that the increased levels in prostaglandin-like material in platelets in diabetics may result in spontaneous PTB.[72] Yet another study suggests that diabetics are genetically more susceptible to PTB.[73] Unfortunately, to date,

the exact mechanism responsible for spontaneous PTB in this population has yet to be defined.

2.8 Infant Sex and Preterm Birth

The association between sex and pregnancy-related health outcomes has always been an area of interest in Maternal Fetal Medicine. Recent studies have suggested that sex differences may also affect preterm birth. Using population-based data from the Medical Birth Registry of Norway, Vatten et al[74] studied 1 691 053 singleton births (representing 92.8% of all births in the country) between 1967 and 1998. The researchers were able to demonstrate a higher frequency of male births compared with female births occurring before gestational week 37. The male:female ratio ranged from 1.28-1.32:1.00 for births occurring between 25 and 36 completed gestational weeks. At term, the ratio at birth approached 1.00 (from 40-42 weeks). The authors concluded that male sex was associated with a higher risk of preterm birth.

Data exploring the relationship between male sex and preterm birth among pregnancies complicated by diabetes is sparse. Evers and associates noted a higher incidence of preterm birth among male infants (39.5% versus 28.7%, p=0.04) in 324 pregnancies complicated by type 1 diabetes mellitus.[75]

Garcia-Patterson conducted a retrospective cohort study of pregnancies complicated by pre-gestational diabetes proceeding beyond 22 weeks.[76] The group observed a higher frequency of preterm birth among male fetuses versus female fetuses (23.8% versus 20.9%), though the observed difference was not statistically different. They also studied the composite perinatal outcome (which included preterm birth, birth

weight <10th percentile, birth weight >90th percentile, major congenital malformation, and perinatal mortality) which revealed a statistically significant difference between males and females (56.2% and 46.4%, respectively, $p<0.05$).

Few studies have explored the relationship between fetal sex and preterm birth in pregnancies complicated by gestational diabetes. Following adjustment, Tundidor's study did not reveal an association between male fetuses and preterm birth (1.02, 95% CI 0.73-1.42, $p>0.5$).[77]

2.9 Conclusion

Relevant literature supports an increased risk for preterm birth in pregnancies complicated by pre-gestational diabetes, especially type 1 diabetes mellitus. The risk of preterm birth appears to be strongly associated to diabetic complications such as nephropathy. Some researchers suggest an increased incidence in prematurity in pregnancies complicated by gestational diabetes, a finding which may be confounded by other risk factors for prematurity. Many studies do not differentiate between the subtypes of preterm birth (spontaneous versus indicated) when exploring pre-gestational and gestational diabetes mellitus. As well, there is a scarcity of literature exploring the determinants of preterm birth in pregnancies complicated by diabetes.

Table 2.1 Summary of publications examining the association between preterm birth and pre-gestational (type 1 and type 2) diabetes mellitus.

Author	Study Type	Study Period and Location	Subjects	Outcome of Interest	Results
Rosenn[38] (1993)	Retrospective	1978-1992 United States	IDDM n=254 Non-DM n=508	< 37 and <34 wks	IDDM 29.9% (54% SPTB) (<37 wks) 9.4% (63%) (<34 wks) Non-DM 12% (<37 wks) 5.3% (<34 wks)
Zhu[39] (1997)	Retrospective	1984-1996 Japan	PGDM n=482:IDDM n=178;NIDDM n=244	Preterm delivery*	IDDM n=33 (18.5%) NIDDM n=38 (15.6%) p=NS
Reece[39] (1998)	Retrospective cohort	1980-1990 United States	Type 1 DM n=288: 103 microvascular disease, 185 no microvascular Non-DM n=150	Preterm birth <37 wks	Microvascular 18.4% No microvascular 13% p>0.05 Non-DM 6.7% p<0.05
Guntun[41] (2000)	Retrospective	1998-2001 Australia	PGDM n=74:Type 1 n=53, Type 2 n=12	<37 wks	Type 1 n=5(9.6%) Type 2 n=3 (27.3%)
Ekbom[42] (2001)	Prospective cohort	1996-2000 Denmark	Type 1 DM n=240: no microalbunimeria n=203; microalbumineria n=26, overt diabetic nephropathy n=11	<37 wks and <34 wks	No microalbunimeria 35% Microalbumineria 62% Overt diabetic nephropathy 91% p<0.001
Wylie[43] (2002)	Retrospective	1989-1999 Canada	Type 1 DM n=300 Non-diabetic n= 71 636	Preterm delivery <37 wks	45.6% vs 12% RR 3.81 (95% CI 3.34-4.34)
Evers[44] (2004)	Prospective cohort	1999-2000 Netherlands	Type 1 DM n=323 Control n=196 981	Delivery < 37 wks	Pre-gestational 32.2% (95% CI 27.0-37.4) SPTB 11.8% IPTB 20.4% Control 7.1% RR 4.5 (95% CI 3.8-5.3)
Jensen[45] (2004)	Prospective	1993-1999 Denmark	Type 1 DM n=1215 Non-diabetic n=70 089	Preterm delivery <37 wks	Type 1 DM n=507 (41.7%) Non-diabetic n=4205 (6.0%) RR 7.0 (95% CI 6.3-7.6)

Author	Study Type	Study Period and Location	Subjects	Outcome of Interest	Results
Eidem[46] (2011)	Retrospective	1985-2004 Norway	Type 1 DM n=1307 Non-DM 1 n=161 092	Delivery before 37 and 32 weeks	Type 1 DM 26.4%(<37 wks) 3.4% (<32 wks) Non-DM 6.8% (<37 wks) 1.4% (<32 wks) OR 4.9, 95% CI 4.3-5.5 aOR 5.0, 95% CI 4.4-5.7 (<37 wks) OR 2.5, 95% CI 1.8-3.4 aOR 2.6, 95% CI 1.9-3.5 (<32 wks)
Murphy[47] (2011)	Prospective cohort	2006-2009 United Kingdom	Type 1 n=408 Type 2 n=274	Preterm birth <37 wks	Type 1 n=120 (37.1%) Type 2 n=38 (17.5%) p<0.0001
				Early preterm birth <34 wks	Type 1 n=23 (7.1%) Type 2 n=8 (3.7%) p=0.1
Knight[48] (2012)	Retrospective cohort	2000-2006 United States	Type 2 DM n=64 Type 1 DM n=64 Control n=256	<37 wks	Type 2 DM n=12 (18%) Type 1 DM n=21 (32.8%) p=NS (Type 1 vs 2) Control 15 (5.9%) p<0.00001 (all grps)
Von Kries[78] (1997)	Retrospective	1988-1993 Germany	Pre-gestational n=2339 Non-diabetic n=585 437	Prematurity <37 wks	Pre-gestational n=493 (21.08%) Non-diabetic n=46 285 (7.91%) RR 2.67, 95% CI 2.46-2.89
Sibai[79] (2000)	Retrospective	1991-1995 (pre-gestational) 1992-1994 (non-diabetic) United States	Pre-gestational n=461 Non-diabetic n=2738	Delivery < 37 wks and < 35 wks Spontaneous and Indicated PTB <37 wks and <35 wks	Pre-gestational n=175 or 38% (<37 wks) n= 75 or 16.3% (<35 wks) Non-DM n=380 or 13.9% (<37 wks) n=167 or 6.1% (<35 wks) OR 2.7 (95% CI 2.3-3.5) - <37 wks OR 2.7 (95% CI 2.1-3.4) -<35 wks OR 1.6 (95% CI 1.2-2.2) - SPTB <37 wks OR 8.1 (95% CI 6.0-10.9) - IPTB <37 wks OR 2.1 (95% CI 1.4-3.0) - SPTB <35 wks OR 4.8 (95% CI 3.0-7.5) - IPTB <35 wks
Wahabi[49] (2012)	Retrospective cohort	2008 Saudi Arabia	PGD n=116: Type 1 n=66, Type 2 n=50 Non-DM n=2472	<37 wks	PGD n=21 (18.1%) Non-DM n=222 (9%) OR 2.24 (95% CI 1.37-3.67) p=0.003
Yanit[80] (2012)	Retrospective cohort	2006 United States	PGDM n=3718 Controls n=522 377	Overall <32 wks	PGDM 19.4%

* Exact gestational age not provided in article.

Table 2.2 Summary of publications examining the association between preterm birth and gestational diabetes mellitus.

Author	Study Type	Study Period and Location	Subjects	Outcome of Interest	Results
Bar-Hava[50] (1997)	Retrospective	1990-1994 United States	GDM n=550 Non-DM n=14 552	Preterm delivery <37 wks	GDM n=34 (6.2%) Non-GDM n=948 (6.5%) OR 0.94 (95% CI 0.65-1.36) p=0.82
Sendag[51] (2001)	Retrospective	1995-2000 Turkey	GDM n=128 Non-DM n=138	Preterm birth <37 wks	GDM n=20 (15.6) Non-DM n=8 (5.8) p=0.009
Xiong[52] (2001)	Retrospective cohort	1991-1997 Canada	GDM n=2755 Non-DM n=108 664	Preterm birth <37 wks	GDM 10.4% Non-DM 7.5% OR 1.42 (1.26-1.61) aOR 1.13 (1.08-1.18)[a] p<0.01
Jensen[53] (2004)	Prospective	1993-1999 Denmark	GDM n=143 Non-DM n=143	Preterm delivery <37 wks	GDM n=15 (10.5%) p=0.12 Non-DM n=7 (4.9%)
Odar[54] (2004)	Prospective cohort	2001 Uganda	GDN n=30 Non-DM n=60	Preterm labour*	GDM n=1 (3.7%) Non-DM n=0
Keshavarz[55] (2005)	Prospective cohort	1999-2001 Iran	GDM n=63 Non-DM n=1247	Preterm delivery	GDM n=4 (6.5%) Non-DM n=53 (4.3%) OR 1.6 (95% CI 0.5-4.4) p=NS
Fadl[56] (2010)	Retrospective cohort	1991-2003 Sweden	GDM n=10 525 Non-DM n=1 249 772	Preterm birth <37 wks	GDM 8.6% Non-DM 5.0% OR 1.78 (95% CI 1.66-1.90) aOR 1.71 (95% CI 1.58-1.86)[+] p<0.001
Bener[57] (2011)	Prospective cohort	2010-2011 Qatar	GDM n=262 Non-DM n=1346	Preterm birth*	GDM n=33 (12.6%) p=0.03 Non-DM n=112 (8.3%)
Amarzouki[58] (2012)	Retrospective	2008 Saudi Arabia	GDM n=69 Non-DM n=80	Preterm delivery <37 wks	GDM n=12 (17.4%) Non-DM n=5 (6.3%) OR 3.2 (95% CI 1.1-9.5) p=0.04
Bhat[59] (2012)	Retrospective	2007-2008 India	GDM n=286 Non-DM n=292	Preterm labour*	GDM n=33 (11.6%) Non-DM n=15 (5.4%) OR 2.30 (95% CI 1.24-4.27)

Author	Study Type	Study Period and Location	Subjects	Outcome of Interest	Results
Gasim[60] (2012)	Retrospective	2001-2008 Saudi Arabia	GDM n=220 Non-DM n=220	Preterm delivery*	GDM n=25 (11.4%) p=0.0226 Non-DM n=11 (5.0%) OR 2.44 (95% CI 1.17-5.08) aOR 2.01 (95% CI 1.06-4.86)
Capula[61] (2013)	Retrospective cohort	2010-2012 Italy	GDM n=171 Non-DM n=367	Preterm delivery < 37 wks	GDM n=14 (8.2%) Non-DM n=31 (8.4%) OR 2.43 (95% CI 1.11-5.29) p=0.025 aOR 1.94 (95% CI 0.84-4.48) p=0.118
Nayak[62] (2013)	Prospective cohort	2011-2012 India	GDM n=83 Non-DM n=221	Preterm delivery <37 wks	GDM n=8 (9.6%) p=0.20 Non-DM n=12 (5.4%)
Wahabi[63] (2013)	Retrospective cohort	2010 Saudi Arabia	GDM n=569 Non-DM n=2472	Preterm delivery <37 wks	GDM n=48 (8.5%) Non-DM n=222 (9%) OR 0.94 (95% CI 0.68-1.29) p=0.696

[a]Adjusted for parity, maternal age, maternal weight, maternal smoking, alcohol use, history of neonatal death, history of delivery <37 wks, history of caesarean section, and history of major fetal anomaly.

[+] Adjusted for maternal age, body mass index, parity, chronic hypertensive disorder, smoking habits, and ethnicity.

* Exact gestational age not provided in the article.

Table 2.3 Summary of publications examining the association between preterm birth and diabetes mellitus by subtype.

Author	Study Type	Study Period and Location	Subjects	Outcome of Interest	Results		
El Mallah[64] (1997)	Retrospective cohort	1991-1994 Saudi Arabia	Pre-gestational (n=71) GDM (n=972) Non-DM (n=8904)	<36 weeks	Pre-gestational GDM Non-DM	7.0% 3.6% 0.4%	p=0.001
Ray[65] (2001)	Prospective	1993-1998 Canada	Pre-gestational (n=428) (type 1 74.5% and type 2 24.5%) GDM (n=196	<37 weeks	Pre-gestational GDM OR 3.8 95% CI 2.5-2.9	43.4% 19.2%	
Sobande[66] (2005)	Retrospective cohort	2000-2003 Saudi Arabia	Type 1 (n= 27) Type 2 (n=19) GDM (n= 139)	Preterm delivery*	Type 1 Type 2 GDM	0% 10.5% 2.8%	p=0.123
Diejomoah[67] (2008)	Retrospective cohort	2005 Kuwait	Pre-gestational n=24, IGT n=25, GDM n= 128 Study group (n=177)	Preterm labour*	Study group Controls	4.5% 5.6%	p=0.80
Pettica[68] (2008)	Retrospective cohort	2005-2006 Canada	Type 1 (n=904) Type 2 (n=516) GDM (n= 3188) Control (n=115 996)	<37 weeks	Type 1 Type 2 GDM Control	19.0% (OR 2.69, 95% CI 2.25-3.22) 14.0% (OR 1.70, 95% CI 1.29-2.25) 11.3% (OR 1.43, 95% CI 1.27-1.61) 8.4%	
Shand[69] (2008)	Cross-sectional	1998-2002 Australia	Pre-gestational (n=1248) (of whom 57% type 1, 20% type 2, and 23% unknown) GDM (n=17 128)	32-36 weeks	Pre-gestational GDM Control	16.9% (OR 4.55 95% CI 3.91-5.31) 6.3% (OR 1.47 95% CI 1.38-1.57) 4.4%	

* Exact gestational age not provided in article.

Chapter 3 Research Objectives

3.1 Primary Objectives

The primary goals of this research study were to quantify the association between diabetes and preterm birth and to identify the risk factors predisposing to preterm birth in a cohort of pregnant women who delivered an infant between January 1, 1988 and December 31, 2009 in Nova Scotia. Specifically, this study had three objectives:

1. To determine and compare the rates and relative risks of preterm birth (overall, spontaneous, and indicated) at <37 and <34 weeks' gestation among pre-gestational diabetic, gestational diabetic, compared to non-diabetic women.

2. To determine and compare the rate of preterm birth among non-diabetic, pre-gestational, and gestational diabetic pregnancies during three distinct time intervals: 1988-1994, 1995-2002, and 2003-2009.

3. To identify the risk factors leading to overall, spontaneous, and indicated preterm birth in pregnancies complicated by pre-gestational and gestational diabetes.

3.2 Secondary Objective

As a secondary objective, this study attempted to explore infant sex as a possible effect modifier between diabetes and risk of preterm birth.

- To investigate whether infant sex modifies the effect of pre-gestational and gestational diabetes mellitus on preterm birth (<37 weeks, <34 weeks, spontaneous preterm birth and indicated preterm birth).

Chapter 4 Methodology

4.1 Study Population

Nova Scotia is one of four Atlantic Provinces within Canada. Its population is 940 000 with approximately 9000 births occurring annually in the province.[24] A population-based retrospective cohort study of live singleton births in Nova Scotia between January 1, 1988 and December 31, 2009 (15 years) was undertaken. Subjects were identified using the Nova Scotia Atlee Perinatal Database.

4.2 Exclusion Criteria

Conditions that intrinsically had an increased risk of preterm birth were excluded from this study. These conditions included multiple births, congenital anomalies, and stillbirths. It is universally accepted that multiple pregnancies are predisposed to preterm delivery, with the risk of preterm birth in twin and triplet gestations quoted as 50% and 97%, respectively.[81] Several studies have suggested that pregnancies affected by major congenital anomalies are also more likely to result in preterm delivery (OR 4.5-6.65).[82,83,84] This research was limited to only live births, therefore data about stillbirths was not included. Information about births occurring prior to 20 weeks or less than 500 grams is not collected in the Nova Scotia Atlee Perinatal Database and could not be explored.

4.3 Variables of Interest

Information pertaining to all variables of interest was obtained exclusively from one clinical database, the Nova Scotia Perinatal Atlee Database. Further details describing the Nova Scotia Atlee Perinatal Database can be found in the Introduction section.

4.3.1 Preterm Birth Outcome

Gestational age was the term employed to quantify pregnancy duration. It was defined as the time elapsed since the first day of the last menstrual period.[85] An uncertain or unknown gestational age can also be determined based on first or early second trimester ultrasound dating. In an average term pregnancy, about 40 weeks (280 days) elapse between the first day of the last menstrual period and the birth of the infant.[19] Preterm birth referred to any delivery prior to 37 completed weeks' gestation (less than 259 days), but after 20 weeks' gestation, regardless of birth weight.[11] Preterm births less than 37 weeks and less than 34 weeks were outcomes of interest in this study. In this study, preterm births were further categorized into one of two etiologic possibilities: spontaneous or indicated. In this study, spontaneous preterm birth was defined as spontaneous preterm labour, preterm premature rupture of membranes, and/or cervical incompetence resulting in birth prior to 37 or 34 completed weeks' gestation. Indicated preterm birth referred to all births induced or surgically delivered prior to the onset of labour for medical or obstetric conditions which place the mother or fetus at risk.

4.3.2 Diabetes Mellitus

The modified White classification was initially used by the NSAPD until March 31, 2003 (Please refer to Appendix). Using White's classification, it was possible to distinguish between infants born to women diagnosed with gestational diabetes from those diagnosed with pre-gestational diabetes. As of April 1, 2003, the Atlee developed its own R codes as well as using ICD-10 codes to classify women whose pregnancies had been complicated by diabetes. R coding was created by the RCP to enhance capture of certain medical conditions. Between April 1, 2003 and December 31, 2009, it was possible to distinguish between type 1 diabetes and type 2 diabetes mellitus. However, to keep study groups consistent in the two time periods, those women diagnosed with type 1 or type 2 using ICD-10 coding were grouped together under the category of pre-gestational diabetes.

4.4 Covariates

The variables selected for analysis were identified as risk factors associated with preterm delivery in non-diabetic pregnancies, as demonstrated in previous published and unpublished studies.[86-92]

The selected variables were classified in the following groups:

- Demographic and lifestyle factors
- Past history
- Maternal medical complications
- Pregnancy complications
- Infant

Demographic and lifestyle factors associated with preterm birth are gravidity, parity, marital status, residence, socio-economic status, maternal age, pre-pregnancy maternal weight, smoking, chemical abuse, and attendance at prenatal classes.

The patient's past obstetrical history may also contain risk factors predisposing her current pregnancy to preterm delivery. These include ≥ 1 previous abortions, previous stillbirth, previous neonatal death, previous low birth weight infant, and previous placental abruption, prior history of gestational diabetes, prior history of hypertensive disease in pregnancy, and previous eclampsia.

As well, maternal conditions such as pre-existing hypertension, asthma, and chronic renal disease have been identified as risk factors for preterm birth. As has been identified in several studies, the presence of nephropathy may play a significant role in the risk of preterm birth in pregnancies complicated by pre-gestational diabetes mellitus. Its association with preterm birth will be examined.

The pregnancy complications assessed in this analysis included placental abruption, antenatal bleeding occurring beyond 12 weeks gestation, placenta previa, SGA $<3^{rd}$ percentile, urinary tract infection, genital infections, hypertensive disease in pregnancy, oligohydramnios, hydramnios, chorioamnionitis, appendicitis, and anemia.

In addition, the influence of infant sex was examined.

Most variables were dichotomous (i.e. condition present or absent). However, continuous variables such as maternal age and maternal pre-pregnancy weight were converted to categorical variables.

Please refer to the Appendix for the complete list and definition of variables.

4.5 Statistical Analysis

Primary Objectives

1. To determine and compare the rate and relative risks of overall, spontaneous, and indicated preterm birth at <37 and <34 weeks' gestation among pre-gestational diabetic and gestational diabetic women compared with non-diabetic women.

The rate of preterm births at <37 and <34 weeks' gestation for pre-gestational, gestational, and non-diabetic pregnancies was determined. As well, the rate of spontaneous and indicated preterm births in pre-gestational and gestational diabetic pregnancies was considered. For example, the spontaneous preterm birth rate (<37 weeks) among pregnancies complicated by pre-gestational diabetes was calculated as the number of live births occurring spontaneously at < 37 weeks' gestation in pregnancies complicated by pre-gestational diabetes mellitus divided by the total number of live born pregnancies occurring during the period of 1988 to 2009.

Additionally, the magnitude of the association between the pre-gestational diabetic group and the non-diabetic group was calculated. The relative risk was calculated as the probability of a pregnancy complicated by preterm birth among pre-gestational diabetic women compared with the relative probability among non-diabetic women. Both crude and adjusted relative risks were computed. Relative risks were adjusted for the following potential confounders: antepartum hemorrhage, placental abruption, appendicitis, asthma, male sex, chorioamniotis, 1 or more previous abortions, parity, gravidity, marital status, low socio-economic status, urban residence, history of

prior stillbirth, non-attendance prenatal class, previous low birth weight infant, previous neonatal death, pregravid maternal weight, smoking, maternal age, small for gestational age <3rd percentile, genital infection, oligohydramnios, placenta previa, urinary tract infection (UTI), chemical abuse, maternal anemia, mild or severe preeclampsia , eclampsia, previous history of placental abruption, previous history of hypertension, pre-existing hypertension, and maternal renal disease.

The following rates were calculated:

- Rate of preterm births at <37 weeks' gestation in pre-gestational diabetic, gestational diabetic, and non-diabetic pregnancies
- Rate of preterm births at <34 weeks' gestation in pre-gestational diabetic, gestational diabetic, and non-diabetic pregnancies
- Rate of spontaneous preterm births in pre-gestational diabetic and gestational diabetic pregnancies
- Rate of indicated preterm births in pre-gestational diabetic and gestational diabetic pregnancies

Crude and adjusted relative risks were calculated for overall, spontaneous, and indicated pre-gestational diabetic and gestational diabetic pregnancies at less than 37 weeks and less than 34 weeks gestation.

2. To determine and compare the rate of preterm birth among non-diabetic, pre-gestational, and gestational diabetic pregnancies during three distinct time intervals: 1988-1994, 1995-2002, and 2003-2009.

The study was divided into three epochs: 1988-1994, 1995-2002, and 2003-2009. The frequency of preterm birth was determined during each time period. Test of trend was performed for each study group (pre-gestational, gestational, and non-diabetes).

3. To identify the risk factors leading to overall, spontaneous and indicated preterm birth in pregnancies complicated by pre-gestational and gestational diabetes.

Initially, each covariate was examined in a univariate analysis for each potential risk factor. Variables with a p-value of <0.10 on univariate analysis were entered into a logistic regression model. Backward stepwise regression was used to identify factors to retain in the final, parsimonious model. Significant variables (at the $p<0.05$ level) in the multivariable analyses were considered risk factors for preterm birth less than 37 weeks' gestation among pre-gestational and gestational pregnancies as well as for each preterm birth subtype.

The models were constructed using the same procedure in order to assess the following associations:

- Independent variables associated with overall, spontaneous, and indicated preterm births in pre-gestational diabetic pregnancies.
- Independent variables associated with overall, spontaneous, and indicated preterm birth in gestational diabetic pregnancies.

For each of the models, subsets of the data were analyzed according to diabetes status.

Logistic regression was used to determine the odds ratio and then converted to a relative risk using the formula described by Zhang and Yu.[93] All statistics were two-sided, and the significance level was set at $p<0.05$.

The odds ratio can be used to estimate the relative risk for rare outcomes (<10%). The Zhang and Yu method was used to convert all odds ratios to an estimate of relative risk.

$$\text{Relative Risk} = \frac{\text{Odds Ratio}}{1\text{-Risk}_0 + \text{Risk}_0 * \text{Odds Ratio}}$$

Where Risk_0=risk of positive outcome in controls or non-diabetic group

Source Wang (2013)[93]

Secondary Objective

To investigate whether infant sex modifies the effect of pre-gestational and gestational diabetes mellitus on preterm birth <37 and <34 weeks' gestation and preterm birth subtypes (spontaneous and indicated).

Infant sex was explored as an effect modifier of the diabetes mellitus-preterm birth relationship. The interactions between infant sex and diabetic sub-type (pre-gestational or gestational) on preterm birth less than 37 weeks or less 34 weeks were statistically tested through the use of interaction term using -2 log likelihood test from the logistic regression model. Risk estimates, stratified by infant sex, were calculated for each model which was found to be statistically significant.

Statistical analysis was performed using SAS 9.1 statistical software (SAS Institute, Inc., Cary, N.C.) and Epi-Info™7 from the Centers for Disease Control and Prevention, Atlanta, Georgia.

4.6 Study Sample Size

Assuming a two-sided level of significance (α) of 0.05 and power (1-β) of 80%, given the numbers of pre-gestational, gestational, and non-diabetic pregnancies in the study cohort, the smallest significant relative risks that can be identified are displayed in Table 4.1 (using an overall preterm birth rate of 4.9% among non-diabetic pregnancies). For example, when examining overall preterm birth among pre-gestational diabetics compared to non-diabetics, 793 pre-gestational diabetic pregnancies and 173 511 non-diabetic pregnancies will enable us to detect a statistically significant risk ratio of 1.5 (calculated using Epi-Info™7).

4.7 Ethical Considerations

This study received approval from the Research Ethics Board of the IWK Health Centre and the Data Access Committee of the Reproductive Care Program. All data analysis was conducted on a password secured computer in a locked office. Only Thesis Committee members had access to the data. Following completion of the study, the dataset was returned to the Reproductive Care Program.

The dataset used for analysis did not contain any patient identifiers. All results with a cell size less than 5 people were not reported.

Table 4.1 Smallest detectable relative risk given study sample, power 80% and alpha 0.05.

Outcome	Prevalence of outcome in non-diabetics (%)	Smallest detectable significant relative risk
Preterm birth <37 weeks		
Pre-gestational diabetes	4.9	1.5
Indicated	1.8	2.3
Spontaneous	3.1	2.0
Gestational diabetes	4.9	1.2
Indicated	1.8	1.6
Spontaneous	3.1	1.4
Preterm birth <34 weeks		
Pre-gestational	1.0	2.0
Indicated	0.3	4.2
Spontaneous	0.7	2.8
GDM	1.0	1.4
Indicated	0.3	2.2
Spontaneous	0.7	1.5

Chapter 5 Results

Between January 1, 1988 and December 31, 2009, a total of 205 921 live singleton births met this thesis project's inclusion and exclusion criteria and occurred to women residing in Nova Scotia from a potential study population of 220 353 pregnancies. There were 6450 pregnancies complicated by diabetes mellitus, a live birth incidence of 3.1%. Of these identified diabetic pregnancies, 905 were pre-gestational (14.0%) and 5545 were gestational (86.0%). Figure 5.1 summarizes the derivation of the study population and details the number of births that occurred in each study group.

Table 5.1 compares the baseline maternal and infant characteristics among the three study groups. Women with gestational diabetes were more likely to be multiparous, married or common-law, and to reside in a rural area of Nova Scotia. Conversely, women with pre-existing diabetes mellitus were more likely to smoke at the time of admission to hospital, to abuse a chemical substance, to have experienced poor obstetrical outcome (such as one or more spontaneous abortions, previous low birth weight infant, neonatal death, and stillbirth), and to suffer from renal disease and pre-existing hypertension.

The rate of preterm birth for non-diabetics, pre-gestational and gestational diabetes mellitus is shown in Table 5.2. The rate of preterm birth <37 weeks among non-diabetics was 4.9%. The rate of preterm birth less than 37 weeks in women with pre-gestational diabetes was 22.0% (199/905). The rate of preterm birth less than 34 was considerably lower at 4.1% (37/905) for this same group.

Among women with pregnancies complicated by gestational diabetes, the rate of preterm birth was 8.1% (447/5545). The rate of preterm birth less than 34 weeks was quite low at 1.2% (67/5545).

Tables 5.3 and 5.4 show the preterm birth rates during 3 distinct birth-year epochs (1988-1994, 1995-2002, and 2003-2009) among non-diabetic, pre-gestational, and gestational diabetic pregnancies. For pregnancies complicated by pre-gestational diabetes, the preterm birth rate at less than 37 weeks' gestation steadily decreased during the three birth year intervals: 26.43% in 1988-1994, 21.92% in 1995-2002, and 19.43% in 2003-2009. A test of trend reveals this decrease in incidence of preterm birth to be statistically significant ($p<0.001$). The preterm birth rate less than 34 weeks decreased during the years 1995 to 2002, but appears to rise again to earlier observed rates (4.41% in 1988-1994, 3.42% in 1995-2002, and 4.40% in 2003-2009).

Among pregnancies complicated by gestational diabetes, there was no clear trend noted during the three birth year intervals for preterm birth rate at less than 37 weeks and less than 34 weeks; though a sharp rise in preterm birth rate less than 37 weeks was observed in the 1995 to 2002 epoch.

Table 5.5 presents the crude and adjusted relative risk of preterm birth among pregnancies complicated by pre-gestational and gestational diabetes mellitus compared with non-diabetic pregnancies.

There was a four-fold increased risk of preterm birth less than 37 weeks among women with pre-gestational diabetes compared with non-diabetics (aOR 4.00, 95% CI 3.19-5.02). The adjusted relative risks for spontaneous and indicated preterm birth less than 37 weeks for pre-gestational pregnancies were significantly higher when compared

with non-diabetics. The overall and spontaneous preterm birth rates for less than 34 weeks remained significantly higher among women with pre-gestational diabetes. However, after adjustment for potential confounders, there was no difference in indicated preterm birth rate less than 34 weeks among pre-gestational diabetic women compared with non-diabetics (aRR 1.40, 95% CI 0.62-3.15).

Among pregnancies complicated by gestational diabetes, the adjusted relative risk for preterm birth less than 37 weeks was 1.63 (95% CI 1.43-1.85) compared with non-diabetic pregnancies. Both adjusted relative risks for spontaneous preterm birth and indicated preterm birth less than 37 weeks were also high compared with non-diabetics (aRR 1.75, 95% CI 1.50-2.05 and aRR 1.38, 95% CI 1.11-1.70, respectively). At less than 34 weeks, there was no statistically significant difference between gestational diabetes and non-diabetics for risk of overall, spontaneous, and indicated preterm births less than 34 weeks (refer to Table 5.5).

5.1 Risk Factors for Preterm Birth < 37 weeks

In univariate analysis, 35 of 37 covariates were identified as significantly associated with preterm delivery less than 37 weeks' gestation among all pregnancies at a p-value <0.10. Variables tested for inclusion in the models included 11 demographic and lifestyle variables (gravidy, parity, marital status, residence, socio-economic status, maternal age <20 years, maternal age ≥35 years, maternal weight <45 kilograms, alcohol consumption during pregnancy, chemical abuse, and attendance at prenatal classes), 7 past obstetrical history variables (≥1 previous abortions, previous stillbirth, previous neonatal death, previous low birth weight infant, previous placental abruption, prior

history of gestational diabetes mellitus, and prior history of gestational hypertension), 3 maternal medical complications variables (asthma, pre-existing hypertension, maternal renal disease), 13 pregnancy-related complication variables (placental abruption, antenatal bleeding occurring beyond 12 weeks gestation, placenta previa, appendicitis, SGA <3rd percentile, urinary tract infection, anemia, gestational hypertension, severe preeclampsia, genital infections, oligohydramnios, hydramnios, and chorioamnionitis), and infant sex.

These identified variables were used in the multivariate analysis to determine risk factors for preterm birth less than 34 weeks' gestation among non-diabetic, pre-gestational, and gestational pregnancies. They were also used to identify risk factors for spontaneous and indicated preterm birth in each of the above noted groups.

5.1.1 Risk factors for preterm birth less than 37 weeks in pregnancies complicated by pre-gestational diabetes mellitus

Table 5.6 presents the three risk factors for preterm birth less than 37 weeks among pre-gestational diabetic pregnancies identified from multivariate analysis. Severe preeclampsia (RR 4.96, 95% CI 2.05-11.42) had the strongest association for preterm birth less than 37 weeks' gestation. However, gestational hypertension/mild preeclampsia was identified as having no effect on risk of preterm birth less than 37 weeks' gestation in this group.

5.1.2 Risk factors for spontaneous preterm birth less than 37 weeks in pregnancies complicated by pre-gestational diabetes mellitus

No risk factors were identified as having an association with spontaneous preterm birth less than 37 weeks' gestation in pregnancies complicated by pre-gestational diabetes.

5.1.3 Risk factors for indicated preterm birth less than 37 weeks in pregnancies complicated by pre-gestational diabetes mellitus

There was a strong association between severe preeclampsia /eclampsia (RR 8.32, 95% CI 2.98-20.76) and indicated preterm birth less than 37 weeks' gestation among pregnancies complicated by pre-gestational diabetes. As was noted for overall preterm birth less than 37 weeks, mild preeclampsia was not a risk factor towards preterm birth (Please refer to Table 5.6).

5.1.4 Risk factors for preterm birth less than 37 weeks in pregnancies complicated by gestational diabetes mellitus

Table 5.7 displays the relative risks of six variables identified on multivariable analysis as risk factors for preterm birth less than 37 weeks in pregnancies complicated by gestational diabetes. Chemical abuse (RR 5.27, 95% CI 1.69-15.45), severe preeclampsia (RR 4.07, 95% CI 2.00-8.08), placental abruption (RR 3.51, 95% CI 1.10-10.85) and pre-existing hypertension (RR 3.09, 95% CI 1.56-6.05) were identified as significant risk factors.

5.1.5 Risk factors for spontaneous preterm birth less than 37 weeks in pregnancies complicated by gestational diabetes mellitus

Chemical abuse was a strong risk factor for spontaneous preterm birth in pregnancies complicated by gestational diabetes mellitus (Table 5.7). Absence of attendance to prenatal classes was associated with a reduced risk of spontaneous preterm birth less than 37 weeks in these pregnancies.

5.1.6 Risk factors for indicated preterm birth less than 37 weeks in pregnancies complicated by gestational diabetes mellitus

Table 5.7 reveals the five risk factors associated with indicated preterm birth in pregnancies with gestational diabetes. Among these pregnancies, previous placental abruption (RR 9.57, 95% CI 1.26-59.32) was strongly associated with risk of indicated preterm birth less than 37 weeks' gestation. The extremes of pre-pregnancy maternal weight had differing associations with indicated preterm birth. Pre-pregnancy maternal weight >90 kilograms was protective against indicated preterm birth (RR 0.37, 95% CI 0.16-0.83). No association was seen between indicated preterm birth and pre-pregnancy maternal weight < 45 kilograms (RR 1.36, 95% CI 0.72-2.35) or gestational hypertension/mild preeclampsia (RR 1.54, 95% CI 0.78-2.87).

5.2 Risk Factors for Preterm Birth < 34 weeks

In univariate analysis, 30 of 37 covariates were identified as significantly associated with preterm delivery less than 37 weeks' gestation among all pregnancies at a p-value <0.10. Variables tested for inclusion in the models included 10 demographic and

lifestyle variables (gravidy, parity, marital status, socio-economic status, maternal age <20 years, maternal age ≥35 years, maternal weight <45 kilograms, alcohol consumption during pregnancy, chemical abuse, and attendance at prenatal classes), 5 past obstetrical history variables (≥1 previous abortions, previous stillbirth, previous neonatal death, previous low birth weight infant, and previous placental abruption), 3 maternal medical complications variables (asthma, pre-existing hypertension, and maternal renal disease), and 12 pregnancy-related complication variables (placental abruption, antenatal bleeding occurring beyond 12 weeks gestation, placenta previa, appendicitis, urinary tract infection, anemia, gestational hypertension/mild preeclampsia, severe preeclampsia, genital infections, oligohydramnios, hydramnios, and chorioamnionitis).

These identified variables were used in the multivariate analysis to determine risk factors for preterm birth less than 34 weeks' gestation among non-diabetic, pre-gestational, and gestational pregnancies. They were also used to identify risk factors for spontaneous and indicated preterm birth in each of the above noted groups.

5.2.1 Risk factors for preterm birth less than 34 weeks in pregnancies complicated by pre-gestational diabetes mellitus

Only two risk factors were identified for preterm birth less than 34 weeks for pre-gestational pregnancies (Table 5.8). Placental abruption (RR 33.87, 95% CI 1.87- 126.69) was strongly associated with preterm birth less than 34 weeks in pregnancies complicated by pre-gestational diabetes.

5.2.2 Risk factors for spontaneous preterm birth less than 34 weeks in pregnancies complicated by pre-gestational diabetes mellitus

On multivariate analysis, there were too few observations to run the variables identified in univariate analysis. No further analyses were conducted on this subset.

5.2.3 Risk factors for indicated preterm birth less than 34 weeks in pregnancies complicated by pre-gestational diabetes mellitus

As with spontaneous preterm birth, multivariate analysis could not be conducted for risk factors due to too few observations. No further analyses were conducted on this subset.

5.2.4 Risk factors for preterm birth less than 34 weeks in pregnancies complicated by gestational diabetes mellitus

Table 5.9 reveals four risk factors leading to preterm birth less than 34 weeks in gestational diabetic pregnancies. Placental abruption, chemical abuse, pre-existing hypertension, and antepartum hemorrhage were identified as significant risk factors. Absence from attending prenatal classes was identified as a protective factor against preterm birth less than 34 weeks in this group (RR 0.50, 95% CI 0.23-0.91).

5.2.5 Risk factors for spontaneous preterm birth less than 34 weeks in pregnancies complicated by gestational diabetes mellitus

Chemical abuse (RR 10.15, 95% CI 1.16-55.07) was strongly associated with spontaneous preterm birth less than 34 weeks' gestation. Three other risk factors were

identified (Table 5.9). Absence from attending prenatal classes was the only protective factor identified in the modelling.

5.2.6 Risk factors for indicated preterm birth less than 34 weeks in pregnancies complicated by gestational diabetes mellitus

Two variables, placental abruption and pre-existing hypertension, were identified as risk factors for indicated preterm birth less than 34 weeks on multivariate analysis (Table 5.9).

5.3 Effect Modifier and Preterm Birth

Infant sex was explored as an effect modifier for the diabetes mellitus-preterm birth relation. Statistical significance was present for only one interaction term. Infant sex appeared to significantly modify the effect of pre-gestational diabetes on indicated preterm birth less than 34 weeks. The odds ratio for indicated preterm birth less than 34 weeks was 1.62 with 95% confidence interval between 0.72-3.66 among female infants. There was over a four-fold increased risk of indicated preterm birth less than 34 weeks among male infants (odds ratio 4.62, 95% confidence interval 2.56-8.34). Among all infants, the odds ratio was 2.88 (95% confidence interval 1.79-4.64).

Figure 5.1 Total numbers of study population, Nova Scotia, 1988-2009.

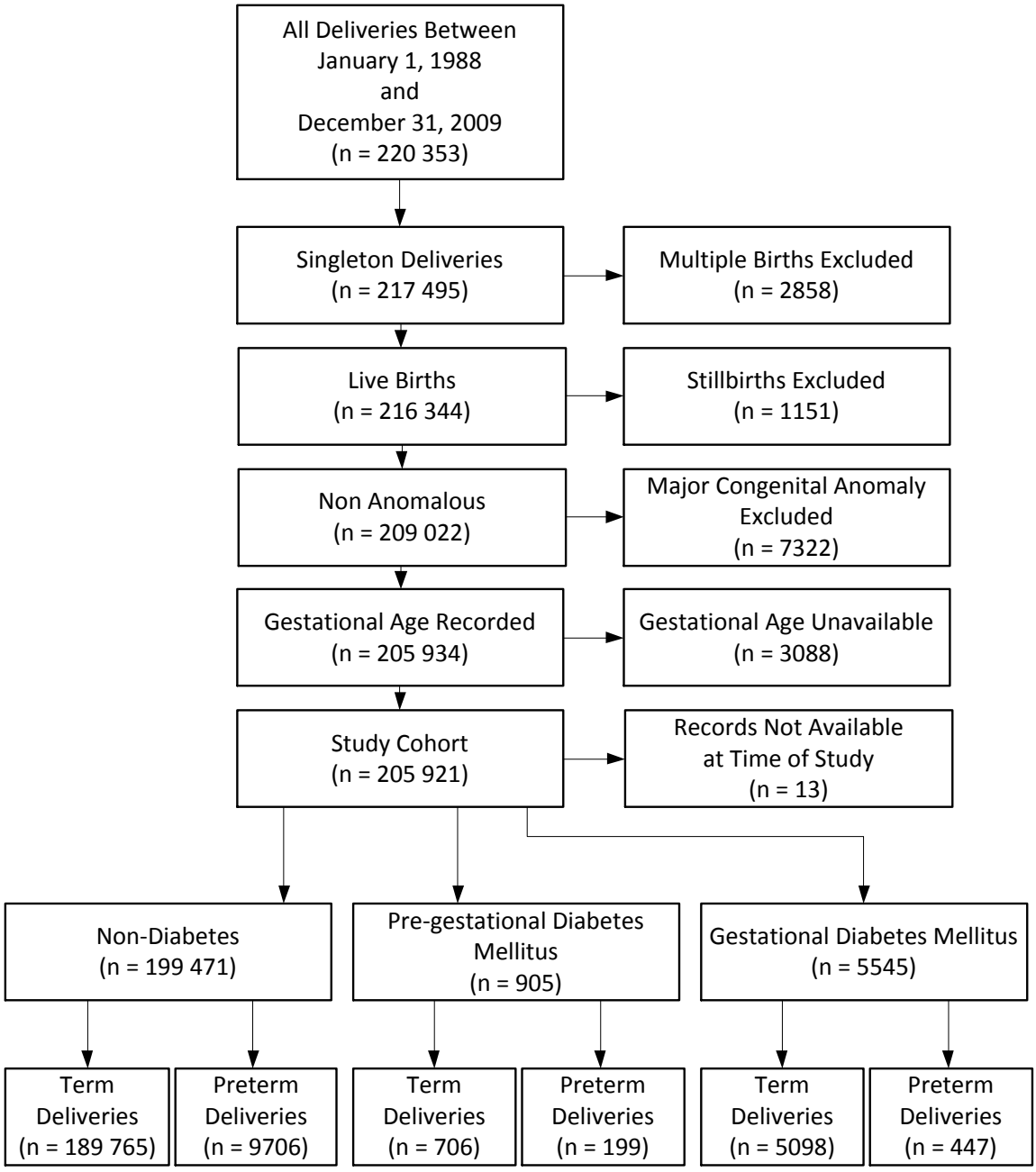

Table 5.1 Baseline maternal and fetal characteristics among study groups.

Characteristic	Non-diabetics n = 199 471 (%)		Pre-gestational Diabetes n = 905 (%)		Gestational Diabetes n = 5545 (%)		p-value
Maternal age (years)							
<20	14 785	(7.4)	20	(2.2)	138	(2.5)	<0.001
20-34	162 748	(81.6)	727	(80.3)	4309	(77.7)	
≥35	21 938	(11.0)	158	(17.5)	1098	(19.8)	<0.001
Pre-pregnancy Maternal Weight (kgs)							
<45	27 778	(13.9)	154	(17.0)	775	(14.0)	<0.001
45-90	157 366	(78.9)	564	(62.3)	3531	(63.7)	
>90	14 327	(7.2)	187	(20.7)	1239	(22.3)	<0.001
Parity							
0	89 158	(44.7)	406	(44.9)	2245	(40.5)	<0.001
≥1	110 295	(55.3)	498	(55.0)	3299	(59.5)	
Missing	18	(0.009)	1	(0.1)	1	(0.02)	
Marital Status							
Single, divorced, or widowed	47 268	(23.7)	208	(23.0)	1071	(19.3)	<0.001
Married or common-law	140 253	(70.3)	648	(71.6)	4074	(73.5)	
Unknown	11950	(6.0)	49	(5.4)	400	(7.2)	
Residence							
Urban	125 233	(62.8)	569	(62.9)	3338	(60.2)	0.001
Rural	73 604	(36.9)	334	(36.9)	2193	(39.5)	
Missing	634	(0.3)	2	(0.2)	14	(0.3)	
Socio-economic status							
Low	80 430	(40.3)	401	(44.3)	2388	(43.1)	<0.001
High	116 535	(58.4)	495	(54.7)	3084	(55.6)	
Missing	2506	(1.3)	9	(1.0)	73	(1.3)	
Cigarette smoking							
No	141 677	(71.0)	655	(72,4)	3991	(72.0)	0.46
Yes	50 217	(25.2)	214	(23.7)	1383	(24.9)	
Missing	7586	(3.8)	36	(4.0)	171	(3.1)	
Chemical abuse							
No	197 701	(99.1)	891	(98.5)	5513	(99.4)	0.04
Yes	1770	(0.9)	14	(1.5)	32	(0.6)	
Attendance at prenatal class							
No	93 343	(46.8)	390	(43.1)	2686	(48.4)	0.004
Yes	63 180	(31.7)	240	(26.5)	1668	(30.1)	
Missing	42 948	(21.5)	275	(30.4)	1191	(21.5)	
History of spontaneous abortion							
0	149 344	(74.9)	473	(52.3)	3908	(70.5)	<0.001
≥1	50 088	(25.1)	431	(47.6)	1636	(29.5)	
Missing	39	(0.02)	1	(0.1)	1	(0.02)	
Previous low birth weight infant							
No	188 574	(94.5)	817	(90.3)	5210	(94.0)	0.003
Yes	7425	(3.7)	66	(7.3)	234	(4.2)	
Missing	3472	(1.7)	22	(2.4)	101	(1.8)	
Previous stillbirth							
No	195 546	(98.0)	866	(95.7)	5375	(96.9)	<0.001
Yes	1594	(0.8)	22	(2.4)	102	(1.8)	
Missing	2331	(1.2)	17	(1.9)	68	(1.2)	
Previous neonatal death							
No	196 167	(98.3)	871	(96.2)	5435	(98.0)	<0.001
Yes	963	(0.5)	17	(1.9)	46	(0.8)	
Missing	2341	(1.2)	17	(1.9)	64	(1.2)	
Pre-existing hypertension							
No	197 691	(99.1)	840	(92.8)	5363	(96.7)	<0.001
Yes	1780	(0.9)	65	(7.2)	182	(3.3)	
Renal disease							
No	196 706	(98.6)	866	(95.7)	5449	(98.3)	0.001
Yes	2765	(1.4)	39	(4.3)	96	(1.7)	
Infant sex							
Female	97 714	(49.0)	467	(51.6)	2679	(48.3)	0.5
Male	101 757	(51.0)	438	(48.4)	2866	(51.7)	
SGA<3rd percentile							
No	193 154	(96.8)	891	(98.5)	5411	(97.6)	0.001
Yes	5901	(3.0)	13	(1.4)	121	(2.2)	
Missing	416	(0.2)	1	(0.1)	13	(0.2)	

kgs = kilograms SGA = small for gestational age

Table 5.2 Incidence of preterm birth among study population.

Study Population	n (%)	
Entire Population (n=205 921)		
<37 weeks	10 352	(5.0)
Spontaneous	6549	(3.2)
Indicated	3803	(1.8)
<34 weeks	2122	(1.0)
Spontaneous	1388	(0.7)
Indicated	734	(0.3)
Non-diabetic (n=199 471)		
<37 weeks	9706	(4.9)
Spontaneous	6206	(3.1)
Indicated	3500	(1.8)
<34 weeks	2018	(1.0)
Spontaneous	1326	(0.7)
Indicated	692	(0.3)
Pre-gestational diabetes (n=905)		
<37 weeks	199	(22.0)
Spontaneous	82	(9.1)
Indicated	117	(12.9)
<34 weeks	37	(4.1)
Spontaneous	19	(2.1)
Indicated	18	(2.0)
GDM (n=5545)		
<37 weeks	447	(8.1)
Spontaneous	261	(4.7)
Indicated	186	(3.4)
<34 weeks	67	(1.2)
Spontaneous	43	(0.8)
Indicated	24	(0.4)

Table 5.3 Rates of preterm birth < 37 weeks' gestation for non-diabetic, pre-gestational, and gestational diabetic pregnancies in Nova Scotia, across three time epochs.

Birth Years	Non-Diabetic n=9706 (%)	Pre-gestational Diabetic n=199 (%)	Gestational Diabetic n=447 (%)
1988-1994	3432 (4.29%)	60 (26.43%)*	130 (6.97%)
1995-2002	3467 (5.04%)	64 (21.92%)*	177 (9.45%)
2003-2009	2997 (5.44%)	75 (19.43%)*	140 (7.75%)

* Based on test of trend p-value <0.001

Table 5.4 Rates of preterm birth < 34 weeks' gestation for non-diabetic, pre-gestational, and gestational diabetic pregnancies in Nova Scotia, across three time epochs.

Birth Years	Non-Diabetic n=2018 (%)	Pre-gestational Diabetic n=37 (%)	Gestational Diabetic n=67 (%)
1988-1994	721 (0.95%)	10 (4.41%)	15 (0.96%)
1995-2002	729 (1.06%)	10 (3.42%)	29 (1.08%)
2003-2009	568(1.03%)	17 (4.40%)	23 (1.06%)

Table 5.5 Crude and adjusted relative risk of preterm birth among pregnancies complicated by pre-gestational and gestational diabetes compared with non-diabetic pregnancies.

Study Group	Crude Relative Risk (95% CI)	Adjusted* Relative Risk (95% CI)
Pre-gestational		
<37 weeks'	4.52 (3.99-5.12)	4.00 (3.19-5.02)
Indicated	7.37 (6.20-8.75)	4.23 (3.10-5.78)
Spontaneous	2.91 (2.37-3.59)`	3.20 (2.37-4.33)
<34 weeks'	4.04 (2.94-5.56)	2.15 (1.29-3.60)
Indicated	5.73 (3.61-9.11)	1.40 (0.62-3.15)
Spontaneous	3.16 (2.02-4.94)	3.47 (1.84-6.56)
Gestational		
<37 weeks'	1.66 (1.51-1.81)	1.63 (1.43-1.85)
Indicated	1.91 (1.65-2.21)	1.38 (1.11-1.70)
Spontaneous	1.51 (1.34-1.71)	1.75 (1.50-2.05)
<34 weeks'	1.19 (0.94-1.52)	1.09 (0.78-1.52)
Indicated	1.25 (0.83-1.87)	0.73 (0.40-1.34)
Spontaneous	1.17 (0.86-1.58)	1.36 (0.92-2.02)

*Adjusted for the following variables: antepartum hemorrhage, placental abruption, appendicitis, asthma, infant sex, chorioamniotis, 1 or more previous abortions, parity, gravidity, marital status, low socio-economic status, urban residence, history of prior stillbirth, non-attendance prenatal class, previous low birth weight infant, previous neonatal death, pregravid maternal weight, smoking, maternal age, small for gestational age <3rd percentile, genital infection, oligohydramnios, hydramnios, placenta previa, urinary tract infection, chemical abuse, maternal anemia, gestational hypertension/mild preeclampsia, severe preeclampsia, previous history of placental abruption, previous history of hypertensive disorders in pregnancy, pre-existing hypertension, maternal renal disease.

Table 5.6 Risk factors for overall and indicated preterm births (<37 weeks) among pre-gestational diabetic women, Nova Scotia, 1988-2009.

Risk Factor	Relative Risk (95% CI)		
	Overall	Spontaneous	Indicated
History of SA	1.68 (1.10-2.31)	-	2.21 (1.34-3.00)
Preeclampsia			
Absent	1.0	-	1.0
GH/Mild	0.99 (0.40-1.20)	-	1.53 (0.50-4.08)
Severe	4.96 (2.05-11.42)	-	8.32 (2.98-20.76)
Urban Residence	1.23 (1.01-1.39)	-	1.38 (1.11-1.51)

SA = spontaneous abortion
GH =gestational hypertension

Table 5.7 Risk factors for overall, spontaneous, and indicated preterm births (<37 weeks) among gestational diabetic women, Nova Scotia, 1988-2009.

Risk Factor	Relative Risk (95% CI)		
	Overall	Spontaneous	Indicated
Placental abruption	3.51 (1.10-10.85)	-	-
Antepartum hemorrhage	2.49 (1.42-4.20)	2.91 (1.50-5.31)	-
Previous LBW infant	2.62 (1.59-4.22)	2.44 (1.26-4.52)	-
Chemical abuse	5.27 (1.69-15.45)	4.57 (1.33-14.70)	-
Did not attend prenatal classes	-	0.76 (0.56-0.97)	-
Previous stillborn	-	-	4.29 (1.34-13.12)
Pre-pregnancy maternal weight			
<45 kgs	-	-	1.36 (0.72-2.35)
45-90 kgs	-	-	1.0
>90 kgs	-	-	0.37 (0.16-0.83)
Oligohydramnios	-	-	4.06 (1.38-10.98)
Preeclampsia			
Absent	1.0	-	1.0
GH/Mild	1.22 (0.77-1.91)	-	1.54 (0.78-2.87)
Severe	4.07 (2.00-8.08)	-	7.11 (2.99-15.79)
Pre-existing hypertension	3.09 (1.56-6.05)	-	5.30 (1.91-13.97)
Previous placental abruption	-	-	9.57 (1.26-59.32)

LBW = low birth weight
kgs = kilograms
GH = gestational hypertension

Table 5.8 Risk factors for overall, spontaneous, and indicated preterm birth (<34 weeks) among pre-gestational diabetic women, Nova Scotia, 1988-2009.

Risk Factor	Relative Risk (95% CI)		
	Overall	Spontaneous	Indicated
Placental abruption	33.87 (1.87- 126.69)	-	-
History of SA	2.61 (1.10-3.60)	-	-

SA=Spontaneous abortion

Table 5.9 Risk factors for overall, spontaneous, and indicated preterm births (<34 weeks) among gestational diabetic women, Nova Scotia, 1988-2009.

Risk Factor	Relative Risk (95% CI)		
	Overall	Spontaneous	Indicated
Placental abruption	17.18 (4.17-54.91)	8.17 (1.26-42.04)	59.97 (7.53-126.69)
Did not attend prenatal classes	0.50 (0.23-0.91)	0.36 (0.12-0.84)	-
Antepartum hemorrhage	5.98 (2.36-11.74)	8.28 (3.11-15.02)	-
Chemical abuse	14.34 (1.85-63.60)	10.15 (1.16-55.07)	-
Pre-existing hypertension	12.00 (4.11-30.46)	8.93 (1.01-28.21)	29.81 (6.34-74.63)

Chapter 6 Discussion

This thesis study sought to investigate the rates and risk factors of preterm birth in a large population of women with pre-gestational and gestational diabetes mellitus compared with women without diabetes using the Nova Scotia Atlee Perinatal Database.

6.1 Rates of Preterm Birth in Diabetes Mellitus

Between 1988 and 2009, there were 6450 pregnancies complicated by diabetes in Nova Scotia, representing a prevalence of 3.1%. Approximately 905 women were classified as having pre-gestational diabetes mellitus; 14.0% of all diabetics within the study population. The prevalence of pre-gestational diabetes in Nova Scotia was 0.5% during this 15-year study period; this falls outside the commonly quoted range of 0.7 to 2.5% that is reported for the female Canadian population.[94] It is unknown whether this discrepancy was due to differences in methodology (i.e. ascertainment of cases), underestimation of true prevalence, or reduction of fecundity among women with pre-gestational diabetes.

This study was unable to further extrapolate the exact percentage of type 1 and type 2 diabetes mellitus for the entire study period due to diabetes classification used by the NSAPD. Prior to March 31, 2003, women with pre-existing diabetes were classified using the White Classification (see Appendix). However, since April 1st, 2003, the NSAPD adopted the ICD-10-CA, followed by specific RCP coding for identifying pregnancies complicated by pre-gestational diabetes mellitus. As with all conversions to a new system, errors in classification may have occurred during the transition from the

previous to the updated version. It is assumed that the levels of coding mistakes should reduce with increasing familiarity to the new classification system.[34]

In Nova Scotia, the prevalence of gestational diabetes was 2.69% during the study period from 1988 until 2009. A prevalence of 3.5-3.8% has been reported among non-Aboriginal Canadians[95]; a rate slightly lower than that was observed in this study. However, the calculated prevalence is well within the 1-14% often described in the world literature for gestational diabetes. [96,97]

The strong association between pre-existing diabetes mellitus and preterm birth seen in this study is consistent with several published studies.[17-19] The rate of preterm birth less than 37 weeks among women with pre-gestational diabetes was 22.0% in this study, which is slightly lower than the rate of 38% found by Sibai.[79] The women with pre-gestational diabetes in Sibai's study had all required insulin prior to conception. Therefore, this higher preterm birth rate may reflect the severity of diabetes in the group.

The relative risk of preterm birth less than 37 weeks in pregnancies complicated by gestational diabetes was concordant with risks found in large studies conducted by Fadl[56] (aOR 1.71, 95% CI 1.568-1.86), Pettica[68] (OR 1.43, 95% CI 1.27-1.61), and Shand[69] (OR 1.47, 95% CI 1.38-1.57). Even after controlling for several possible confounders in our study, a significant association between gestational diabetes and preterm birth less than 37 weeks still persisted.

Unfortunately, our study was not able to control for glycemic levels among women with diabetes. Controlling for pre-conception and pregnancy glucose levels may have further lowered the risk of preterm birth, thereby helping to explain the association between gestational diabetes and preterm birth.

The rate of preterm birth less than 34 weeks was quite low for both pre-gestational and gestational diabetes mellitus. The morbidity and mortality are significantly higher among infants delivered less than 34 weeks. From this study's results, delivery less than 34 weeks among pre-gestational and gestational diabetic pregnancies occurred for serious obstetrical complications, for example placental abruption, suggesting a non-modifiable indication for delivery. Therefore, the rate of preterm birth less than 34 weeks may currently be near its lowest level.

Findings from the HAPO study were paramount to the new set of criteria for the diagnosis of gestational diabetes introduced by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). In December 2010, the American Diabetes Association adopted these new guidelines.[36] Many recently published studies have examined the possibility of an increase in disease prevalence with these new diagnostic criteria, as well as the effect on the preterm birth rate.

Capula and associates studied the incidence rate and perinatal complications among women less than 35 years old who were diagnosed with GDM using the new IADPSG criteria.[61] Between May 2010 and December 2012, the incidence of GDM among Italian women less than age 35 years rose to 31.8%. The risk of preterm delivery was 8.2% among women with GDM compared with 3.5% among non-diabetic women. Over a two-fold increased risk was noted, though the risk did not remain statistically significant after adjusting for maternal age, pregravid body mass index, and parity (8.2% vs 3.5 %, respectively; unadjusted OR 2.43, 95% CI 1.11-5.29, p=0.025; adjusted OR 1.94, 95% CI 0.84-4.48, p=0.12).

Two separate studies comparing the previous ADA and CDA guidelines with the new IADPSG criteria have recently been published. Shang and Li conducted a prospective study to assess the IADPSG criteria compared with the American Diabetes Association (ADA) criteria to determine the association between GDM and adverse pregnancy outcomes, including preterm birth.[98] The study was conducted in a Beijing hospital in China between January 2012 and March 2013. A total of 3083 Chinese women met the inclusion and exclusion criteria. The group noted a statistically higher incidence of women diagnosed with GDM using the IADPSG criteria versus the ADA criteria (19.9% vs 7.98%, $p<0.001$). Interestingly, the group noted a lower risk of preterm birth among women with IADPSG diagnosed GDM compared with Chinese women without GDM (6.2% vs 9.0%, OR 0.67, 95% CI 0.47-0.95, $p=0.025$).

Brodner-Roy's group evaluated the incidence of GDM based on IADPSG criteria that did not fulfill the Canadian Diabetes Association criteria in women who attended the Centre Hospitalier Universitaire Sainte-Justine in Montreal.[99] They conducted a retrospective observational study between November 1, 2008 and October 31, 2010. Following inclusion and exclusion criteria, one hundred eighty-six women met the IADPSG criteria (group 1) but not that of CDA criteria for diagnosis of GDM. This group was compared with 372 women who did not fulfill either criterion for GDM (group 2). The study revealed that the risk of preterm birth was not statistically different between the two groups (6.5% vs 5.9%, OR 1.10, 95% CI 0.53-2.27, $p=0.85$).

The use of the new IADPSG criteria may result in an even higher incidence rate of gestational diabetes. This must be taken into account in future research that compares the rate of gestational diabetes mellitus.

The rate of indicated preterm birth less than 37 weeks among women with pre-gestational diabetes mellitus was 12.9%, which was almost six times higher compared with non-diabetics and nearly four times higher compared with gestational diabetics. Severe pregnancy-induced hypertension/eclampsia was the strongest indicator leading to iatrogenic delivery among women with pre-existing diabetes mellitus. Studies conducted by Sibai[79] and Greene[100] also found preeclampsia as the leading cause of indicated preterm birth less than 37 weeks among this group of diabetic women.

Spontaneous preterm birth was the predominant subtype (58.4%) in pregnancies complicated by gestational diabetes. This proportion was similar to what was noted among non-diabetic pregnancies in this study. Previous low birth weight infant and antepartum hemorrhage are the two factors that gestational diabetics and non-diabetics share in common. This observation can be added to the body of knowledge on this issue. The higher proportion of this sub-type of preterm birth was similar to findings in the literature for non-diabetic population.[14,15] The spontaneous preterm labour may be due to high glycemic levels among pregnancies complicated by gestational diabetes compared with non-diabetics. Glucose control represented an additional risk which needs to be considered.

A recent study from Nova Scotia found that gestational diabetes was not associated with iatrogenic preterm birth (aRR 0.92, 95% CI 0.59-1.43, p=0.70) for the period 1988-2003.[101] Key differences in cohort between Joseph's study (which included multiple births and stillbirths) and this study, may explain the contradictory rate of preterm birth less than 37 weeks due to induced labour.

The decreasing rate of preterm birth among pregnancies complicated by pre-gestational diabetes observed during three epochs may signify a reduction in complications requiring induction in labour. While the peak in the rate of preterm birth among women with gestational diabetes between 1995 and 2002 may be associated with the change in glucose tolerance test.

6.2 Determinants of Preterm Birth

Almost one quarter (23.98%) of pre-gestational diabetic pregnancies delivering at less than 37 weeks' were complicated by severe preeclampsia compared to 5.25% of term deliveries. Sibai et al noted that preeclampsia occurred in 38% of their pre-gestational population.[79] Interestingly, when exploring the relationship between diabetes mellitus and spontaneous preterm birth, Köck et al excluded all women with maternal complications such as HELLP syndrome, preeclampsia, and severe chronic diseases because of their known association with high risk of preterm birth.[102] In our study, severe preeclampsia was indeed a powerful risk factor for preterm birth among pregnancies complicated by pre-gestational diabetes mellitus. Examining the influence of preeclampsia was important; its exclusion would remove a significant number of subjects from this study which would result in erroneous findings.

Severe preeclampsia also played a significant role in indicated preterm birth less than 37 weeks among pregnancies complicated by gestational diabetes. This was the only risk factor shared between the two categories of diabetes analyzed in this study. It suggests that the pathophysiology related to hypertensive disorders in pregnancy may be a more complex issue. Some authors have hypothesized that poor vascularity due to diabetes results in an increased risk of preeclampsia /eclampsia.[23] Pre-gestational

diabetes, specifically type 1, has traditionally been known to be associated with microvascular disease; however it may be postulated that women diagnosed with gestational diabetes, may have an underlying vascular condition which has been unmasked during pregnancy. The presence of hyperglycemia and insulin resistance may hasten the progression to atherosclerotic disease through injury of the systemic vascular endothelium.[103] Hypertensive disorders of pregnancy was sub-divided based on severity. Gestational hypertension/mild preeclampsia did not have an effect on preterm birth. Therefore, it appears that it is the severity of preeclampsia, and not solely its presence that plays a significant role in increasing the risk of preterm birth less than 37 weeks gestation in pregnancies complicated by pre-gestational diabetes.

Women who had experienced at least one spontaneous abortion also appeared to be at risk for indicated preterm birth less than 37 weeks in pregnancies complicated by pre-gestational diabetes mellitus. Some researchers postulated that spontaneous abortion resulted from a hostile in utero environment due to high pre-conception glucose levels.[104,105] Women in this study with previous spontaneous abortion(s) may represent those who continue to have less than optimal glycemic control in subsequent pregnancies, thus increasing the risk of preterm birth.

Placental abruption (RR 33.87, 95% CI 1.87- 126.69) was identified as a strong risk factor for preterm birth less than 34 weeks' gestation in women with pregnancies complicated by pre-gestational diabetes. In the study by Kyrklund-Blomberg et al, pre-gestational diabetes was found to be a risk factor for abruptio placentae.[106] This current research supports Kyrklund-Blomberg's paper's findings.

Preterm birth less than 37 weeks' gestation in women with gestational diabetes was strongly associated with chemical abuse (RR 5.27, 95% CI 1.69-15.45). Chemical abuse (RR 4.57, 95% CI 1.33-14.70) was also a risk factor for spontaneous preterm birth less than 34 weeks' gestation in pregnancies complicated by gestational diabetes. Chemical abuse included alcohol and other substances consumed during pregnancy. Each substance was not differentiated according to type and the exact amount consumed was not quantified in our data source. The apparent association was independent of smoking, given that smoking did not remain in the model. The role of chemical abuse in preterm birth among pregnancies complicated by gestational diabetes was a unique study finding.

Previous placental abruption and previous stillbirth (RR 9.57, 95% CI 1.26-59.32; RR 4.29, 95% CI 1.34-13.12, respectively) were strongly associated with increased risk of indicated preterm birth less than 37 weeks gestation among gestational diabetic women. These findings may possibly be explained by the current standard to care, where health care providers intervene early to reduce the potential risk of a repeat adverse outcome.[107]

Among pregnancies complicated by pre-gestational diabetes mellitus, the risk factors identified for overall preterm birth less than 34 weeks are not easily modifiable (such as history of spontaneous abortion and placental abruption of unknown etiologies); this limits the possible strategies that can be implemented pre-conceptional or during pregnancy to reduce the risk of preterm birth.

Suboptimal glucose control has been suggested as a possible mechanism for preterm birth among pregnancies complicated by diabetes mellitus. Parameters of metabolic control, such as glycosylated hemoglobin, were not consistently available to

many researchers. Investigators have hypothesized that poor metabolic control may be the underlying mechanism for the increased risk of preterm delivery and that improved glycemic control may result in a reduction or elimination of preterm birth risk in type 1 diabetic pregnancies.

Some authors were able to explore a possible association between elevated glycosylated levels and preterm birth. Rosenn retrospectively identified 254 pregnancies complicated by insulin-dependent diabetes mellitus between 1978 and1992.[38] A comparison group of 508 non-diabetic women were randomly selected from their database. The non-diabetic comparison group was matched based on age, race and parity. Findings from Rosenn's study supported the theory that poor glycemic control in each trimester, was, in fact, associated with an increase in preterm birth prior to 37 weeks. However, elevated glycosylated A1C levels did not result in an increased risk of preterm birth less than 34 weeks when compared with non-diabetics. In another study, using multivariate logistic modelling, Kovilam determined that for each 1% increase in hemoglobin A1C, the risk of spontaneous preterm birth increased by 37% (95% CI 6% - 78%).[108]

However, Evers' study rejects the suggestion that optimal glucose control in type 1 diabetic pregnancies reduces the rate of preterm birth to that of the background risk.[44] In a one-year population-based prospective study, the researchers recruited 323 women with type 1 diabetes from 118 hospitals in the Netherlands. The data from the non-diabetics group (196 981) was obtained from the 1998 Dutch Perinatal database and data from Statistics Netherlands. Glycosylated hemoglobin A1C levels were obtained during each trimester of pregnancy in women with diabetes. Even though glycemic control was

considered ideal (target goal based on the American Diabetes Association criteria of ≤ 7%), the preterm delivery rate was still quite high: 32.2% among type 1 diabetics compared to 7.1% in non-diabetic controls, signifying a relative risk of 4.5 (95% CI, 3.8-5.3).

Even though poor glycemic control increases a type 1 diabetic's risk of preterm delivery, the reverse does not appear to hold true. This may suggest an inherent risk of preterm birth due to the disease itself.

Bar-Hava et al. evaluated the incidence of preterm birth in pregnancies complicated by GDM and the possible link with glycemic control.[50] Metabolic control was assessed by frequent daily and every other day capillary blood glucose levels. HbA_{1C} concentrations were not reported. A power analysis was conducted to determine the sample size required to detect a significant difference in the incidence of preterm birth between women with gestational diabetes and women without diabetes (controls). The authors found no statistically significant difference between the spontaneous PTB rate in the GDM group and the control group (6.2% vs 6.5%, p=0.82). Even though there were more hyperglycemic episodes occurring one week prior to preterm birth in pregnancies complicated by GDM (n=34), this finding was not found to be statistically significant compared with the week prior to term deliveries (n=68); research findings examining levels of glycemic control between women with gestational diabetes who delivered prematurely compared with term deliveries was likely underpowered (50% vs 33.3%, p=0.54). Thus, the researchers questioned the role of glycemic control in the risk of preterm birth among pregnancies complicated by GDM. The authors only included pregnancies complicated by spontaneous PTB.

A paper originating from Saudi Arabia explored the role of glycemic control on preterm birth rate. Based on O'Sullivan and Carpenter National Diabetes Data Group criteria, the prevalence of gestational diabetes in Amarzouki's study was 5.9%.[58] There was still a three-fold increased risk (OR 3.2, 95% CI 1.1-9.5) of preterm birth among women with gestational diabetes mellitus compared with non-diabetic women (17.4% vs 6.3%, p=0.04), even though there was good glycemic control among the diabetic group.

Given the discrepancy between the association of glucose control among women with diabetes and preterm birth, this remains an important area of study.

6.3 Protective Factors

It was not anticipated that protective factors against preterm birth would be identified in this study. Pre-pregnancy maternal weight >90 kg was strongly protective against indicated preterm birth less than 37 weeks' among women with gestational diabetes. One may hypothesize that health care providers may have a higher threshold for planning a delivery in women with pre-pregnancy weight >90 kg, given the increased risk of operative delivery with induction of labour and the potential postpartum complications associated with cesarean section.[109]

An interesting finding was the apparent inverse association between attending prenatal class and indicated preterm birth less than 37 weeks among women with gestational diabetes (RR 0.50, 95% CI 0.23-0.91). The possibility of reverse causation must be considered if the signs and symptoms of preterm labour appear before women are able to attend prenatal classes. Another possibility could be that women with diabetes receive such intensive care in Nova Scotia that they may undervalue the added benefit of attending prenatal classes. Additionally, multiparous women may be less likely to attend

prenatal classes. Further studies are needed to explore the effectiveness of prenatal education and its relationship with preterm birth in women with diabetes.

6.4 Infant Sex and Preterm Birth

Sex was viewed as an effect modifier in the relationship between pre-gestational diabetes and indicated preterm birth less than 34 weeks.

Numerous hypotheses are presented in the review by Di Renzo et al regarding the possible mechanism leading to preterm birth in male fetuses.[110] A biological mechanism inducing preterm birth may be directly influenced by male sex. Several theories exist including earlier timing of conception during the fertile cycle,[111] high male sex hormones,[112] greater male fetal weight at earlier gestational age,[113] and vulnerability to intrauterine infection or hypertension.[114] Findings from this study suggested that infant sex may affect indicated preterm birth less than 34 weeks among pregnancies complicated by pre-gestational diabetes. Researchers postulated that male fetuses are more prone to causing maternal hypertension.[115] Pregnancy-induced hypertension was a common indication for preterm delivery. In this study, there were too few pregnancies to effectively study the risk of pregnancy hypertension associated with male fetuses and indicated preterm birth less than 34 weeks among women with pre-gestational diabetes.

6.5 Study Strengths and Limitations

There are several strengths to this research study. Firstly, this is one of the largest studies exploring the rates and risk factors of preterm birth in pregnant women with

diabetes mellitus. Even though the study conducted by Pettica[56] was comprised of a larger study population, it examined a large number of different perinatal outcomes; while this research's focus was on the association between diabetes mellitus and preterm birth. Secondly, data was obtained from a single, well-established provincial population-based database that has been validated. The NSAPD is not an administrative database, but rather a clinical database used for clinical audit and research. Thirdly, this is one of the few studies that assessed both pre-gestational and gestational diabetes mellitus within one research study.

Limitations of this study must be mentioned. The findings from this study were based on secondary data analysis from a provincial perinatal database. Thus, additional important clinical variables could not be explored. Body mass index (BMI), race/ethnicity, and glycemic control are examples of variables which may have been beneficial to examine.

BMI has been found to be associated with preterm delivery in non-diabetic pregnancies.[87] Although maternal height first began being collected in the NSAPD in 2003, the rate of missing data is still quite high. Thus, it was not possible to calculate each subject's BMI. Therefore, only maternal weight could be explored as a possible risk factor associated with preterm birth.

Black race has been identified as a risk factor for preterm birth.[89] Black Canadians are the largest visible minority group in the Atlantic Provinces. However, based on the 2011 Census conducted by Statistics Canada, Black residents represent over 2% of Nova Scotians.[116] Race/ethnicity was not consistently collected in the NSAPD during the study period.

Missing data for some variables was noted. For example, as much as 30.4% of prenatal class attendance status was missing from the dataset among pre-gestational diabetic women. This may be a result of inconsistent chart completion by health care providers or incorrect data entry. Using multiple imputation is an option to address the number of missing values.

After March 31, 2003, the White classification was replaced by the ICD-10 coding for diabetes mellitus. Between 2003 and 2004, prior to the implementation of R coding, there were likely some missed cases of diabetes mellitus (especially gestational).

The NSAPD does not contain history of preterm birth as a variable. Rather, it uses previous infant birth weight <2500 g as a proxy for previous preterm birth. Low birth weight is a heterogeneous condition and includes preterm infants and term infants who are born small for gestational age. According to the study conducted by Savitz and associates based out of Mount Sinai Hospital in New York City, 69.2% infants less than 2500 grams are actually born prior to 37 weeks.[117] Even though the concordance is not high, previous preterm birth is an important factor which should be explored in the future.

It is recognized that multiple statistical tests were conducted, which increases the risk of a Type 1 error.

Potential multicollinearity must also be considered. For example, variables related to vascular risk (gestational hypertension, small for gestational age infant, fetal distress, and placental abruption) may in fact be correlated with each other. However, with the inclusion of each variable in the model, we felt that the lower precision in the estimates due to multicollinearity was a better alternative to potential bias from the exclusion of some variables.[118]

The effect of glucose control on preterm birth risk could not be assessed during the study period. In April 1995, the Diabetes in Pregnancy Database was initiated which collects information about glycosylated hemoglobin for a select subset of diabetics. Unlike the NSAPD, the quality and validity of the Diabetes in Pregnancy Database had not undergone quality assurance reviews or linkage to the NSAPD at the time that analysis for this study was initially conducted.

Given the discrepancy between the association of glucose control among women with diabetes and preterm birth, this remains an important area of study. Over time, as the Diabetes in Pregnancy Database begins to expand its data collection, glycemic control and risk of preterm birth can be studied.

6.6 External Validity

Nova Scotia is comprised of a homogenous population. Based on the 2001 Canadian census, Caucasians represent approximately 96% of Nova Scotia residents.[119] This may be one explanation as to the relatively low risk of gestational diabetes mellitus detected in this study. The racial composition may not be comparable to that of other Canadian provinces, such as Ontario or Manitoba. The findings from this research project may be more applicable to European nations. However, these results are an important foundation to future research which may be undertaken in a more ethnically diverse population.

6.7 Future Research

Future research should examine the relationship of varying levels of glucose control and preterm birth among women with gestational diabetes mellitus especially in the face of findings from The Hyperglycemic and Adverse Pregnancy Outcome study.[17]

Chapter 7 Conclusions

This study emphasizes the important association that exists between diabetes and preterm birth. When controlling for identified demographic and lifestyle, past obstetrical history, maternal conditions, and pregnancy-related factors, there remains a significant risk of preterm birth less than 37 and less than 34 weeks among women with pre-gestational diabetes and women with gestational diabetes less than 34 weeks. This study also identified risk factors of preterm birth less than 37 weeks and less than 34 weeks among women with pregnancies complicated by pre-gestational and gestational diabetes. Severe preeclampsia was identified as a risk factor for both pre-gestational and gestational diabetes mellitus, suggesting that the two disorders possess a common pathophysiology. Male fetal sex appeared to modify the effect of pre-gestational diabetes on indicated preterm birth less than 34 weeks.

Ultimately, the goal of health care with regard to management of pregnancies among women with diabetes is to reduce the burden of disease through prevention of preterm birth. The determinants identified in this study leading to preterm birth among pregnancies complicated by diabetes will also be useful to researchers, governments, and policy analysts. Health care providers can effectively counsel women about their patient's potential risk of preterm birth and increase surveillance accordingly.

Appendix Description and Treatment of Variables in Nova Scotia Atlee Perinatal Database.

Variable	Description	Treatment of Variable
	General Obstetrical Information	
Date of patient's last menstrual period	Date of patient's last menstrual period	Converted to gestational age of delivery
Maternal age	Mother's age at time of delivery	Converted into three categories: younger than 19 years, 19-35, and 35 years and older
Gravida	Number of pregnancies including the present pregnancy, which the mother has had	Dichotomized into primigravid or multigravida
Parity	Number of pregnancies excluding the present pregnancy, which resulted in 1 or more infants weighing ≥500 grams at birth (regardless of whether such infants were stillborn, died after birth, or lived)	Converted into nulliparous or parous
Previous spontaneous abortion	Pregnancy, excluding the present pregnancy, which resulted in a fetus weighing <500 grams or, when weight not known, <20 weeks gestation, regardless of whether the fetus was born alive	Dichotomized: none, or 1 or more
Previous fetal deaths (Stillbirth)	Previous intrauterine death of a fetus specifically recorded as weighing ≥500 grams, and/or than ≥20 weeks gestation, or when documented as a fetal death by the physician	Retitled as Stillbirth. Dichotomized: no or yes
Previous neonatal death	Previous death of an infant in first 28 days of life specifically recorded as weighing ≥500 grams or when documented as a neonatal death by the physician	Dichotomized: no or yes
Previous low birth weight infants	Previous infants with birth weight to ≤2499 grams (5lbs. 8 oz.)	Reported as yes or no
Antepartum bleeding ≥20 weeks	Maternal bleeding in present pregnancy ≥20 weeks gestation	Reported as no or yes
Pre-pregnancy maternal weight	Maternal pre-pregnancy weight	Converted into 3 categories: <45 kgs, 45-90 kgs, and >90 kigs
Attendance at prenatal classes	Maternal attendance at any prenatal classes	Reported as no or yes
Smoking at time of delivery	Number of cigarettes smoked per day at time of delivery	Categorized as no if 0 cigarettes smoked or yes irrespective of number of cigarettes smoked
Marital status	Marital status, as collected after delivery	Dichotomized: no partner (includes single, divorced, or widowed) and partner (married or common-law)

Variable	Description	Treatment of Variable
Labour	Initiation of labour (spontaneous onset of labour or artificial induction of labour)	Used to select subjects with outcome of interest
	Previous Pregnancy Maternal Diseases	
Obstetrical		
Hypertensive disease in previous pregnancy	High blood pressure, toxemia, pre-eclampsia or hypertension	Reported as no or yes
Previous abruption placenta	As stated in chart	Reported as no or yes
Previous eclampsia	Convulsion or eclampsia, excluding epilepsy	Reported as no or yes
Previous gestational diabetes	Previous gestational diabetes	Reported as no or yes
	Maternal Diagnoses in Present Pregnancy	
Abortion	Threatened abortion (uterine bleeding <20 weeks gestation)	Retitled as antepartum hemorrhage. Reported as no or yes
Hypertensive disease	History of hypertensive disease when not pregnant prior to current pregnancy or prior to 20 weeks of current pregnancy; not due to trophoblastic disease	Reported as no or yes
Preeclampsia	Includes pre-eclampsia, toxemia, and HELLP syndrome	Categorized according to severity: absent, prreclamsia (≤150/100 mmHg), and severe preeclampsia (≥150/100mmHg) or eclampsia
Eclampsia	One or more convulsions not attributable to other cerebral conditions such as epilepsy or cerebral hemorrhage in a patient with hypertension or as stated on chart by physician	If yes, categorized with severe preeclampsia
Oligohydramnios	As stated in chart	Reported as no or yes
Polyhydramnios	As stated on chart or if >2000 cc	Reported as no or yes
Placenta previa	Confirmed by double set-up or at time of cesarean section; diagnosis not to be made on ultrasound alone	Reported as no or yes
Abruptio placenta	Concealed or revealed placental abruption, not marginal separation, as stated at delivery – diagnosis not to be made on ultrasound alone	Reported as no or yes
Other antepartum hemorrhage per vagina (≥20 weeks gestation)	Any unspecified hemorrhage occurring before the onset of labour, ≥20 weeks gestation. Include a suspected previa or abruption in an undelivered patient. Include a patient who presents with bleeding which has resolved on admission	Categorized as antepartum hemorrhage Reported as no or yes
Premature rupture of membranes	Spontaneous rupture of membranes before onset of contractions, regardless of gestation	If yes and resulting in preterm birth, used in classification as spontaneous preterm birth
Intrauterine growth restriction	As stated in chart	Reported as no or yes

Variable	Description	Treatment of Variable
Non-Obstetrical		
Chemical abuse	Includes alcohol, prescription medication and narcotic abuse. N.B. Code for hash, marijuana, cocaine, etc if used anytime during pregnancy	Reported as no or yes
Nephritic syndrome	As stated in chart	Retitled as Renal disease. Reported as no or yes
Anemia	Antepartum hemoglobin <10gram% e.g.9.5 hemoglobin (antepartum) recorded on prenatal record	Reported as no or yes
Uterine abnormalities	Includes septate uterus, unicornuate, bicornuate, cervical incompetence. Exclude cervical stenosis, and fibroids unless causing antenatal concerns	Reported as no or yes
Asthma	As stated in chart	Reported as no or yes
Infection in Present Pregnancy		
Lower urinary tract infection	Confirmed by culture >100 000 colonies/mL, or as stated by physician	Reported as no or yes
Genital infections	Includes group B streptococcal infection, Listeria infection, Syphilis, Gonorrhea, herpes simplex infection, Mycoplasma disease, and Chlamydia	Reported as no or yes
Non-Delivery Procedures		
Appendectomy	As stated in chart	Reported as no or yes
	Classification of neonatal Diseases and Procedures	
Metabolic disease		
Infant of diabetic mother		
Class A	Two abnormal values on maternal glucose tolerance test using either Joslin Clinic or the O'Sullivan criteria, whichever is positive	Used in classifying diabetes mellitus by subtype: pre-gestational and gestational diabetes mellitus
Class B	Less than 10 years duration, no vascular disease; onset after age 20 years	
Class C	Duration 10-19 years, minimal vascular disease; onset after age 10	
Class D	Duration 20 years or more; benign retinopathy; onset before age 10 years	
Class F	Class D and nephropathy	
Class R	Proliferative retinopathy	
Class T	Diagnosis made by Trutol greater than 10.3 mmol/L	

Variable	Description	Treatment of Variable
Placental and Umbilical Cord Anomalies		
Chorioamniotis, marked or severe	Not chorionitis or chorangiosis, as stated on pathology report	Reported as yes or no
Infant		
Sex	Legal phenotypic sex of the infant, regardless of karyotype	Reported as female or male

Source: Adapted from RCP 2001[31]

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