

Pregnancy Outcomes in Diabetes Subtypes: How Do They Compare? A Province-based Study of Ontario, 2005–2006

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Abstract

Objective: To ascertain differences in pregnancy outcomes between women with diabetes subtypes (type 1 [DM1], type 2 [DM2], women with gestational [GDM]) and non-diabetic women within a large Canadian population.

Methods: We performed a retrospective multi-cohort analysis of all obstetrical deliveries that occurred in the province of Ontario between April 1, 2005, and March 31, 2006. Data were extracted from the Ontario Niday Perinatal Database.

Results: Increased rates of major negative maternal and perinatal outcomes (i.e. preterm delivery, Caesarean section, pregnancy-induced hypertension/preeclampsia) occurred in women with DM1. Both DM1 and GDM subtypes were associated with the greatest risk of macrosomia, shoulder dystocia, and congenital anomalies. DM2 did not demonstrate an association with an increased risk of congenital malformations and stillbirth.

Conclusion: Diabetes in pregnancy, irrespective of subtype, predisposes women to poorer outcomes than those of the general obstetric population. However, this large population analysis is consistent with previous studies in showing that the adversity remains greatest for women with type 1 diabetes.

Résumé

Objectif : Déterminer les différences en matière d'issues de grossesse entre les femmes présentant divers sous-types de diabète (type 1 [DM1], type 2 [DM2], gestationnel [GDM]) et les femmes non diabétiques au sein d'une importante population canadienne.

Méthodes : Nous avons mené une analyse multicohorte rétrospective portant sur tous les accouchements obstétricaux qui ont eu lieu en Ontario entre le 1^{er} avril 2005 et le 31 mars 2006. Les données ont été tirées de la *Ontario Niday Perinatal Database*.

Key Words: Diabetes and pregnancy, diabetes subtypes, pre-gestational diabetes, congenital malformation, stillbirth

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Résultats : Des taux accrus d'importantes issues négatives maternelles et périnatales (c.-à-d. l'accouchement préterme, la césarienne et l'hypertension/prééclampsie gravidique) ont été constatés chez les femmes présentant un DM1. Les sous-types DM1 et GDM ont été associés au risque le plus élevé de macrosomie, de dystocie de l'épaule et d'anomalies congénitales. Aucune association n'a été constatée entre le DM2 et un risque accru de malformations congénitales et de mortinaissance.

Conclusion : Le diabète au cours de la grossesse, peu en importe le sous-type, prédispose les femmes à l'obtention d'issues inférieures à celles que l'on constate au sein de la population obstétricale générale. Cependant, les résultats de cette analyse menée auprès d'une importante population concordent avec ceux d'études précédentes : ils indiquent que l'adversité demeure à son paroxysme chez les femmes qui présentent un diabète de type 1.

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INTRODUCTION

Diabetes mellitus (diabetes) is a common disorder in pregnancy that is recognized as producing higher rates of unfavourable obstetrical outcomes.^{1,2} The disturbance in glucose metabolism may be due to insulin resistance (type 2 and gestational diabetes), or a consequence of autoimmune induced insulin deficiency (type 1). Differences in maternal characteristics such as age, obesity, ethnic background, and the duration of fetal exposure to hyperglycemia between subtypes of DM may result in a different level of risk for pregnancy. The epidemic of obesity in women of childbearing age, and resulting increase in DM2 in pregnancy,³ makes it essential that we better understand the risks to mothers and fetuses exposed to hyperglycemia, and how they vary between diabetes subtypes. There is a paucity of information on pregnancy outcomes between DM subtypes and the background population.^{4,5} In fact, the majority of studies to date have exclusively focused on individuals with DM1^{6–9}

or DM2,^{10–12} compared DM1 with DM2,^{13–18} or combined DM1 and DM2 under the term “pre-gestational diabetes.”^{19–25}

Despite previous efforts to elucidate variations in pregnancy outcomes among women with diabetes, a large-scale assessment of how these outcomes differ between DM subtypes has not been performed. Moreover, there is a deficiency in references using Canadian data. Administrative databases are being increasingly implemented to identify disease prevalence, trends, and clinical outcomes. This comparative analysis was performed to assess maternal and perinatal outcomes between DM subtypes and the general obstetric population from Ontario, using a provincial perinatal surveillance system.

MATERIALS AND METHODS

We conducted a population-based multi-cohort analysis of the records of all women who delivered in Ontario between April 1, 2005, and March 31, 2006. This study used data from the 2005–2006 fiscal year of the Ontario Niday Perinatal Database,²⁶ a branch of the provincial Perinatal Surveillance System. It is a web-based data entry application that houses information on the number of women giving birth and infants born in the province, maternal and perinatal characteristics, use of health care services, intrapartum interventions, birth outcomes and infant health.

Participation from each site is voluntary; sites consist of hospitals and midwifery groups across the province. Currently, there are 82 participating sites, 72 of which are hospitals. Data are collected by nursing staff at each site, using a paper format, and subsequently entered into the database by either nurses or clerical staff. Some hospitals upload their data directly into the Niday database from their respective health records systems. Diagnoses are extracted by codes that are unique to the database. Personnel at each site receive training prior to data collection for the database in order to properly manage the systems data entry and reporting capabilities. Passwords protect access to the data and generation of reports.

Data quality is ensured from the inception of data entry by extensive quality checks, including enhanced verifications

at the time of data entry and the addition of key required fields in the various system modules (e.g., the perinatal module). An analyst then sees the data through to processing and registration. In addition, a user guide is available to all participating sites in both web-based and paper format to ensure standardization of definitions for each measured variable.

For this study, the study population was divided into three groups: the first comprised women with a diagnosis of DM1, the second DM2, and the third GDM. The characteristics of these groups were compared with the background population. Data from all pregnancies (singleton and multiple gestations) and from women with pre-existing co-morbidities (e.g., chronic hypertension, nephropathy) were included in the comparative analysis.

DM cohorts were compared by key pregnancy outcomes, which included both maternal and perinatal events. The maternal outcomes of interest were induction of labour, Caesarean section, preterm delivery (defined as < 37 weeks' gestation), shoulder dystocia, and pregnancy-induced hypertension/preeclampsia. Perinatal outcomes included macrosomia (defined by a birth weight of > 4000 g), congenital anomalies (composite and system specific), stillbirth (defined as fetal death between 20 weeks' gestation and term), low birth weight (defined by birth weight of < 2500 g), and Apgar scores (≤ 3 at 5 minutes after birth). Major indications for induction of labour and operative delivery were also analyzed.

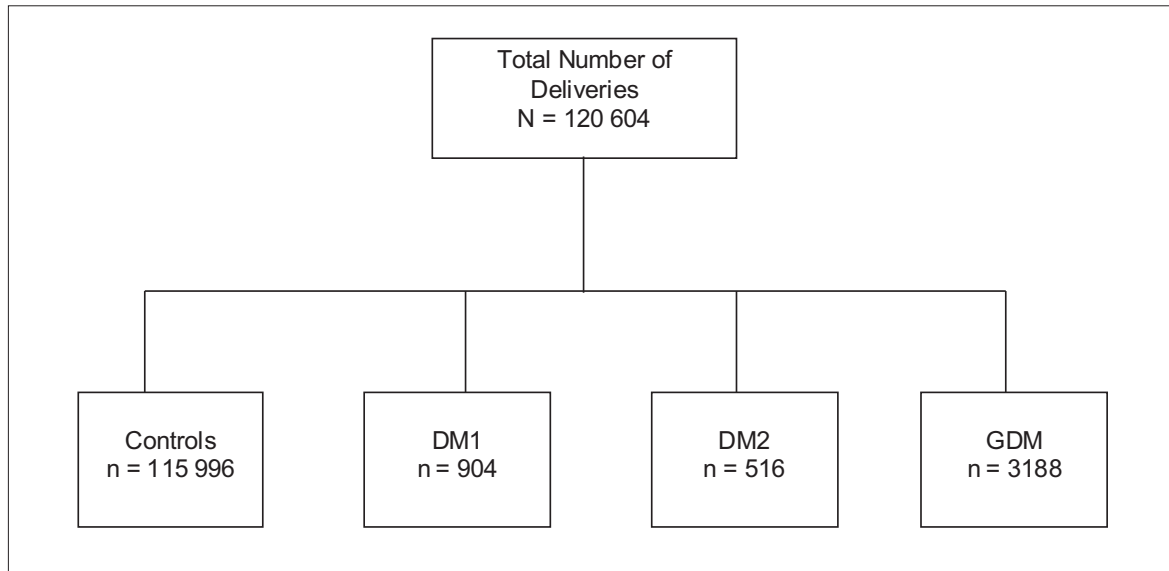
The prevalence of pre-pregnancy diabetes and gestational diabetes was calculated among the deliveries with reporting of maternal and obstetric complications. We first compared the distribution of maternal and infant characteristics of the three subtype cohorts to the controls. The mean values and standard deviations were calculated on quantitative outcomes to summarize the discrepancy between the subtype cohorts and controls. Chi-square test was used to test the difference in category outcomes, and analysis of variance was used to test the differences in quantitative outcomes. Differences between groups were considered significant with *P* values of < 0.05. The excess risks of each birth outcome by DM subtype were calculated by unconditional logistic regressions, using pregnancies without maternal complications as the reference (i.e., controls), and expressed by odds ratio and 95% confidence intervals.

The independent variables that were entered into the regression models as dummy variables were: maternal age (≤ 35 years, > 35 years), region of residence (north west, north east, central, central west, east, south west), smoking (yes or no), parity (0, 1, 2+), multiple birth (yes, no), use of assisted reproductive technology for this pregnancy (yes,

ABBREVIATIONS

DM1	diabetes mellitus type 1
DM2	diabetes mellitus type 2
GDM	gestational diabetes mellitus
PIH	pregnancy-induced hypertension

Total number of obstetrical deliveries for each DM subtype



no), attendance at a first trimester visit for this pregnancy (yes, no, not recorded), and type of antenatal provider (family physician, midwife, obstetrician, other, not recorded). Adjusted odds ratios and confidence intervals do not include maternal co-morbidities (i.e., chronic hypertension and heart disease), but the inclusion of these data in the analysis did not significantly alter the final results. All data were analyzed using Statistical Analysis System, Version 9.1 (SAS Institute Inc., Cary NC).

Permission to use the Niday Perinatal Database was granted by the database subcommittee. Approval to analyze the data was obtained from The Ottawa Hospital Research Ethics Board.

RESULTS

There were 120 604 deliveries entered into the Ontario Niday Perinatal Database between April 1, 2005 and March 31, 2006. We identified 904 cases (0.75%) of women with DM1, 516 cases (0.43%) with DM2, and 3188 cases (2.64%) with GDM (Figure). The control group comprised 115 996 non-DM women. One half of all study participants resided in central Ontario, with the second largest proportion originating from the eastern regions of the province (data not shown).

Key maternal and perinatal characteristics are shown in Table 1. Baseline maternal characteristics were comparable between cohorts. Approximately 50% of women with DM were at least 30 years of age or older. The majority of women with DM attended an antenatal visit in first trimester with a healthcare provider (family physician, obstetrician, or midwife); however, the data reflect only 60% of all women with DM during this time period. The mean

gestational age at the time of delivery was 38 weeks' gestation, and the average fetal birth weight exceeded 3300 g.

Table 2 illustrates the crude and adjusted odds ratios for major maternal and perinatal outcomes according to DM subtypes. All subtypes were associated with increased rates of induction of labour, Caesarean section, preterm delivery, and pregnancy-induced hypertensive disorders compared with controls. DM1 was associated with a near three-fold increase in risk of induction (AOR 2.68; 95% CI 2.32–3.09) and preterm delivery (AOR 2.88; 95% CI 2.38–3.48). The most common indications for induction were intrauterine growth restriction, premature rupture of membranes, post-dates, preeclampsia, and maternal-related causes (data not shown). Similarly, DM1 conferred the greatest risk of requiring Caesarean section (AOR 2.65; 95% CI 2.30–3.05) and of preeclampsia (AOR 2.80; 95% CI 2.20–3.50). Delivery by Caesarean section occurred most frequently in the setting of breech presentation, non-reassuring fetal heart rate, failure to progress and a previous history of Caesarean section (data not shown).

The rate of shoulder dystocia in women with DM1 (2.8%) was twice that of both controls (1.1%) and DM2 (1.2%), though the latter cohort did not achieve significance when odds ratios were adjusted for confounding variables. Likewise, rates of macrosomia and congenital anomalies were not found to be statistically significant with the DM2 subtype ($P > 0.05$). Women with DM1 and GDM demonstrated the greatest risk of delivering a macrosomic infant (AOR 1.78; 95% CI 1.47–2.14, and AOR 1.16; 95% CI 1.03–1.30, respectively). In contrast, the odds of having an infant with low birth weight (< 2500 g) were highest in the DM2 subtype (AOR 1.81; 95% CI 1.29–2.48, $P < 0.01$).

Table 1. Baseline maternal and fetal characteristics according to DM subtypes

Characteristic	Controls n = 115 996 n (%)	DM1 n = 904 n (%)	DM2 n = 516 n (%)	GDM n = 3188 n (%)
Maternal age (years)				
< 20	3985 (3.4)	8 (0.9)	1 (0.2)	29 (0.9)
20–29	48 970 (42.2)	287 (31.8)	146 (28.3)	922 (28.9)
30–34	45 631 (39.3)	395 (43.7)	234 (45.4)	1402 (44.0)
≥ 35	17 410 (15.0)	214 (23.7)	135 (26.2)	835 (26.2)
Cigarette smoking				
No	88 177 (76.0)	721 (79.8)	395 (76.6)	2602(81.6)
Yes	11 330 (9.8)	91 (10.1)	53 (10.3)	297 (9.3)
Unknown	16 489 (14.2)	92 (10.2)	68 (13.4)	289 (9.1)
Parity				
0	51 318 (44.2)	364 (40.3)	205 (39.7)	1251 (39.2)
1	39 385 (34.0)	312 (34.5)	175 (33.9)	1179 (37.0)
≥ 2	23 938 (20.6)	226 (25.0)	136 (26.4)	752 (23.6)
Unknown	1355 (1.2)	2 (0.2)	0 (0.0)	6 (0.2)
Multiple gestation				
No	11 1945 (96.5)	873 (96.6)	500 (96.9)	3054 (95.8)
Yes	4051 (3.5)	31 (3.4)	16 (3.1)	134 (4.2)
First trimester visit				
No	10 067 (8.7)	82 (9.1)	55 (10.7)	369 (11.6)
Yes	48 352 (41.7)	532 (58.9)	270 (52.3)	1440 (45.2)
Unknown	57 577 (49.6)	290 (32.0)	191 (37.0)	1379 (43.3)
Gestational age (weeks)*	38.7 ± 2.3	37.4 ± 2.1	38.1 ± 2.1	38.2 ± 1.7
Birth weight (grams)*	3333.3 ± 627.4	3379 ± 740.6	3301 ± 670.7	3333.0 ± 618.4

*Mean ± SD

Congenital anomalies were most frequently observed in women with DM1 and GDM, the risk approaching 1.5 to 2 times that of controls ($P < 0.05$). Further sub-analysis demonstrated a cumulative total of 44 birth defects (6.1%) among all women with DM. The frequency was greatest for cardiovascular ($n = 16$), musculoskeletal ($n = 11$), and genitourinary system ($n = 6$) malformations (Table 3). This composite total excludes cases of spontaneous or therapeutic terminations of pregnancy (less than 20 weeks' gestation) that occurred as a result of a congenital malformation.

Infants born to mothers with DM1 and GDM were more likely to have poor Apgar scores at birth than controls. The prevalence of Apgar scores ≤ 3 at five minutes after delivery doubled in the setting of DM1 (AOR 2.48; 95% CI 1.44–4.00, $P < 0.01$). Results for DM2 did not achieve statistical significance.

Lastly, we analyzed rates of stillbirth between DM subtypes and controls. The risk of stillbirth was greatest in women

with DM1 (AOR 2.30; 95% CI 1.14–4.11) and lowest in GDM (AOR 0.31; 95% CI 0.11–0.67).

DISCUSSION

Persistent hyperglycemia in pregnancy disrupts the intrauterine milieu, causing morbidity and mortality for mothers and infants alike. Studies to date have consistently found that women with diabetes in pregnancy experience worse obstetrical, perinatal and neonatal outcomes than non-DM women.^{6,11,22,23} The principal finding of this study is that pregnancy outcomes are suboptimal for all subtypes of diabetes when compared with healthy controls; however, the complication rate remains most pronounced in women with DM1.

As the incidence of diabetes continues to increase,²⁷ understanding the deleterious effects of DM subtypes on the expectant mother is critical to achieve the goals set forth by the St. Vincent Declaration.²⁸ According to the 2003 National Health Interview Survey, pre-gestational DM

Table 2. Risk of adverse obstetrical and perinatal outcomes according to DM subtypes

Outcome	Controls	DM1	DM2	GDM
Induction				
Rate per 100, %	24.0	44.7	36.6	38.3
Crude OR (95% CI)	Reference	2.57 (2.23–2.95)	1.75 (1.44–2.13)	1.91 (1.77–2.06)
Adjusted OR† (95% CI)		2.68 (2.32–3.09)*	1.86 (1.53–2.27)*	1.89 (1.74–2.04)*
Caesarean section				
Rate per 100, %	27.6	51.6	38.0	38.0
Crude OR (95% CI)	Reference	2.86 (2.49–3.29)	1.69 (1.39–2.04)	1.63 (1.51–1.76)
Adjusted OR† (95% CI)		2.65 (2.30–3.05)*	1.60 (1.31–1.94)*	1.53 (1.41–1.65)*
Preterm birth (less than 37 weeks)				
Rate per 100, %	8.4	19.0	14.0	11.3
Crude OR (95% CI)	Reference	2.69 (2.25–3.22)	1.70 (1.29–2.25)	1.43 (1.27–1.61)
Adjusted OR† (95% CI)		2.88 (2.38–3.48)*	1.85 (1.38–2.49)*	1.41 (1.24–1.60)*
Shoulder dystocia				
Rate per 100, %	1.1	2.8	1.2	1.8
Crude OR (95% CI)	Reference	2.37 (1.48–3.57)	1.23 (0.49–2.52)	1.69 (1.27–2.22)
Adjusted OR† (95% CI)		2.52 (1.62–3.92)*	1.30 (0.58–2.92)	1.68 (1.26–2.22)*
PIH/preeclampsia				
Rate per 100, %	4.6	10.3	8.4	9.1
Crude OR (95% CI)	Reference	2.58 (2.05–3.22)	1.80 (1.24–2.52)	2.06 (1.81–2.35)
Adjusted OR† (95% CI)		2.80 (2.20–3.50)*	1.92 (1.32–2.70)*	2.02 (1.77–2.31)*
Macrosomia (> 4000 grams)				
Rate per 100, %	11.0	17.2	11.1	12.2
Crude OR (95% CI)	Reference	1.68 (1.39–2.02)	1.01 (0.74–1.34)	1.13 (1.01–1.27)
Adjusted OR† (95% CI)		1.78 (1.47–2.14)*	1.01 (0.74–1.35)	1.16 (1.03–1.30)**
Congenital anomalies				
Rate per 100, %	1.9	3.5	1.7	2.5
Crude OR (95% CI)	Reference	1.80 (1.10–3.00)	1.02 (0.42–2.46)	1.42 (1.05–1.91)
Adjusted OR† (95% CI)		1.71 (1.03–2.82)**	1.00 (0.41–2.43)	1.43 (1.05–1.93)**
Apgar score ≤ 3 at 5 mins				
Rate per 100, %	0.91	1.8	1.4	0.44
Crude OR (95% CI)	Reference	2.51 (1.52–4.15)	1.41 (0.58–3.42)	0.56 (0.32–0.97)
Adjusted OR† (95% CI)		2.48 (1.44–4.00)*	1.38 (0.49–3.01)	0.57 (0.31–0.95)**
Stillbirth				
Rate per 100, %	0.6	1.1	0.6	0.2
Crude OR (95% CI)	Reference	2.37 (1.18–4.21)	0.43 (0.02–1.89)	0.33 (0.12–0.71)
Adjusted OR† (95% CI)		2.30 (1.14–4.11)**	0.42 (0.02–1.88)	0.31 (0.11–0.67)*
Low birth weight (< 2500 grams)				
Rate per 100, %	7.0	9.5	10.5	7.4
Crude OR (95% CI)	Reference	1.39 (1.08–1.76)	1.62 (1.17–2.18)	1.11 (0.96–1.28)
Adjusted OR† (95% CI)		1.39 (1.05–1.79)**	1.81 (1.29–2.48)*	1.04 (0.88–1.21)

* $P < 0.01$, ** $P < 0.05$

†Odds ratios (95% CI) were adjusted for maternal age, multiple birth, cigarette smoking in pregnancy, parity, use of assisted reproductive technology, first trimester visit and antenatal care provider.

Table 3. Frequency of congenital anomalies, by body system, according to DM subtype

Congenital Anomalies	Controls n = 50 914 n (%)	DM1 n = 547 n (%)	DM2 n = 344 n (%)	GDM n = 2046 n (%)	P
Cardiovascular	258 (0.5)	4 (0.7)	2 (0.6)	10 (0.5)	NS
CNS	43 (0.1)	2 (0.4)	0 (0.0)	1 (0.1)	NS
Cleft lip and palate	71 (0.1)	1 (0.2)	1 (0.3)	1 (0.1)	NS
Trisomy 21	47 (0.1)	1 (0.2)	0 (0.0)	2 (0.1)	NS
Gastrointestinal	35 (0.1)	2 (0.4)	0 (0.0)	0 (0.0)	< 0.01
Musculoskeletal	171 (0.3)	4 (0.7)	0 (0.0)	7 (0.3)	NS
Genitourinary	102 (0.2)	1 (0.2)	0 (0.0)	5 (0.2)	NS
Total	727 (1.4)	15 (2.7)	3 (0.9)	26 (1.3)	< 0.01

(type 1 and type 2) is present in 2% of women of reproductive age.²⁹ The province of Ontario reported an increase of 12% in the number of women with DM among those who delivered between 1996 and 1999.³⁰ Furthermore, GDM is estimated to affect 3.5% of all non-Aboriginal pregnancies and up to an astonishing 18% of Aboriginal women.³¹ The prevalence of pre-gestational DM and GDM in our study population is similar to the above estimates, at 1.2% and 2.6%, respectively. In the United Kingdom, DM2 affected 0.10% and DM1 0.27% of all births.² This two-fold increase in prevalence of DM1 compared with DM2 is similar to our findings (0.75% DM1 vs. 0.43% DM2).

Our comparative analysis found that rates of induction of labour, Caesarean section, preterm birth and hypertensive disorders are consistently higher in Canadian mothers with diabetes than the reference population ($P < 0.001$). In fact, the risk of encountering such complications for DM1 was, on average, 2.5 to 3.0 times greater than that of healthy controls. In Canada, Feig et al.¹⁹ and Yang et al.²⁰ reported similar findings for pregnancy outcomes in women with pre-gestational diabetes (i.e., the studies did not differentiate between DM1 and DM2). Rates of Caesarean section in pre-gestational DM women and controls were 34.9% versus 22.7%¹⁹ ($P < 0.001$) and 49.9% versus 19.5%²⁰ ($P < 0.001$). These rates are similar to our study population (i.e., 51.6% for DM1, 38.0% for DM2 and 27.6% for controls; $P < 0.01$). One fifth (20%) of our DM1 cohort delivered before 37 weeks' gestation; the associated AOR was 2.88 (95% CI 2.38–3.48). Yang et al.²⁰ reported a higher rate of premature birth (defined as less than 37 weeks' gestation) in the pre-gestational DM group (27.7% vs. 5.2% in non-DM mothers; $P < 0.001$). The exact proportion of DM1 in this group is unknown, although a larger number would be expected to alter the results.

Hypertensive disorders of pregnancy are associated with insulin resistance, obesity, and microvascular complications

of diabetes. The observed 2.5 times increase in risk of developing PIH/preeclampsia within our DM1 cohort (AOR 2.80; 95% CI 2.20–3.50) may be related to underlying microvascular disease, which was not captured in the database. Our rate of PIH/preeclampsia of 10% in DM1 is in agreement with a recent UK study⁷ in which the rate of preeclampsia in women with DM1 ($n = 290$) was 13.1% in those who received pre-pregnancy care and 12.7% in those who did not.

DM2 and GDM subtypes are similar disease entities characterized by glucose intolerance, obesity, and insulin resistance. Related mechanisms of pathophysiology may explain the comparable risk of hypertensive disorders noted for these two cohorts (AOR for DM2 1.92, 95% CI 1.32–2.70; AOR for GDM 2.02, 95% CI 1.77–2.31). Interestingly, the prevalence of hypertensive disorders of pregnancy according to DM subtype was found to be non-significant in other published reports.^{4,14,32} In contrast, in a retrospective study of 972 women with GDM,²³ a significant increase in rates of preeclampsia in women with GDM versus women with pre-gestational DM was identified (2% vs. 1.4%; $P < 0.001$). The small sample size for pre-gestational DM ($n = 71$) should be taken into account in the interpretation of these results.

The effect of diabetes during pregnancy on the growing fetus is uncertain, although recently published reports have suggested that DM2 confers a larger risk of perinatal and neonatal complications than other DM subtypes.^{10,11,32} The uncertainty about fetal outcomes in women with DM2 may be related to discrepancies in preconception planning and early antenatal care. In an Italian study, Lapolla et al.¹⁶ found that 29.1% of women with DM2 received pre-pregnancy counselling versus 43.9% of women with DM1 ($P < 0.01$). Clausen et al.³² found that only 5% of pregnancies in women with DM2 were planned, compared with an estimated 70% for women with DM1. Similarly, in a

multicentre study in Spain,¹³ 22.5% of women with DM1 attended a pre-conception clinic but only 9.5% of women with DM2 did so ($P = 0.001$). However, a shorter duration of diabetes exposure (2–8 years vs. 5–16 years; $P = 0.001$) and lower levels of HbA1C in first trimester (6.6 ± 1.51 vs. 7.1 ± 1.22 , $P = 0.001$) did not confer a protective effect on women with DM2 when compared to women with DM1, with no statistically significant difference in perinatal outcomes between the two subtypes.

Several studies have reported that poorer outcomes for women with DM2 may correlate with delayed presentation to a pregnancy clinic for antenatal care. Cundy et al.¹¹ found that women with known DM2 and newly diagnosed DM2 presented significantly later in pregnancy than women with DM1 (16 ± 8 weeks and 24 ± 9 weeks vs. 11 ± 6 weeks, respectively; $P < 0.001$). Clausen et al.³² noted that more than 50% of women with DM2 attended an obstetrical clinic for the first time after the first trimester. The opportunity to optimize folate supplementation and glycemic control before fetal organogenesis is lost if women present after 8 weeks' gestation. Approximately 52% of our DM2 cohort attended an obstetrical visit with a health care provider (family physician, obstetrician, or midwife) in the first trimester. However, this proportion does not include the almost 40% of women for whom status regarding attendance in first trimester was either not entered in the database or was unknown. It is possible that Canadian women with DM2 are entering pregnancy with better glycemic control, and accessing health care earlier in pregnancy than other populations, accounting for somewhat better outcomes.

Macrosomia predisposes the pregnant woman to pelvic injury during delivery because of cephalopelvic disproportion and increased rates of invasive obstetrical interventions (Caesarean section and forceps delivery). We found that women with DM1 and GDM were more likely to have a macrosomic infant (birth weight > 4000 g) than controls (AOR 1.78, 95% CI 1.47–2.14, and AOR 1.16, 95% CI 1.03–1.30, respectively). This is consistent with some published reports,^{6,9,22,23} but contrasts with others, suggesting no significant difference in risk of macrosomia between subtypes of pre-gestational diabetes and/or GDM.^{4,13,14,32}

Rates of shoulder dystocia in our study cohorts appear to correspond with rates of macrosomia. A similar trend was reported by Evers et al.⁸ (associated RR 5.8; 95% CI 2.3–14.7). However, these perinatal outcomes were not found to be statistically significant in our DM2 cohort. A retrospective study of UK women by Dunne et al.¹⁰ also found no significant difference in macrosomia between women with DM2 and the background population (14% versus 10%). Our DM2 population had a greater

proportion of lower birth weight infants, a finding that remains difficult to interpret.

Diabetic embryopathy results from several complex metabolic disturbances, such as maternal hyperglycemia, hyperketonemia, and free oxygen radicals, that induce congenital malformations of major organ systems within the fetus.³³ The overall incidence of major congenital anomalies for women with pre-gestational DM is estimated to be 5% to 10%.⁵ Optimization of maternal glycemic control before and during fetal organogenesis remains our best defence against diabetes-induced anomalies. Our DM1 and GDM cohorts demonstrated a significant risk of congenital anomalies. When compared with the background population, the rate of congenital anomalies in women with DM1 was nearly two-fold in magnitude (AOR 1.71; 95% CI 1.03–2.82, $P < 0.05$). The risk for women with DM2 was equal to the background population. Maternal HbA1C levels were not captured in our database to assess for a correlation with these study outcomes.

The increased risk of congenital malformations in women with DM1 over the general obstetric population has been well established in other studies.^{7–9,16} A prospective multicentre Danish study that included both singleton and multiple gestations⁹ reported a similar relative risk of congenital anomalies for women with DM1 versus controls (RR 1.7; 95% CI 1.3–2.2). The authors also identified the absence of daily blood glucose monitoring before conception and HbA1C levels in each trimester as significant predictors of serious adverse outcomes (congenital malformations or perinatal mortality). The most frequent types of malformations were cardiac (44%), musculoskeletal (18%) and genitourinary (13%). These findings are concordant with the distribution of congenital anomalies observed in Table 3.

The risk potential for congenital malformations across DM subtypes has been investigated in numerous studies and ethnic populations.^{4,5,13,15–17,22,24,32,34} A comparison of outcomes between DM subtypes has produced conflicting results. Women with DM2 have demonstrated worse fetal outcomes for congenital malformations in several studies comparing pre-gestational DM cohorts.^{32,34} In a 2005 Danish study,³² a non-significant trend towards a higher malformation rate in women with DM2 (6.6%) was identified compared with women with DM1 (2.9%). These authors further indicated that more than 50% of their DM2 cohort attended a first antenatal care visit after first trimester. These findings were consistent with those of a prospective, multicohort UK study³⁴ in which the rate of congenital malformation in women with DM2 (12.3%) was three times higher than in women with DM1 (4.4%) ($P = 0.002$). Both studies cited a delay in antenatal care, suboptimal glycemic

control prior to conception, inadequate folate supplementation, and maternal obesity as possible mechanisms to explain the worse outcomes in women with DM2.

In contrast, Lapolla et al.¹⁶ found that the rate of birth defects was significantly higher in women with DM1 (5.9%) than in women with DM2 (2.0%) ($P < 0.001$). These authors postulated that increased disease severity, and more frequent episodes of hypoglycemia and ketoacidosis, might explain the discrepancy between DM cohorts. Conversely, in a population-based study¹⁷ the risk of birth defects in the offspring of women with DM1 and DM2 was found to be similar for both groups.

The risk of congenital anomalies for women with GDM has been analyzed in several recent trials, and found not to be significantly different from the risk to women with pre-gestational DM.^{4,5,13} However, Farrell et al.⁵ noted that GDM conferred the lowest risk with a prevalence ratio of 1.4 (95% CI 0.9–2.0). A subanalysis of this cohort revealed a large proportion of newly diagnosed DM2. The frequency of major congenital anomalies for women with DM1 was 5.9% (95% CI 3.2–9.8) and 4.4% (95% CI 2.4–7.3) for women with known DM2. In our study the increased risk in women with GDM is difficult to explain. The number of women with previously undiagnosed DM2 captured as GDM, use of preconception medication including folate, and maternal BMI are unknown, but may be underlying confounders.

Perinatal mortality is yet another consequence of diabetes for the growing fetus. The CEMACH report² identified that the perinatal mortality rate (defined as the number of stillbirths and early neonatal deaths per 1000 live births and stillbirths) was nearly four times higher in babies born to mothers with DM than in the general obstetric population. However, there was no difference between DM1 and DM2 subtypes in perinatal mortality rate. The overall rate of perinatal mortality and morbidity could not be addressed in our comparative analysis because key variables (e.g., neonatal hypoglycemia, NICU admissions, perinatal mortality as defined by CEMACH) were not captured by the Niday database. However, stillbirth occurred at a rate of 1.1% for women with DM1 in our study population, which is nearly double the rate for the background population (AOR 2.30; 95% CI 1.14–4.11), but not increased in DM2 or GDM.

These findings are comparable to the rates in 1996–1999 outlined in *Diabetes in Ontario: An ICES Practice Atlas*.³⁰ The Practice Atlas reports a stillbirth rate of 1.5% for all women with pre-gestational DM in Ontario in 1999. Lauenborg et al.³⁵ also observed higher rates of stillbirth in DM1 (defined as fetal death at > 24 weeks' gestation) in a 2003 retrospective analysis. The authors identified HbA1C levels that were > 4 SD above the non-DM population, a

history of previous stillbirth, diabetic nephropathy, current smoking, and low socioeconomic status as risk factors for this adverse outcome.

In contrast, Cundy et al.¹¹ found in a retrospective observational study that the overall perinatal mortality across DM subtypes was worse for women with DM2. The composite rate for known and newly diagnosed DM2 was 4.61%, compared with 1.25% for DM1 and 0.89% for GDM ($P < 0.001$). A seven-fold increase in late perinatal death (defined as fetal death between 28 weeks' gestation and term) was found in DM2 relative to the background population. Higher rates were noted for intermediate perinatal death (defined as fetal death between 20 and 28 weeks' gestation) and early neonatal death (defined as infant death between 1 day and 1 month after delivery), but these were statistically non-significant. The authors acknowledged that the rate of perinatal mortality for DM1 was substantially lower than international standards. Our higher rate in DM1 could be the result of "mislabelling" of more severe DM2 as DM1, or possibly less optimal glycemic control in our DM1 population. Further follow-up studies are required.

There are several strengths to our study that should be highlighted. First, the study provides the first analysis of maternal and perinatal outcomes in DM subtypes and non-DM controls within a Canadian population. Our data originate from a large province with an average of 130 000 obstetrical deliveries annually.³⁶ Ontario's ethnic diversity (visible minorities make up approximately one fifth of Ontario's population) and vast size make it suitable to assess trends on a large scale. Results from similar studies to date are limited by data from a single centre.^{4,22} The total number of deliveries captured by the Niday database is consistent with results from a recent study that examined pregnancy outcomes in Ontario women with pre-gestational diabetes, using a similar and well-validated provincial database.¹⁹ Our GDM rate of almost 3.0% of the study population is concordant with current epidemiological estimates for gestational diabetes.^{31,37}

Secondly, though a relatively new initiative, the Ontario Niday Perinatal Database is a fundamental branch of the integrated Ontario Perinatal Surveillance System—a system that is becoming instrumental in providing timely and accurate maternal and newborn information for provincial planning, evaluation and research. Studies like ours are important to highlight deficiencies and opportunities for improved data capture.

Despite its originality and robust size, our study has several limitations. The Ontario Niday Perinatal Database does not capture all key variables of interest; missing variables include pre-pregnancy BMI, pregnancy-associated weight gain, ethnicity, HbA1C levels, rates of folic acid

supplementation, and differences in DM management strategies in both the antepartum and intrapartum periods (i.e., insulin versus oral hypoglycemic agents). Furthermore, as with any administrative database, chart audits are not available, study variables are preset, and under-reporting of mandatory fields and susceptibility to coding errors are inherent problems. We acknowledge the possibility that women were mislabelled within DM cohorts because of these limitations (e.g., women with more severe DM2 mislabelled as DM1 because of early insulin use, and women with DM2 misdiagnosed as GDM). Strategies to ensure quality assurance and validity studies for this database are also recognized as ongoing projects.

CONCLUSION

Compared with other DM subtypes and the general obstetric population, women with DM1 are at greatest risk of encountering major maternal and perinatal complications. Our analysis did not identify worse outcomes in women labelled in our database as having DM2. However, this should not lead to complacency in the detection and treatment of DM2. The progressive rise in maternal age and increasing obesity in women of reproductive age predict a worsening burden of diabetes in pregnancy. Perinatal databases are important tools for understanding the impact of diabetes in pregnancy. Clinicians, researchers, and administrators must continue to work together to ensure accurate data collection that provides meaningful guidance in health care delivery.

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