Rebecca Karkia, Tara Giacchino, Helen Watson, Andrew Gough, Ghada Ramadan and Ranjit Akolekar*

Maternal and neonatal complications in pregnancies with and without pre-gestational diabetes mellitus

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Abstract

Objectives: To compare pregnancy complications in pregnancies with and without pre-gestational diabetes mellitus (DM) managed in a multidisciplinary high-risk diabetes antenatal clinic.

Methods: This screening cohort study was undertaken at a large maternity unit in the United Kingdom between January 2010 and December 2022. We included singleton pregnancies that booked at our unit at 11–13 weeks' gestation. Univariate and multivariate logistic regression analysis was carried out to determine risks of complications in pregnancies with type 1 and type 2 DM after adjusting for maternal and pregnancy characteristics. Effect sizes were expressed as absolute risks (AR) and odds ratio (OR) (95 % confidence intervals [CI]).

Results: The study population included 53,649 singleton pregnancies, including 509 (1.0 %) with pre-existing DM and 49,122 (99.0 %) without diabetes. Multivariate logistic regression analysis demonstrated that there was a significant contribution from pre-existing DM in prediction of adverse outcomes, including antenatal complications such as fetal defects, stillbirth, preterm delivery, polyhydramnios, preeclampsia and delivery of large for gestational age (LGA) neonates; intrapartum complications such as caesarean delivery (CS) and post-partum haemorrhage; and neonatal complications including admission to neonatal intensive care unit, hypoglycaemia, jaundice and hypoxic ischaemic encephalopathy (HIE). In particular, there was a 5-fold increased risk of stillbirth and HIE.

Conclusions: The maternal and neonatal complications in pregnancies with pre-existing DM are significantly increased compared to those without DM despite a decade of intensive multidisciplinary antenatal care. Further research is required to investigate strategies and interventions to prevent morbidity and mortality in pregnancies with pre-gestational DM.

Keywords: diabetes mellitus; insulin-dependent diabetes; pre-gestational diabetes mellitus; adverse pregnancy outcomes

Introduction

Type 1 and 2 diabetes mellitus (DM) are associated with a significantly increased risk of pregnancy complications such as congenital fetal defects, preterm delivery, preeclampsia, large for gestational age (LGA) neonates and caesarean delivery as well as an increased risk of neonatal complications including admission to neonatal intensive care unit (NICU), hypoglycaemia, respiratory distress syndrome (RDS), jaundice and neonatal death [1–4]. Since the 1980s and over the last 4-5 decades, national and international professional bodies such as the World Health Organisation (WHO), International Diabetes Federation (IDF) and the Diabetes National Service Framework (NSF) in the United Kingdom (UK) emphasized the need to optimise care for such high-risk pregnancies in order to reduce the risk of these major pregnancy complications [5, 6]. A report of the Confidential Enquiry into Maternal and Child Health (CEMACH) in 2003 stated that despite the introduction of such policies there was no reduction in the rate of pregnancy complications and in fact, the risk

***Corresponding author: Professor Ranjit Akolekar**, MD, MRCOG, Institute of Medical Sciences, Canterbury Christ Church University, Kent, UK; and Medway Fetal and Maternal Medicine Centre, Medway NHS Foundation Trust, Medway Maritime Hospital, Gillingham, Kent ME7 5NY, UK, E-mail: ranjit.akolekar@canterbury.ac.uk. https://orcid.org/0000-0001-7265-5442

Rebecca Karkia, Department of Obstetrics, Medway NHS Foundation Trust, Kent, UK; and Institute of Medical Sciences, Canterbury Christ Church University, Kent, UK

Tara Giacchino, Institute of Medical Sciences, Canterbury Christ Church University, Kent, UK; and Medway Fetal and Maternal Medicine Centre, Medway NHS Foundation Trust, Kent, UK

Helen Watson, Department of Obstetrics, Medway NHS Foundation Trust, Kent, UK

Andrew Gough, Department of Endocrinology and Diabetes, Medway NHS Foundation Trust, Kent, UK

Ghada Ramadan, Oliver Fisher Neonatal Unit, Medway NHS Foundation Trust, Kent, UK

of stillbirth was nearly 4-fold higher amongst mothers with pre-existing DM compared to those without DM [7]. This led the National Institute of Clinical Excellence (NICE) to recommend in 2008 that the management of all pregnancies with pre-gestational DM should be undertaken by a multidisciplinary team of specialists including obstetricians, endocrinologists or diabetes physicians and specialist midwives [8, 9]. These recommendations have been in vogue for more than a decade but there is limited evidence about the impact of such multidisciplinary care on pregnancy complications in pregnancies with pre-gestational DM and whether the rates of complications and in particular, stillbirth have changed since the introduction of these policies [10–13].

The objectives of our study were to first, assess the rates of antenatal, intrapartum and neonatal complications in pregnancies with pre-gestational DM compared to without; second, to derive accurate estimates of risks for these complications after adjustment for maternal and pregnancy characteristics using multivariable logistic regression analysis for each of these adverse outcomes and third, to undertake a stratified analysis in pregnancies with type 1 and type 2 DM.

Materials and methods

Study population

This was a retrospective cohort study undertaken at Medway Fetal and Maternal Medicine Centre, United Kingdom between January 2010 and December 2022 in a prospectively screened large, unselected population. At our hospital, all women attend at 8–10 weeks' gestation for booking their pregnancy care at our hospital and then at 11–13 weeks' gestation for dating of the pregnancy, combined screening for fetal aneuploidies and systematic examination of fetal anatomy [14–16]. At this visit, we record maternal demographic characteristics, obstetric and medical history. Those with risk factors such as pre-existing DM are referred to specific multidisciplinary clinics for management of their pregnancy. Data regarding maternal demographic characteristics, medical history, ultrasound findings and pregnancy outcome is recorded on an electronic database (Viewpoint version 5.6; GE Healthcare, Buckinghamshire, UK). Neonatal outcome data is recorded on BadgerNet Database (Clevermed Ltd, UK). The protocol for this study was approved by the National Research Ethics Committee (REC reference number 20/HRA/3076).

Inclusion and exclusion criteria

The inclusion criteria for this study were first, singleton pregnancies; second, those that booked at our hospital prior to 14 weeks' gestation; third, those that were managed in the antenatal period in the diabetes multidisciplinary clinic and lastly, those that delivered at our hospital. We included each pregnancy as a single event and included more than one pregnancy for the same woman. We excluded multifetal pregnancies and those that were lost to follow-up. The pregnancies meeting inclusion criteria were divided into those that had pre-existing DM type 1 or 2, those that were diagnosed with gestational DM (GDM) during their pregnancy and those that were non-diabetic. We excluded pregnancies with GDM from further analysis. The study groups for this cohort study were formed of pregnancies with pre-existing DM and those without DM, which formed the control group.

Multidisciplinary management of pregnancies with pre-existing diabetes mellitus

Mothers with pre-existing DM were offered pregnancy care by a multidisciplinary team (MDT) in a dedicated high-risk obstetric clinic, which included a Consultant Obstetrician with a special interest in diabetes, Consultant endocrinologist/diabetes physician, dedicated diabetes specialist midwives supported by a dietician.

The antenatal care was divided into appointments to assess maternal and fetal well-being. Appointments to ensure maternal well-being included immediate contact with the DM MDT following booking of the pregnancy and the antenatal care was in line with national recommendations from NICE and RCOG [8, 9]. Pregnancies with pre-existing DM were followed up for assessment every 1–2 weeks, depending on their control of glycaemia. All women were offered retinal and renal assessment at their first antenatal clinic appointment if this was not already undertaken in the 3 months prior to conception. Women were offered dedicated advice from the MDT clinic regarding treatment plan along with recommendations for maintaining blood glucose and ketones within normal ranges. Women were offered elective delivery around 37–38 completed weeks' gestation unless there were standard obstetric indications for an iatrogenic preterm delivery prior to this gestation [8, 9]. Fetal assessments for pregnancies with DM included ultrasound scans, which were carried out in a dedicated clinic in the Fetal Medicine Unit, which was held on the same day as the obstetric MDT DM high-risk clinic to ensure that there was a holistic approach to management of these pregnancies. All women were offered a scan at 11–13 and 20–22 weeks' gestation for fetal anatomy with an additional fetal echocardiography scan to examine fetal cardiac anatomy and growth/Doppler assessments from 28 weeks every 3–4 weeks until delivery. Additional ultrasound scans were arranged if there were concerns with fetal anatomy, growth or Doppler findings.

Outcome measures

The outcome measures were divided into antenatal and intrapartum adverse outcomes; antenatal outcomes included fetal defects, fetal demise, preterm delivery, fetal growth abnormalities, polyhydramnios and hypertension in pregnancy. Fetal defects were divided into those related to the central nervous system (CNS), cardiovascular system (CVS), renal, gastrointestinal, musculoskeletal and genetic causes. Fetal demise included miscarriages, defined as pregnancy loss prior to 24 weeks' gestation and stillbirth defined as fetal death after this gestational age but before birth of the neonate. Preterm births were classified into those that delivered <32 (early) and <37 (any) weeks' gestation. Neonates with birthweight (BW) <10th percentile were classified as small for gestational age (SGA) and those >90th percentile were classified as LGA [17]. Polyhydramnios was diagnosed when the deepest pool of amniotic fluid was >8 cm; a deepest pool of 8–11 cm was

classified as mild and ≥12 cm as moderate/severe [18]. Gestational hypertension was diagnosed when there was new-onset of hypertension in pregnancy with maternal blood pressure (BP) >140/90 mm Hg at or after 20 weeks' gestation without significant proteinuria; the presence of gestational hypertension with significant proteinuria with a protein-creatinine ratio of >30 mg/mmol was defined as preeclampsia [19]. Intrapartum adverse outcomes included rates of induction of labour (IOL), operative deliveries, postpartum haemorrhage (PPH), obstetric anal sphincter injury (OASIS) and shoulder dystocia. Lucas classification was used to classify caesarean delivery as scheduled or emergency [20]. PPH was defined as an estimated blood loss (EBL)>1,000 mL in third stage of labour and was classified as either moderate (1,001–2000 mL) or severe (>2000 mL) [21]. OASIS encompassed third- and fourth-degree vaginal tears, which involved a perineal injury to the anal sphincter complex and anorectal mucosa [22]. Shoulder dystocia was defined as a vaginal delivery that required additional obstetric manoeuvres to deliver the fetus after delivery of the head and failure of gentle traction; severe dystocia was defined as one requiring the need for internal fetal manoeuvres [23].

The neonatal outcome measures examined were admission to neonatal intensive care unit (NICU), hypoxic ischaemic encephalopathy (HIE), hypoglycaemia, respiratory distress syndrome (RDS), jaundice, and neonatal death. Hypoxic-ischemic encephalopathy (HIE) was diagnosed when there was disturbed neurologic function with evidence of perinatal hypoxia reflected in either a 5-min APGAR score<5 or umbilical artery cord pH<7.0 or base deficit>12 mmol/L, supported by neuroimaging evidence of acute brain injury [24]. Hypoglycaemia was defined by neonatal serum glucose level<2.6 mmol/L [25]. Respiratory distress syndrome was defined as the inability to maintain adequate oxygen saturations with spontaneous respirations and need for additional respiratory support. Neonatal jaundice was based on visual inspection and observation of yellow discoloration of skin or sclera coupled with an elevated serum total bilirubin measurement.

Statistical analysis

Data were expressed as median (interquartile range) for continuous variables and as n (%) for categorical variables. Comparison of the maternal and pregnancy characteristics between those with and without pre-existing DM was by the χ^2-square test or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables, respectively. Significance was assumed at 5 %.

Data for maternal and neonatal complications were inputted in contingency tables and absolute risks (AR) with 95 % confidence intervals (CI) were estimated by determining the prevalence of these complications in all pregnancies with Type 1 DM, Type 2 DM and non-diabetic controls. Univariate logistic regression analysis was carried for each maternal and neonatal complication to derive unadjusted odds ratio (OR) with 95 % CI. Multivariate logistic regression analysis with backwards stepwise elimination was then carried out to estimate adjusted OR (95 % CI) for each maternal and neonatal complications after adjustment for maternal and pregnancy characteristics. Prior to the regression analysis, the continuous variables were centred by subtracting the arithmetic mean from each value to avoid the effects of multicollinearity. The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) and MedCalc Statistical Software version 18.5 (MedCalc Software, Ostend, Belgium, 2018) were used for data analyses.

Results

Study population

During the study period, 53,649 women with singleton pregnancies were booked for delivery at our hospital. We excluded 1,929 pregnancies (3.6 %) who were lost to follow up and 2,089 (3.9 %) who were diagnosed with GDM during the pregnancy; the study population was therefore formed of 49,631 singleton pregnancies, including 509 (1.0 %) with pre-gestational DM and 49,122 (99.0 %) controls without DM. In the pre-gestational DM group, there were 237 (46.6 %) pregnancies with type 1 DM and 272 (53.4 %) with type 2 DM.

Maternal and pregnancy characteristics

The maternal and pregnancy characteristics in the study population are shown in Table 1. In pregnancies with pre-existing DM compared to non-diabetic controls, the median maternal age, weight, BMI and BW percentile were higher whereas gestational age at delivery was lower. In pregnancies with pre-gestational DM, there was a higher prevelance of obesity with BMI>35 and>40, women of Afro-Carribean and South Asian racial origin, cigarette smokers, pregnancies conceived by IVF and those with chronic hypertension, epilepsy and autoimmune disorders. In pregnancies with type 1 DM compared to pregnancies without DM, the maternal age was lower, there were fewer women of Afro-Carribean origin who delivered at an earlier gestational age whereas there was a higher prevalence of Caucasian women, those with chronic hypertension and autoimmune disorders who delivered a neonate with a higher birth weight centile. In contrast, in pregnancies with type 2 DM compared to those without DM, maternal age was higher, there was a signficantly higher proportion of women with BMI>35 and 40, those from Afro-Caribbean, South Asian and mixed racial origin and those with medical co-morbidities such as chronic hypertension and Epilepsy. In pregnancies with type 2 compared to type 1 DM, there were fewer women of Caucasian race, more women from Afro-carribean and South Asian racial origin, significantly higher proportion of women with BMI>35 and 40 and fewer women with autoimmune disorders (Table 1).

Antenatal adverse outcomes

In pregnancies with pre-existing DM compared to non-diabetic controls, there were significantly increased rates of antenatal complications (Supplementary Table S1).

Table 1: Maternal demographic and pregnancy characteristics in pregnancies with pre-gestational diabetes mellitus (DM) compared to those without diabetes.

Maternal demographics	Non-diabetes (n=49,122)	Pre-gestational DM (n=509)	Type 1 DM (n=237)	Type 2 DM (n=272)
Maternal age in years, median (IQR)	29.0 (25.0–32.9)	30.3 (26.2–34.7)[a]	28.2 (24.4–31.3)[b]	33.1 (28.7–37.2)[a]
Maternal weight in kg, median (IQR)	68.6 (59.5–81.0)	82.0 (70.0–98.0)[a]	74.6 (63.9–83.4)[a]	92.0 (76.2–105.0)[a]
Maternal height in cm, median (IQR)	165 (160–169)	164 (160–168)	164 (159–168)	164 (160–168)
Maternal BMI in kg/m^2, median (IQR)	25.2 (22.2–29.6)	30.2 (26.0–36.5)[a]	27.5 (24.0–31.2)[a]	34.0 (28.4–39.2)[a]
BMI in kg/m^2>35, n, %	4,592 (9.3)	157 (30.8)[a]	29 (12.2)	128 (47.1)[a]
BMI in kg/m^2>40, n, %	1,564 (3.2)	77 (15.1)[a]	16 (6.8)[b]	61 (22.4)[a]
Racial origin				
Caucasian, n, %	44,819 (91.2)	430 (84.5)[a]	226 (95.4)[b]	204 (75.0)[a]
Afro-Caribbean, n, %	1,519 (3.1)	28 (5.5)[b]	2 (0.8)[b]	26 (9.6)[a]
South Asian, n, %	2,004 (4.1)	40 (7.9)[a]	6 (2.5)	34 (12.5)[a]
East Asian, n, %	205 (0.4)	2 (0.4)	1 (0.4)	1 (0.4)
Mixed, n, %	575 (1.2)	9 (1.8)	2 (0.8)	7 (2.6)[b]
Conception				
Spontaneous, n, %	48,357 (98.4)	495 (97.2)	231 (97.5)	264 (97.1)
In vitro fertilisation, n, %	765 (1.6)	14 (2.8)[b]	6 (2.5)	8 (2.9)
Cigarette smoking, n, %	7,575 (15.4)	114 (22.4)[a]	47 (19.8)	67 (24.6)[a]
History of medical disorders				
Chronic hypertension, n, %	502 (1.0)	27 (5.3)[a]	8 (3.4)[b]	19 (7.0)[a]
Bronchial asthma, %	3,079 (6.3)	35 (6.9)	13 (5.5)	22 (8.1)
Epilepsy, n, %	410 (0.8)	9 (1.8)[b]	2 (0.8)	7 (2.6)[b]
Thyroid disorders, n, %	579 (1.2)	10 (2.0)	4 (1.7)	6 (2.2)
Inflammatory bowel disorders, n, %	167 (0.3)	0	0	0
Autoimmune disorders, n, %	506 (1.0)	185 (36.3)[a]	179 (75.5)[a]	6 (2.2)
Birth weight in grams, median (IQR)	3,420 (3,065–3,750)	3,305 (2,910–3,670)[a]	3,350 (2,891–3,678)[b]	3,288 (2,918–3,643)[a]
Birth weight percentile, median (IQR)	52.4 (25.5–77.1)	82.8 (52.4–96.8)[a]	88.0 (65.7–97.3)[a]	78.1 (39.6–96.3)[a]
Gestation at delivery, median (IQR)	39.5 (38.6–40.5)	37.1 (36.0–38.1)[a]	37.0 (35.1–37.5)[a]	37.2 (36.2–38.2)[a]

IQR, interquartile range; BMI, body mass index; Mann-Whitney U test for continuous variables and X^2 test and Fishers exact test for categorical variables. Adjusted significance level after *post-hoc* Bonferroni correction for multiple comparisons, [a]p<0.01; [b]p<0.05.

In pregnancies with pre-gestational DM, there was a higher prevalence of fetal defects; in particular, there was an increased prevalence of defects of the central nervous system and cardiovascular system but there was no significant difference in the rate of defects in renal (p=0.915), gastrointestinal (p=0.251), musculoskeletal (p=0.868) or genetic defects (p=0.134). With regard to risk of fetal death, in pregnancies with pre-gestational DM compared to controls, there was no significant difference in risk of miscarriage (p=0.454) but there was a significant increase in risk of stillbirth (1.8 vs. 0.3 %; p<0.001). Similarly, the risk of preterm delivery <32 weeks and <37 weeks; mild and moderate/severe polyhydramnios, preeclampsia and delivery of LGA neonates was significantly higher in pregnancies with pre-existing DM compared to non-diabetic controls but there was no significant difference in the rate gestational hypertension (p=0.531). In pregnancies with type 1 and type 2 DM compared to non-diabetic controls, there was a higher prevalence of fetal defects, stillbirths, risk of preterm birth, polyhydramnios, preeclampsia, and delivery of LGA neonates (Supplementary Table S1).

Multivariate logistic regression analysis demonstrated that even after adjusting for maternal and pregnancy characteristics, there remains an increased risk of antenatal complications in pregnancies with pre-gestational DM (Supplementary Table S2, Figure 1). In pregnancies with type 1 DM compared to non-diabetic controls, there was a 3-fold increased risk of fetal defects, 7-fold increased risk of CVS defects, 3-fold increased risk for stillbirths, 11-fold increased risk of preterm delivery<37 weeks', 7-fold increased chance of a LGA neonate and a 5-fold increased risk of developing polyhydramnios and preeclampsia (Table 2). In pregnancies with type 2 DM, the odds ratios and strength of association with adverse outcomes such as preterm delivery, polyhydramnios, preeclampsia and delivery of a LGA neonate were less than that for type 1 DM but there remained a significantly higher risk of stillbirth with a 6-fold increase compared to non-diabetic pregnancies (Table 3).

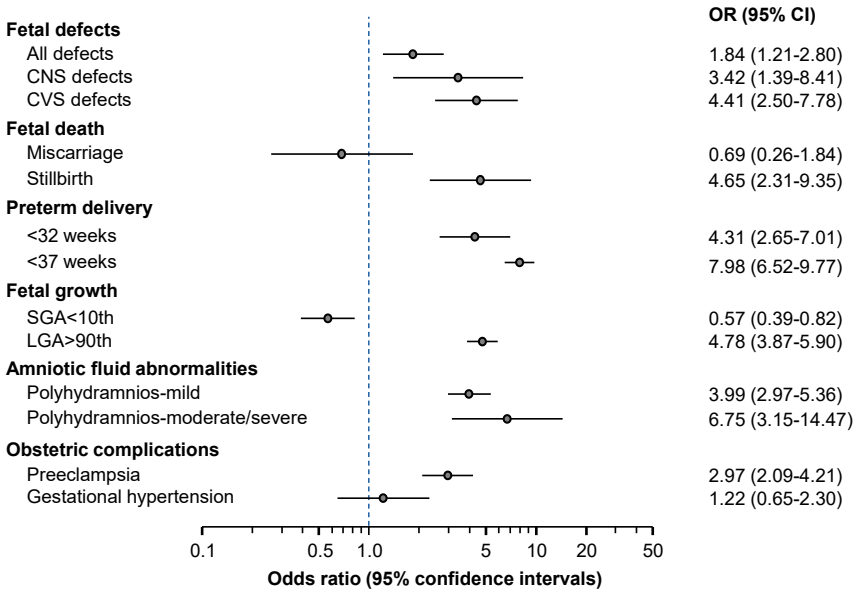

Figure 1: Forest plot demonstrating odds ratios (OR) with 95 % confidence intervals (CI) for antenatal complications in pregnancies with pre-existing diabetes mellitus (DM) compared to those without diabetes mellitus.

Table 2: Univariate and multivariate logistic regression analysis demonstrating the association of type 1 diabetes mellitus with antenatal pregnancy complications.

Antenatal adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-Value	OR (96 % CI)	p-Value
Fetal defects	2.68 (1.61–4.47)	<0.001	2.72 (1.62–4.57)	<0.001
Central nervous system	4.33 (1.37–13.68)	0.013	4.39 (1.39–13.92)	0.012
Cardiovascular	7.94 (4.17–15.13)	<0.001	7.22 (3.76–13.84)	<0.001
Renal	1.35 (0.33–5.45)	0.674	–	–
Gastrointestinal	–	–	–	–
Musculoskeletal	1.82 (0.25–13.10)	0.551	–	–
Genetic	–	–	–	–
Fetal death				
Miscarriage	0.74 (0.18–2.97)	0.668	–	–
Stillbirth	4.08 (1.29–12.87)	0.017	3.37 (1.06–7.16)	0.040
Preterm delivery				
<32 weeks	5.73 (3.18–10.32)	<0.001	5.90 (3.11–11.20)	<0.001
<37 weeks	11.96 (9.23–15.50)	<0.001	11.20 (8.45–14.85)	<0.001
Fetal growth abnormalities				
SGA <10th percentile	0.40 (0.22–0.73)	0.003	0.31 (0.16–0.60)	<0.001
LGA >90th percentile	6.75 (5.21–8.73)	<0.001	7.12 (5.28–9.60)	<0.001
Polyhydramnios		<0.001		<0.001
Mild	7.39 (4.98–10.95)	<0.001	4.19 (2.75–6.38)	<0.001
Moderate/severe	10.36 (3.23–33.19)	<0.001	4.60 (1.40–15.08)	0.012
Obstetric complications				
Gestational hypertension	0.26 (0.04–1.85)	0.177	–	–
Preeclampsia	4.95 (3.26–7.53)	<0.001	4.55 (2.87–7.22)	<0.001

OR, odds ratio; CI, confidence interval; SGA, mall for gestation; LGA, large for gestation.

Table 3: Univariate and multivariate logistic regression analysis demonstrating the association of type 2 diabetes mellitus with antenatal pregnancy complications.

Antenatal adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-Value	OR (96 % CI)	p-Value
Fetal defects	1.12 (0.55–2.27)	0.749	–	–
Central nervous system	2.50 (0.62–10.15)	0.199	–	–
Cardiovascular	2.01 (0.64–6.31)	0.232	–	–
Renal	0.59 (0.08–4,018)	0.593	–	–
Gastrointestinal	–	–	–	–
Musculoskeletal	–	–	–	–
Genetic	–	–	–	–
Fetal death				
Miscarriage	0.64 (0.16–2.58)	0.532	–	–
Stillbirth	7.17 (3.15–16.36)	<0.001	5.90 (2.49–14.01)	<0.001
Preterm delivery				
<32 weeks	3.26 (1.60–6.62)	<0.001	3.12 (1.50–6.47)	0.002
<37 weeks	6.37 (4.90–8.29)	<0.001	5.87 (4.41–7.84)	<0.001
Fetal growth abnormalities				
SGA <10th percentile	0.79 (0.52–1.20)	0.267	–	–
LGA >90th percentile	4.40 (3.42–5.66)	<0.001	3.30 (2.45–4.44)	<0.001
Polyhydramnios		<0.001		<0.001
Mild	8.14 (5.69–11.63)	<0.001	3.82 (2.55–5.72)	<0.001
Moderate/severe	15.32 (6.12–38.34)	<0.001	9.70 (3.79–24.84)	<0.001
Obstetric complications				
Gestational hypertension	2.09 (1.07–4.07)	0.031	–	–
Preeclampsia	2.98 (1.84–4.82)	<0.001	1.95 (1.16–3.29)	0.012

OR, odds ratio; CI, confidence interval; SGA, small for gestation; LGA, large for gestation.

Intrapartum adverse outcomes

In pregnancies with pre-existing DM compared to non-diabetic controls, there was an increased rate of intrapartum adverse outcomes; there was a significantly lower rate of unassisted and operative vaginal births, increased rate of elective and emergency CS and PPH but no significant difference in OASIS (p=0.710) or shoulder dystocia (p=0.433) (Supplementary Table S3). These trends were also noted separately in pregnancies with type 1 and type 2 DM compared with non-diabetic controls (Supplementary Table S3).

Multivariate logistic regression analysis demonstrated that even after adjusting for maternal and pregnancy characteristics, there remains an increased risk of intrapartum complications in pregnancies with pre-gestational DM (Supplementary Table S4, Figure 2). In pregnancies with type 1 DM compared to non-diabetic controls, there were 80 % lower odds of having an unassisted vaginal delivery and a 3-fold increased risk of elective or emergency CS for fetal distress (Table 4). In pregnancies with type 2 DM, there were 60 % lower odds of having an unassisted vaginal delivery and a 2-fold increased rate of elective CS but no significant increase in rate of emergency CS (p=0.103), PPH (p=0.096) after adjusting for maternal and pregnancy characteristics (Table 5).

Neonatal adverse outcomes

In pregnancies with pre-existing DM compared to non-diabetic controls, there was a significantly increased risk of neonatal complications with a higher incidence of admission to NICU, HIE, hypoglycaemia, jaundice, RDS and rate of neonatal death (Supplementary Table S5). These trends were also noted separately in pregnancies with type 1 and type 2 DM compared with non-diabetic controls (Supplementary Table S5).

Multivariate logistic regression analysis demonstrated that, as with antenatal and intrapartum complications, in pregnancies with pre-gestational DM, there is an increased association with neonatal complications, which is significant even after adjusting for maternal and pregnancy

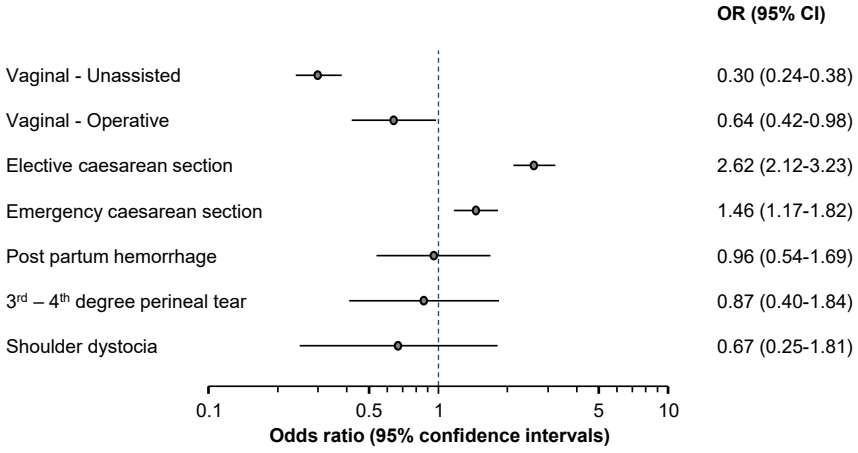

Figure 2: Forest plot demonstrating odds ratios (OR) with 95 % confidence intervals (CI) for intrapartum complications in pregnancies with pre-existing diabetes mellitus (DM) compared to those without diabetes mellitus.

Table 4: Univariate and multivariate logistic regression analysis demonstrating the association of type 1 diabetes mellitus with intrapartum pregnancy complications.

Intrapartum adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-Value	OR (95 % CI)	p-Value
Mode of delivery				
Unassisted vaginal	0.18 (0.13–0.24)	<0.001	0.21 (0.15–0.30)	<0.001
Operative vaginal	0.66 (0.38–1.13)	0.129	–	–
Elective caesarean delivery	4.16 (3.18–5.44)	<0.001	3.28 (2.36–4.58)	<0.001
Emergency caesarean delivery	2.69 (2.06–3.51)	<0.001	1.74 (1.24–2.43)	<0.001
Failure to progress	1.12 (0.66–1.89)	0.673	–	–
Fetal distress	2.96 (2.17–4.04)	<0.001	3.18 (2.27–4.47)	<0.001
Postpartum haemorrhage				
Moderate	2.33 (1.64–3.32)	<0.001	1.12 (0.78–1.61)	0.543
Severe	1.17 (0.43–3.15)	0.758	–	–
Obstetric anal sphincter injury	1.07 (0.40–2.88)	0.896	–	–
Shoulder dystocia				
All	0.72 (0.18–2.92)	0.649	–	–
Severe	2.30 (0.32–16.60)	0.408	–	–

OR, odds ratio; CI, confidence interval.

Table 5: Univariate and multivariate logistic regression analysis demonstrating the association of type 2 diabetes mellitus with intrapartum pregnancy complications.

Intrapartum adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (96 % CI)	p-Value	OR (96 % CI)	p-Value
Mode of delivery				
Unassisted vaginal	0.28 (0.22–0.36)	<0.001	0.40 (0.30–0.53)	<0.001
Operative vaginal	0.36 (0.18–0.70)	0.002	–	–
Elective caesarean delivery	4.00 (3.11–5.14)	<0.001	2.28 (1.74–2.99)	<0.001
Emergency caesarean delivery	2.12 (1.63–2.74)	<0.001	1.27 (0.95–1.70)	0.103
Failure to progress	1.83 (1.23–2.72)	0.003	1.42 (0.93–2.18)	0.105
Fetal distress	1.70 (1.20–2.41)	0.003	1.21 (0.82–1.77)	0.336
Postpartum haemorrhage				
Moderate	1.51 (1.02–2.22)	0.038	0.71 (0.48–1.06)	0.096
Severe	2.33 (1.19–4.55)	0.013	1.18 (0.59–2.34)	0.638
Obstetric anal sphincter injury	0.69 (0.22–2.17)	0.530	–	–
Shoulder dystocia			–	–
All	0.63 (0.16–2.54)	0.516	–	–
Severe	2.01 (0.28–14.45)	0.490	–	–

OR, odds ratio; CI, confidence interval.

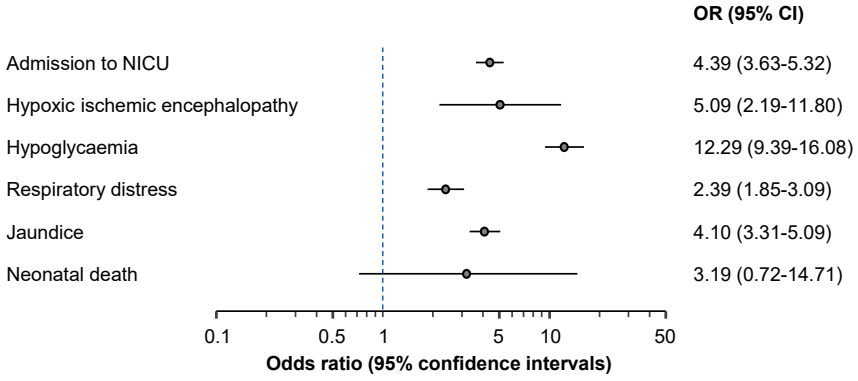

Figure 3: Forest plot demonstrating odds ratios (OR) with 95 % confidence intervals (CI) for neonatal complications in pregnancies with pre-existing diabetes mellitus (DM) compared to those without diabetes mellitus.

characteristics (Supplementary Table S6, Figure 3). In pregnancies with type 1 and type 2 DM, there is a 4-fold increase in admission to NICU, 2-fold increase in RDS, 16-and 12-fold increase in hypoglycaemia, respectively and a 5-fold increase in risk of HIE, compared to non-diabetic controls (Tables 6, 7). There was no significant association with neonatal death in pregnancies with pre-gestational DM after adjusting for maternal and pregnancy characteristics (p=0.127).

Discussion

Principal findings of the study

Our study demonstrates that pre-gestational DM remains an important independent risk factor for major pregnancy complications, despite management of the pregnancy in a multidisciplinary setting over the course of the entire study period. The study confirms that type 1 DM is more common in women of Caucasian racial origin and those with a history of autoimmune medical conditions whereas, type 2 DM is more common in those of Afro-Caribbean and South Asian racial origin, those with obesity and medical conditions such as chronic hypertension. We also demonstrate that in pregnancies with type 1 and 2 DM, there is a substantially increased risk of antenatal, intrapartum and neonatal adverse outcomes, compared to non-diabetic controls and this increased risk remains even after adjusting for other maternal and pregnancy characteristics associated with these adverse outcomes. In pregnancies with type 1 DM, there is an independent increased risk for fetal defects, preterm delivery, pregnancy complications such as polyhydramnios, preeclampsia and stillbirths, caesarean delivery – both elective and emergency, admission to NICU and neonatal complications such as hypoglycaemia, RDS

Table 6: Univariate and multivariate logistic regression analysis demonstrating the association of type 1 diabetes mellitus with neonatal complications.

Neonatal adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-Value	OR (96 % CI)	p-Value
Admission to NICU	7.19 (5.56–9.29)	<0.001	4.67 (3.55–6.16)	<0.001
HIE	5.42 (1.71–17.16)	0.004	5.21 (1.62–16.78)	<0.001
Hypoglycaemia	32.70 (24.04–44.47)	<0.001	16.67 (11.79–23.59)	<0.001
RDS	6.88 (4.96–9.56)	<0.001	2.42 (1.70–3.46)	<0.001
Jaundice	8.16 (6.18–10.78)	<0.001	5.09 (3.79–6.83)	<0.001
Neonatal death	6.12 (0.83–44.87)	0.075	–	–

OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; HIE, hypoxic ischaemic encephalopathy; RDS, respiratory distress syndrome.

Table 7: Univariate and multivariate logistic regression analysis demonstrating the association of type 2 diabetes mellitus with neonatal complications.

Neonatal adverse outcomes	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-Value	OR (95 % CI)	p-Value
Admission to NICU	6.00 (4.73–7.62)	<0.001	4.19 (3.24–5.43)	<0.001
HIE	4.71 (1.49–14.92)	0.008	4.98 (1.55–15.99)	<0.001
Hypoglycaemia	19.04 (13.62–26.60)	<0.001	9.26 (6.37–13.48)	<0.001
RDS	5.51 (2.97–7.66)	<0.001	2.41 (1.69–3.44)	<0.001
Jaundice	5.30 (3.98–7.07)	<0.001	3.32 (2.44–4.50)	<0.001
Neonatal death	5.33 (0.73–39.01)	0.100	–	–

OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; HIE, hypoxic ischaemic encephalopathy; RDS, respiratory distress syndrome.

and HIE. Similarly, in pregnancies with type 2 DM, there is an increased risk of preterm delivery, pregnancy complications such as polyhydramnios, preeclampsia and stillbirths and neonatal adverse outcomes such as hypoglycaemia, RDS and HIE. The main finding of our study is that despite the introduction of multidisciplinary specialist clinics and even after adjustment for maternal and pregnancy characteristics, pregnancies with pre-gestational DM are associated with a 5-fold increased risk of stillbirths and HIE, compared to non-diabetic pregnancies.

Strengths and weaknesses of the study

The strengths of our study are first, the examination of a large cohort of more than 50,000 consecutively screened pregnancies who booked at 11–13 weeks' gestation with available data for antenatal, intrapartum and postnatal outcomes; second, a large cohort of pregnancies with pre-gestational DM that were offered care by a specialist multidisciplinary team; third, antenatal management of pregnancies with pre-gestational DM in a dedicated clinic for such pregnancies in the Fetal Medicine Unit and fourth; the use of multivariable regression analysis to derive adjusted measures of effect size after adjustment for maternal and pregnancy characteristics and to assess for independent contribution from pre-gestational DM in prediction of each adverse outcome. The limitation our study is that this is a study on singleton pregnancies and the estimates for risks in multiple pregnancies may be higher. This is a single centre study and the risks associated with various pregnancy complications are a reflection of care provided in a specialist MDT setting as well as those of the population; therefore, pregnancies with pre-gestational DM who do not receive MDT care may have higher odds of pregnancy complications.

Comparison with other studies

The results of our study are consistent with findings from other studies, which demonstrate that despite provision of intensive, and specialist MDT obstetric care, there remains a significantly increased risk of maternal and neonatal complications in pregnancies with pre-gestational DM [12, 26]. In fact, although the pathways for MDT care for pregnancies with DM were introduced nationally in the UK in 2008, the 5-fold increased stillbirth rate reported in our study is similar to the rates of stillbirth reported over the last 4-5 decades suggesting that the impact of MDT care on fetal mortality has been minimal [1, 7]. A recent population-based study from the Scottish Diabetes Research Network including pregnancies with pre-gestational DM (n=4,681) and those without diabetes (n=808,953) reported that in pregnancies with pre-existing DM, there is evidence of increased risk of preterm delivery and CS but without a reduction in the risk of complications such as stillbirth [27]. The Scottish population study demonstrated that the risk of stillbirth in pregnancies with pre-gestational DM, compared to those without was increased 5-fold (OR 4.65; 95 % CI: 3.59–5.37), which is similar to the findings in our study in which we demonstrate that the risk of stillbirth in pregnancies with DM is increased 5-fold (OR 4.65; 95 % CI: 2.31–9.35). In the same study, Mackin et al., reported that the rate of preterm delivery <37 weeks' in those with and without DM was 30.7 vs. 6.1 %, respectively (OR 6.93; 95 % CI: 6.51–7.38) which is similar to the results of our study with a rate of 36.1 vs. 6.1 % in those with and without DM (OR 6.37; 95 % CI: 4.90–8.29) [27]. There is considerable evidence demonstrating that in pregnancies with pre-gestational DM compared to those without DM, there is a significantly increased risk of fetal defects. In a large nationwide population-based study of 7,296 pregnancies with pre-existing DM, the authors reported a 4-fold increased risk of cardiovascular defects in fetus of mothers with DM compared to those without [28]. In our study, we also found that there was a significantly increased in risk of fetal defects in pregnancies with pre-gestational DM compared to those without; in particular, there was a 3–4 fold increase in defects of the CNS and CVS. A stratified analysis in our study demonstrated that the increased risk was mainly associated with type 1 DM rather than type 2 DM. With regard to intrapartum complications, there is evidence from studies reporting an increased rate of CS and shoulder dystocia [26, 29]. The results from our study also demonstrate that there is a 2–3 fold increased rate of elective CS and emergency CS, but we did not find an association between pre-existing DM and shoulder dystocia, whether mild or severe. A potential explanation for this difference is that in our study population, 67.6 % of pregnancies with pre-gestational DM had a CS and those that delivered vaginally were routinely delivered at 37–38 weeks, thus mitigating the risk of fetal macrosomia in such pregnancies.

Implications for current and future clinical practice

The results of our study demonstrate that despite intensive multidisciplinary management of pregnancies with pre-existing DM from specialist obstetricians, endocrinologists, diabetes physicians and specialist midwives, there remains a significantly increased risk of pregnancy complications

compared to women without diabetes. The main implications of our study are that in order to reduce complications in women with pre-existing DM, further research is required to investigate causes and prevention strategies to reduce the rate of complications in pregnancies with pre-gestational DM. Further research could potentially focus on improving education, support and advice about pre-conception planning and improving glycaemic control prior to embarking on the pregnancy; administration of low-dose Aspirin at a dose of 150 mg/day prior to 16 weeks' gestation to prevent pre-eclampsia and use of CGM/flash monitoring to assess glycaemic status not just in those with type 1 DM but rather type 2 DM. There is limited evidence regarding understanding of the association of complications such as HIE, stillbirths and neonatal deaths in pregnancies with pre-existing DM and further research needs to be carried out to determine the extent to which metabolic complications of hyperglycaemia contribute to adverse outcomes rather than hypoxia secondary to placental dysfunction.

Conclusions

Pregnancies with pre-gestational DM are associated with a substantially increased risk of pregnancy complications despite intensive management in specialist multidisciplinary clinics. In particular, there are significantly increased risks of stillbirth and hypoxic perinatal morbidity in pregnancies with DM compared to those without diabetes. Further research is required to identify strategies to accurately assess and improve glycaemic control during the pregnancy and to investigate the extent to which such strategies reduce adverse outcomes in pregnancies with pre-gestational DM.

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