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ORIGINAL ARTICLE



# Gestational diabetes mellitus: relationship of adverse outcomes with severity of disease

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**ABSTRACT**

**Aims:** To derive accurate estimates of risk of maternal and neonatal complications in women with gestational diabetes mellitus (GDM) and to investigate the association of the effect size of these risks on subgroups of GDM managed with dietary modification, metformin and insulin therapy.

**Methods:** This was a large retrospective cohort study undertaken at a large maternity unit in the United Kingdom between January 2010 and June 2022. We included singleton pregnancies that booked at our unit at 11-13 weeks' gestation. The rates of maternal and neonatal complications in pregnancies with GDM that were managed by a multidisciplinary team (MDT) in the specialist high-risk clinic were compared to those in non-diabetic pregnancies. We stratified pregnancies with GDM into those that were managed with diet, metformin and insulin to pregnancies without diabetes. Logistic regression analysis was carried out to determine risks of pregnancy complications in pregnancies with GDM and its treatment subgroups. Risks were expressed as absolute risks (AR) and odds ratio (OR) (95% confidence intervals [CI]). Forest plots were used to graphically demonstrate risks.

**Results:** The study population included 51,211 singleton pregnancies including 2089 (4.1%) with GDM and 49,122 (95.9%) controls without diabetes. In pregnancies with GDM, there were 1247 (59.7%) pregnancies managed with diet, 451 (21.6%) with metformin and 391 (18.7%) who required insulin for maintaining euglycaemia. Pregnancies with GDM had higher maternal age, body mass index (BMI), higher rates of Afro-Caribbean and South Asian racial origin and higher rates of chronic hypertension. In pregnancies with GDM compared to non-diabetic controls, there was an increased rate of preterm delivery, delivery of LGA neonate, polyhydramnios, preeclampsia, need for IOL, elective and emergency CS and PPH whereas the rate of delivery of SGA neonates and likelihood of an unassisted vaginal delivery were lower. In pregnancies with GDM, there is significantly increased risk of maternal and neonatal complications in those that require insulin compared to those that are managed on dietary modification alone.

**Conclusions:** There is a linear association between the risk of adverse outcomes and the severity of GDM with those on insulin treatment demonstrating an increased association with complications compared to those that have milder disease requiring only dietary modification.

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Gestational diabetes mellitus; pregnancy complications; diet; metformin; insulin

## Introduction

Gestational Diabetes Mellitus (GDM) is characterized by impaired glucose tolerance resulting in hyperglycemia with onset during pregnancy and resolution following childbirth [1,2]. GDM is associated with increased risk of adverse outcomes such as preeclampsia, preterm birth, CS, macrosomia, admission to neonatal intensive care unit (NICU), hyperbilirubinemia and neonatal hypoglycemia [3–5]. There is evidence to suggest that the severity of adverse outcomes depends on the degree of hyperglycemia with a linear association between maternal glucose levels and risk of adverse outcomes [6].

The objectives of our study were to determine the absolute risks (AR) of maternal and neonatal complications in pregnancies with GDM compared to those without DM and to investigate the differences in estimates of risk in pregnancies with GDM managed with

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dietary modification, oral hypoglycemic agents such as metformin and insulin therapy compared to those without diabetes.

## Methods

### Study population

This was a prospective observational cohort study undertaken at Medway Fetal and Maternal Medicine Center, United Kingdom between January 2010 and June 2022 in a large, unselected screening population that booked for their pregnancy care at our hospital prior to 14 weeks' gestation. At our hospital, all women that attend at 11–13 weeks' gestation are offered a scan for dating of the pregnancy, combined screening for fetal aneuploidies and systematic examination of the fetal anatomy [7–9]. We document maternal demographic characteristics and take a detailed obstetric and medical history. The next scan is at 20–22 weeks' gestation for examination of fetal growth and anatomy, placenta and umbilical cord and uterine artery Doppler to assess impedance to blood flow. All women have a structured antenatal care plan depending on presence or absence of risk factors. Those with medical or obstetric risk factors are offered an appointment in specific high-risk clinics whereas those without any risk factors are offered care in the community. Data regarding maternal demographic characteristics, medical history, ultrasound findings and pregnancy outcomes were recorded on an electronic database (Viewpoint version 5.6; GE Healthcare, Buckinghamshire, UK). Neonatal outcome data was 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 for management of their pregnancy prior to 14 weeks' gestation; third, those that were managed in the antenatal period in the specialist diabetes multidisciplinary team (MDT) clinic and lastly, those that delivered at our hospital. We excluded pregnancies with preexisting DM, multiple pregnancies and those that were lost to follow-up. The study therefore included singleton pregnancies with GDM and those without DM; pregnancies with GDM were further stratified into 3 groups based on the treatment plan for management of their glycemia into those that were managed with diet only, those that required oral hypoglycemic agents such as metformin and those that required insulin.

### Screening and management of pregnancies with gestational diabetes mellitus

Screening for pregnancies at risk of GDM is based on specific risk factors from maternal demographics, previous obstetric history, family history and findings from the current pregnancy. Maternal factors include a body mass index (BMI) of >30 kg/m$^2$ and a non-white ethnic origin; previous obstetric risk factors include those who delivered a macrosomic neonate with birthweight (BW) >4500 grams (g), those with a prior diagnosis of GDM; family history of a first-degree relative with a diagnosis of DM and findings from the current pregnancy including a large for gestational age (LGA) fetus, polyhydramnios on ultrasound scan, presence of glycosuria on a urinary dipstick test in pregnancy (1+ on two occasions or 2+ on one occasion) and maternal intake of anti-psychotic drugs such as quetiapine, risperidone, clozapine and olanzapine. In all pregnancies with these risk factors, an oral glucose tolerance test (OGTT) was carried out with administration of a 75 g glucose challenge and a diagnosis of GDM was made if the fasting blood glucose level was ≥ 5.6 mmol/L or the 2-h blood glucose level was ≥ 7.8 mmol/L [2]. The gestational age for OGTT testing depended on the indication; in those with a previous pregnancy with GDM, an OGTT was done in the first trimester and repeated at 24–28 weeks if normal in the first trimester; in those with maternal demographic risk factors or obstetric and family history risk factors the testing was done at 24–28 weeks and in those with current pregnancy risk factors, testing was done when a diagnosis of either a LGA fetus or polyhydramnios was made. During the pandemic, diagnosis of GDM was also based on testing for HbA1C and random or fasting plasma glucose (RPG or FPG, respectively). GDM was diagnosed from either an HbA1c, a random plasma glucose (RPG) test or a fasting plasma glucose (FPG) test and parameters for diagnosis were dependent on the gestational age at testing. GDM at the pregnancy booking appointment was diagnosed when an HbA1c was between 41-47/mmol/mol or when a RPG was between 9-11 mmol/L. Screening for GDM was repeated at 28 weeks for all pregnancies with risk factors and a diagnosis made when an HbA1c ≥ 39 mmol/mol or an FPG ≥ 5.3 mmol/L.

All pregnancies with a diagnosis of GDM were managed by a diabetes MDT in a dedicated high-risk clinic which included a consultant obstetrician with a special interest in diabetes, consultant endocrinologist

or diabetes physician and dedicated diabetes specialist midwives. All mothers are provided advice about diet and exercise by a specialist dietician and nutrition specialist, taught to self-monitor capillary blood glucose levels to maintain a target of <5.3 mmol/L at fasting, <7.8 mmol/L 1-h post meals, and <6.4 mmol/L 2-h post meals. Pregnancies with fasting blood glucose levels of <7.0 mmol/L were offered a 2-week trial of diet modification to assess their glycaemic response to this intervention; if the blood glucose were not below target levels, then they were advised to commence treatment with metformin. Treatment with insulin was advised if the fasting blood glucose levels were ≥ 7.0 mmol/L, there were contraindications to metformin or if there was no satisfactory response to metformin.

### Outcome measures

The outcome measures were divided into maternal and neonatal adverse outcomes. Maternal adverse outcomes included miscarriage, stillbirth, preterm delivery, fetal growth abnormalities, polyhydramnios, preeclampsia, cesarean section and post-partum hemorrhage (PPH). The neonatal outcome measures examined were admission to neonatal intensive care unit (NICU), hypoxic ischemic encephalopathy (HIE), hypoglycemia, respiratory distress syndrome (RDS) and jaundice.

### Statistical analysis

Maternal and pregnancy characteristics were compared between those with GDM and those without diabetes and included a stratified comparison of all 3 treatment groups of GDM to those without DM. We used the $\chi^2$-square test or Fisher's exact test for categorical variables and Kruskal Wallis and Mann-Whitney U-test for continuous variables, respectively. Significance was assumed at 5%. *Post hoc* Bonferroni correction was made to adjust the significance level for multiple comparisons to avoid a type I error. Absolute risks (AR) for maternal and neonatal complications were calculated based on rates in pregnancies with GDM, the treatment sub-groups compared with those in pregnancies without diabetes. Logistic regression analysis was carried out in case of each maternal and neonatal complication to derive odds ratio (OR) with 95% CI. 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 1929 pregnancies (3.7%) who were lost to follow up and 509 (1.0%) pregnancies with preexisting DM, thus forming the study population of 51,211 singleton pregnancies including 2089 (4.1%) with GDM and 49,122 (95.9%) controls without diabetes. In pregnancies with GDM, there were 1247 (59.7%) pregnancies managed with diet, 451 (21.6%) with metformin and 391 (18.7%) who required insulin for maintaining euglycaemia.

### Maternal and pregnancy characteristics

The maternal and pregnancy characteristics in the study population are shown in Table 1.

### Maternal and pregnancy characteristics

In pregnancies with GDM compared to non-diabetic controls, the median maternal age, weight, BMI and BW percentile were higher whereas maternal height and gestational age at delivery were lower. In pregnancies with GDM compared to those without, there was a higher prevelance of obesity with BMI > 35 and 40, women of Afro-Carribbean racial origin, South Asian racial origin, East Asian racial origin, conception by *in vitro* fertilization and maternal chronic hypertension whereas there were fewer women of caucasian origin and cigarette smokers. In sub-group comparison adjusted for *post hoc* significance analysis, similar significant trends of differences were noted in pregnancies with diet control, those on metformin and those on treatment with insulin with the exception that there was no significant difference in rate of pregnancies conceived by *in vitro* fertilization between those with diet control and those on insulin treatment compared to non-diabetic pregnancies but there was a significant difference between those on metformin comapred to those without diabetes. (Table 1).

### GDM-insulin compared to GDM-diet group

In pregnancies treated with insulin compared to those treated with diet al.one, the median maternal age, weight, BMI and BW percentile were higher whereas

**Table 1.** Maternal demographic and pregnancy characteristics in pregnancies with gestational diabetes mellitus (GDM) compared to those without diabetes and stratified by treatment group for GDM.

| Maternal characteristics | Non-diabetes ($n=49,122$) | GDM-All ($n=2,089$) | GDM-Diet ($n=1,247$) | GDM-Metformin ($n=451$) | GDM-Insulin ($n=391$) |
|---|---|---|---|---|---|
| Maternal age in years, median (IQR) | 29.0 (25.0–32.9) | 31.6 (27.9–35.3)** | 31.1 (27.4–34.9)**† | 32.5 (28.6–35.9)** | 32.7 (28.9–36.2)** |
| Maternal weight in kg, median (IQR) | 68.6 (59.5–81.0) | 82.0 (68.5–97.0)** | 79.9 (66.6–94.2)**† | 84.4 (71.2–99.5)** | 86.8 (74.0–100.5)** |
| Maternal height in cm, median (IQR) | 165 (160–169) | 163 (159–168)** | 164 (159–168)** | 163 (158–168)** | 163 (159–168)* |
| Maternal BMI in kg/m$^2$, median (IQR) | 25.2 (22.2–29.6) | 30.8 (26.2–35.8)** | 29.9 (25.4–34.8)**† | 31.9 (27.3–36.5)** | 32.4 (27.2–37.2)** |
| >35, *n* (%) | 4592 (9.3) | 584 (28.0)** | 298 (23.9)**† | 144 (31.9)** | 142 (36.3)** |
| >40, *n* (%) | 1564 (3.2) | 233 (11.2)** | 116 (9.3)**† | 55 (12.2)** | 62 (15.9)** |
| Racial origin | | | | | |
| Caucasian, *n* (%) | 44,819 (91.2) | 1,412 (67.6)** | 971 (77.9)** | 336 (74.5)** | 309 (79.0)** |
| Afro-Caribbean, *n* (%) | 1519 (3.1) | 155 (7.4)** | 99 (7.9)** | 33 (7.3)** | 23 (5.9)* |
| South Asian, n (%) | 2004 (4.1) | 265 (12.7)** | 138 (11.1)** | 72 (16.0)** | 55 (14.1)** |
| East Asian, *n* (%) | 205 (0.4) | 23 (1.1)** | 18 (1.4)** | 2 (0.4) | 3 (0.7) |
| Mixed, *n* (%) | 575 (1.2) | 30 (1.4) | 21 (1.7) | 8 (1.8) | 1 (0.3) |
| Conception | | | | | |
| Spontaneous, *n* (%) | 48,357 (98.4) | 2,029 (97.1) | 1,218 (97.7) | 430 (95.3) | 381 (97.4) |
| *In vitro* fertilization, *n* (%) | 765 (1.6) | 60 (2.9)* | 29 (2.3) | 21 (4.7)** | 10 (2.6) |
| Cigarette smoking, *n* (%) | 7575 (15.4) | 212 (10.1)** | 130 (10.4)** | 38 (8.4)** | 44 (11.3) |
| History of medical disorders | | | | | |
| Chronic hypertension, *n* (%) | 502 (1.0) | 57 (2.7)** | 32 (2.6)** | 6 (1.3)‡ | 19 (4.9)** |
| Epilepsy, *n* (%) | 410 (0.8) | 14 (0.7) | 8 (0.6) | 4 (0.9) | 2 (0.5) |
| Thyroid disorders, *n* (%) | 579 (1.2) | 47 (2.2) | 22 (1.8) | 19 (4.2)** | 6 (1.6) |
| Autoimmune disorders, *n* (%) | 506 (1.0) | 28 (1.3) | 15 (1.2) | 10 (2.2) | 3 (0.8) |
| GA at delivery, median (IQR) | 39.5 (38.6–40.5) | 38.3 (37.5–39.3)** | 39.1 (39.1–40.0)**† | 38.2 (37.4–38.6)**‡ | 37.5 (37.1–38.2)** |
| BW in grams, median (IQR) | 3.42 (3.07–3.75) | 3.42 (3.08–3.77) | 3.48 (3.14–3.82)**† | 3.31 (3.02–3.68)** | 3.37 (3.01–3.69) |
| BW percentile, median (IQR) | 52.4 (25.5–77.1) | 68.5 (38.9–90.4)** | 67.1 (38.7–89.3)**† | 66.8 (37.3–89.4)**‡ | 76.2 (45.9–94.6)** |

IQR, Interquartile range; DM, Diabetes mellitus; GA, Gestational age; BW, Birthweight.
*Comparison with non-diabetes group; †=comparison between GDM-diet and GDM-insulin; ‡=comparison between GDM-metformin and GDM-insulin. Significance level $p$ *$p<0.008$; **$p<0.001$. *Post hoc* Bonferroni correction made for multiple comparisons.

the gestational age at delivery was lower. There was a significanlty higher prevelance of BMI >35 and >40 in pregnancies requring insulin compared to diet al.one but there was no significant difference between the two groups with regard to prevelence of different racial origin ($p=0.058$), cigarette smoking ($p=0.643$), pregnancies conceived by *in vitro* fertilization ($p=0.793$) or those with medical co-morbidities such as chronic hypertension ($p=0.023$), epilepsy ($p=0.773$), thyroid disorders ($p=0.551$) or autoimmune disorders ($p=0.471$). (Table 1).

### *GDM-insulin compared to GDM-metformin group*

In pregnancies treated with insulin compared to those medicated on metformin, there was no significant difference in the median maternal age ($p=0.735$), weight ($p=0.179$), BMI ($p=0.334$) or BW ($p=0.446$) but the gestational age at delivery was lower and BW percentile was higher. Similarly, there was no significant difference in the prevelance of BMI > 35 ($p=0.180$), >40 ($p=0.126$), racial origin ($p=0.159$), cigarette smoking ($p=0.168$), pregnancies conceived by *in vitro* fertilization ($p=0.107$) or those with medical conditions such as epilepsy ($p=0.518$), thyroid disorders ($p=0.919$) or autoimmune disorders ($p=0.089$) except for the high rate of chronic hypertension in those in the insulin treated group. (Table 1).

### *Maternal adverse outcomes*

In pregnancies with GDM compared to non-diabetic controls, there was a significantly increased rate of preterm delivery < 37 weeks, delivery of LGA neonate, polyhydramnios, preeclampsia, need for IOL, elective and emergency CS and PPH whereas the rate of delivery of SGA neonates and likelihood of an unassisted vaginal delivery were lower. There was no significant difference in the rate of miscarriage ($p=0.111$) or stillbirth ($p=0.551$). In sub-group comparisons adjusted for *post hoc* significance analysis, similar trends of significant differences were noted in pregnancies with diet control, those on metformin and those on treatment with insulin with the exception that there was no significant difference in rate of PPH between those on metformin and those on insulin compared to non-diabetic pregnancies. (Table 2). Logistic regression analysis demonstrated that there were higher odds of adverse outcomes in pregnancies that required insulin compared to those that required diet or metformin for management of their dysglycaemia. (Table 3, Figure 1).

**Table 2.** Absolute risk of maternal complications in pregnancies with gestational diabetes mellitus (GDM) compared to those without diabetes and stratified by treatment group for GDM.

| Maternal complications | Non-diabetes ($n=49,122$) | GDM-All ($n=2089$) | GDM-Diet ($n=1247$) | GDM-Metformin ($n=451$) | GDM-Insulin ($n=391$) |
|---|---|---|---|---|---|
| Miscarriage, *n* (%) | 561 (1.1) | 16 (0.8) | 9 (0.7) | 3 (0.7) | 4 (1.0) |
| Stillbirth, *n* (%) | 154 (0.3) | 5 (0.2) | 5 (0.4) | 0 | 0 |
| Preterm delivery | 3015 (6.1) | 227 (10.9)** | 112 (9.0)**† | 44 (9.8)*‡ | 71 (18.2)** |
| SGA <10th percentile, *n* (%) | 5370 (10.9) | 140 (6.7)** | 84 (6.7)** | 33 (7.3) | 23 (5.9)* |
| LGA >90th percentile, *n* (%) | 5262 (10.7) | 529 (25.3)** | 293 (23.5)**† | 107 (23.7)**‡ | 129 (33.0)** |
| Polyhydramnios | 990 (2.0) | 136 (6.5)** | 70 (5.6)**† | 24 (5.3)**‡ | 42 (10.7)** |
| Preeclampsia, *n* (%) | 1142 (2.3) | 86 (4.1)** | 46 (3.7)* | 18 (4.0)* | 22 (5.6)** |
| Induction of labor, *n* (%) | 13,124 (26.7) | 945 (45.2)** | 517 (41.5)**† | 220 (48.8)** | 208 (53.2)** |
| Unassisted vaginal, *n* (%) | 30,820 (62.7) | 917 (43.9)** | 583 (46.8)** | 176 (39.0)** | 158 (40.4)** |
| Elective CS, *n* (%) | 5728 (11.7) | 525 (25.1)** | 268 (21.5)**† | 131 (29.0)** | 126 (32.2)** |
| Emergency CS, *n* (%) | 8326 (16.9) | 496 (23.7)** | 304 (24.4)** | 107 (23.7)** | 85 (21.7)[c] |
| Post-partum hemorrhage, *n* (%) | 4318 (8.7) | 250 (11.9)** | 165 (13.2)** | 44 (9.8) | 41 (10.5) |

SGA = Small for gestational age; LGA = Large for gestational age; CS = caesarean section.
*Comparison with non-diabetes group;
†comparison between GDM-diet and GDM-insulin;
‡comparison between GDM-metformin and GDM-insulin. Significance level *p* *$p<0.008$; **$p<0.001$. *Post hoc* Bonferroni correction made for multiple comparisons.

**Table 3.** Regression analysis demonstrating odds ratio (95% confidence intervals) of maternal adverse outcomes in pregnancies with gestational diabetes mellitus (GDM) stratified by treatment group for GDM.

| | Gestational diabetes mellitus OR (95% CI) | | | |
|---|---|---|---|---|
| Maternal complications | All | Diet | Metformin | Insulin |
| Miscarriage | 0.67 (0.41–1.10) | 0.63 (0.32–1.22) | 0.58 (0.19–1.81) | 0.89 (0.33–2.40) |
| Stillbirth | 0.73 (0.31–1.86) | 1.28 (0.52–3.12) | – | – |
| Preterm delivery | 1.86 (1.62–2.15) | 1.51 (1.24–1.84) | 1.65 (1.21–2.26) | 3.39 (2.62–4.40) |
| SGA <10th percentile | 0.59 (0.49–0.70) | 0.59 (0.47–0.74) | 0.64 (0.45–0.92) | 0.51 (0.33–0.78) |
| LGA >90th percentile | 2.83 (2.55–3.13) | 2.56 (2.24–2.93) | 2.59 (2.08–3.23) | 4.10 (3.32–5.08) |
| Polyhydramnios | 3.39 (2.81–4.07) | 2.89 (2.25–3.71) | 2.73 (1.80–4.14) | 5.85 (4.22–8.11) |
| Preeclampsia | 1.80 (1.44–2.26) | 1.61 (1.19–2.17) | 1.75 (1.09–2.81) | 2.50 (1.62-3.87) |
| Induction of labor | 2.26 (2.07–2.48) | 1.94 (1.73–2.18) | 2.61 (2.17–3.15) | 3.12 (2.55–3.81) |
| Unassisted vaginal | 0.46 (0.43–0.51) | 0.52 (0.47–0.58) | 0.38 (0.31–0.46) | 0.40 (0.33–0.49) |
| Elective CS | 2.54 (2.30–2.82) | 2.07 (1.81–2.38) | 3.10 (2.53–3.81) | 3.60 (2.91–4.46) |
| Emergency CS | 1.53 (1.38–1.69) | 1.58 (1.39–1.80) | 1.52 (1.23–1.90) | 1.36 (1.07–1.73) |
| Post-partum hemorrhage | 1.41 (1.23–1.62) | 1.58 (1.34–1.87) | 1.12 (0.82–1.53) | 1.22 (0.88–1.68) |

SGA, Small for gestational age; LGA; Large for gestational age; CS = cesarean section.

### *GDM-insulin compared to GDM-diet group*

In pregnancies treated with insulin compared to those treated with diet al.one, there was a significantly higher rate of preterm deliveries, delivery of LGA neonates, polyhydramnios, need for IOL and those requring elective CS but no significant difference in the rate of miscarriages ($p=0.558$), stillbirths ($p=0.210$), delivery of SGA neonate ($p=0.551$), preeclampsia ($p=0.754$), emergency CS ($p=0.285$) and PPH ($p=0.153$) (Table 2).

### *GDM-insulin compared to GDM-metformin group*

In pregnancies treated with insulin compared to those medicated on metformin, there was a significantly higher rate of preterm deliveries, delivery of LGA neonates, polyhydramnios but no significant difference in the rate of miscarriages ($p=0.568$), delivery of SGA neonate ($p=0.405$), preeclampsia ($p=0.283$), IOL ($p=0.201$), elective or emergency CS ($p=0.318$ and $p=0.493$, respectively) and PPH ($p=0.726$). (Table 2).

### *Neonatal adverse outcomes*

In pregnancies with GDM compared to non-diabetic controls, there was a significantly increased risk of neonatal complications with a higher incidence of admission to NICU, hypoglycemia, jaundice, and RDS whereas there was no significant difference in the rate of HIE ($p=0.639$). In sub-group comparisons adjusted for *post hoc* significance analysis, similar trends of significant differences were noted in pregnancies with diet control, those on metformin and those on treatment with insulin. (Table 4). Logistic regression analysis demonstrated that there were higher odds of adverse outcomes in pregnancies that required insulin for treatment compared to those that required diet or metformin for management of their dysglycaemia. (Table 5, Figure 1).

### *GDM-insulin compared to GDM-diet group*

In pregnancies treated with insulin compared to those treated with diet al.one, there was a

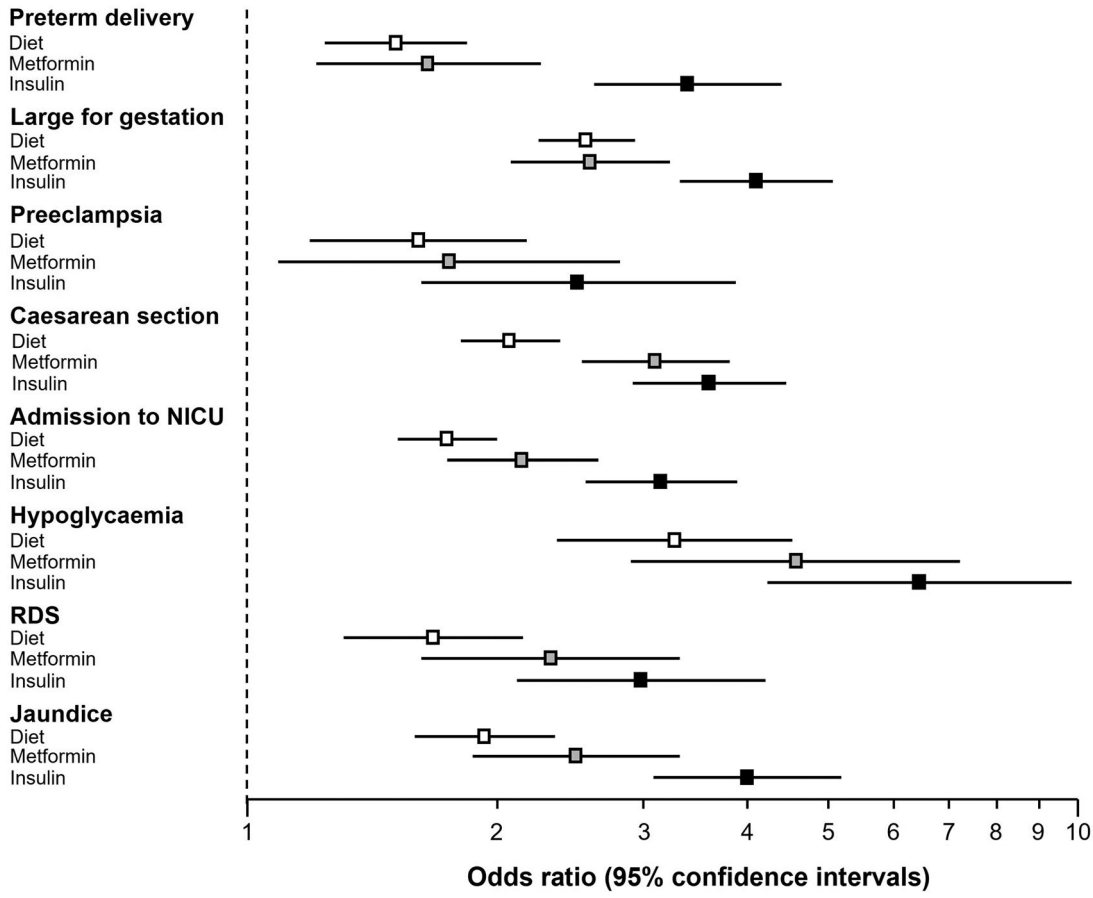


**Figure 1.** Forest plot with odds ratios (OR) with 95% confidence intervals (CI) demonstrating the association of gestational diabetes mellitus (GDM) with pregnancy complications stratified by treatment sub-groups: diet (white squares), metformin (grey squares) and insulin (black squares).

**Table 4.** Absolute risk of neonatal complications in pregnancies with gestational diabetes mellitus (GDM) compared to those without diabetes and stratified by treatment group for GDM.

| Neonatal complications | Non-diabetes ($n=49,122$) | GDM-All ($n=2,089$) | GDM-Diet ($n=1,247$) | GDM-Metformin ($n=451$) | GDM-Insulin ($n=391$) |
|---|---|---|---|---|---|
| Admission to NICU, *n* (%) | 7104 (14.5) | 540 (25.8)** | 284 (22.8)** | 120 (26.6)** | 136 (34.8)** |
| Hypoglycemia, *n* (%) | 493 (1.0) | 94 (4.5)** | 40 (4.0)** | 20 (4.4)** | 24 (6.1)** |
| Respiratory distress syndrome, *n* (%) | 1618 (3.3) | 136 (6.5)** | 67 (5.4)** | 33 (7.3)** | 36 (9.2)** |
| Jaundice, *n* (%) | 2541 (5.2) | 243 (11.6)** | 119 (9.5)** | 54 (12.0)** | 70 (17.9)** |
| HIE, *n* (%) | 116 (0.2) | 6 (0.3) | 5 (0.4) | 1 (0.2) | 0 |

NICU, Neonatal intensive care unit; HIE, Hypoxic ischemic encephalopathy.
Significance level **$p<0.01$. *Post hoc* Bonferroni correction made for multiple comparisons.

significantly higher rate of admission to NICU, RDS and jaundice but no significant difference in the rate of hypoglycemia ($p=0.077$) or HIE ($p=0.210$). (Table 4).

### *GDM-insulin compared to GDM-metformin group*

In pregnancies treated with insulin compared to those medicated on metformin, there was no significant difference in the rate of admission to NICU ($p=0.010$), hypoglycemia ($p=0.268$), RDS ($p=0.319$), jaundice ($p=0.015$) or HIE ($p=0.352$). (Table 4).

## Discussion

### *Principal findings of the study*

The findings of our study demonstrate that first, in pregnancies with diagnosis of GDM, about 20% require treatment with metformin and another 20% require treatment with insulin to manage maternal dysglycaemia; second, the main difference in maternal and pregnancy characteristics that differentiates those that require treatment with insulin, compared to those that are maintained on dietary modification, is the rate of

**Table 5.** Regression analysis demonstrating odds ratio (95% confidence intervals) of neonatal adverse outcomes in pregnancies with gestational diabetes mellitus (GDM) stratified by treatment group for GDM.

| | Gestational diabetes mellitus OR (95% CI) | | | |
|---|---|---|---|---|
| Neonatal complications | All | Diet | Metformin | Insulin |
| Admission to NICU | 2.06 (1.86–2.28) | 1.74 (1.52–2.00) | 2.14 (1.74–2.65) | 3.15 (2.56–3.89) |
| Hypoglycemia | 4.65 (3.71–5.82) | 3.27 (2.36–4.53) | 4.58 (2.90–7.23) | 6.45 (4.23–9.84) |
| Respiratory distress syndrome | 2.05 (1.71–2.45) | 1.67 (1.30–2.14) | 2.32 (1.62–3.32) | 2.98 (2.11–4.21) |
| Jaundice | 2.41 (2.10–2.78) | 1.93 (1.59–2.35) | 2.49 (1.87–3.32) | 4.00 (3.08–5.19) |
| HIE | 1.22 (0.54–2.77) | 1.70 (0.69–4.17) | 0.94 (0.13–6.74) | – |

NICU, Neonatal intensive care unit; HIE, Hypoxic ischemic encephalopathy.

obesity and median maternal age, which is significantly higher in those that require insulin, with no significant differences in other maternal factors; third that the risk of maternal and neonatal complications in pregnancies with GDM is related to the severity of GDM, which is reflected in the treatment required to maintain euglycaemia with a significantly increased rate of complications in pregnancies that have insulin dependent GDM, compared to those that only require dietary modifications.

### *Strengths and limitations*

The strengths of the study are first, examination of a large cohort of consecutively screened and delivered pregnancies in a large tertiary referral fetal medicine, obstetric and neonatal unit; second, the inclusion of pregnancies only managed by a specialist MDT high-risk clinic including a specialist obstetrician, endocrinologist, and specialist midwife; third, the review of case notes of all pregnancies with GDM and ascertainment of maternal and neonatal adverse outcomes by reviewing electronic records and maternity notes to ensure accuracy of outcome records, including the treatment required for management of GDM and fourth, the use of logistic regression analysis to derive measures of effect size for associations of GDM with adverse outcomes. This is a single center study and to a degree, the reported incidence of maternal and neonatal complications is a consequence of contemporary obstetric care provided in a MDT setting but is likely to be affected by the characteristics of our population, such as the racial and socio-cultural mix of the population and the obesity rates as well as the local protocols for antenatal, intrapartum and neonatal care. Our study was limited to singleton pregnancies and the estimates of risk in multiple pregnancies may be higher. Our study highlights the association between BMI and GDM, but a limitation is the lack of data regarding gestational weight gain for the entire cohort. A limitation of our study is that we report results of pregnancies with GDM that have been identified by a risk-factor based screening that is the current guidance in the United Kingdom. It is possible that this approach would underestimate the true prevalence of GDM in the population as this method would not identify GDM in those without risk factors. Our study is over a 12-year period and therefore, included data collected during the COVID pandemic. Nested analysis of data from before and during the pandemic period is not presented in the study and is outside the scope of this manuscript.

### *Comparison with other studies*

Maternal hyperglycemia, which is characteristic of GDM, is associated with increased transplacental passage of glucose to the fetus, resulting in fetal hyperglycemia, hyperinsulinemia and in turn potential maternal and neonatal adverse outcomes [10–14]. There is evidence from studies which demonstrate that effective treatment of hyperglycemia in pregnancies with GDM can potentially reduce adverse pregnancy outcomes [11,15]. The risk of adverse outcomes is related to the degree of hyperglycemia, and this is demonstrated in the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in which the authors reported results on 23,316 pregnancies who completed an oral glucose tolerance test and found that there is a linear association between maternal glycaemic levels and risk of adverse outcomes such as delivery of LGA neonate, preterm delivery, preeclampsia, need for CS, admission to NICU, neonatal hypoglycemia and jaundice [6]. This is consistent with the results of our study in which we demonstrate that there is a linear association in risk of adverse pregnancy outcomes in women with GDM who are treated for maintaining euglycaemia with progressive treatment strategies starting with first, dietary modification; second, oral metformin and third, if still hyperglycemic despite these treatment lines, commencing insulin injections. The risk of preterm delivery in our study was 1.5, 1.7 and 3.4-fold higher than non-diabetic pregnancies in women treated with diet, metformin and insulin, respectively. Similarly, the risk

of preeclampsia was 1.6, 1.8 and 2.5-fold higher in those with GDM treated with diet, metformin and insulin, respectively. Similar trends were also noted for neonatal complications such as neonatal hypoglycemia being 3.3, 4.6 and 6.5-fold high in those that had diet, metformin and insulin for treatment of their GDM, compared to non-diabetic pregnancies. The results of our study also demonstrate that even in GDM pregnancies treated with diet al.one the risks of adverse outcomes are higher compared to those without diabetes, raising the question of whether mild gestational hyperglycemia should be treated early and promptly, rather than not. This was reported in a randomized study - Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial – in which the investigators randomized 1000 women with glucose intolerance/mild GDM to an intervention arm which included treatment with diet and insulin therapy or routine care without intervention. The authors reported that treatment of glucose intolerance/mild GDM reduced the rate of perinatal complications from 4 to 1%. Our study did not find any associations of GDM groups with miscarriage, stillbirth or neonatal deaths, which is consistent with reported literature [11].

## Conclusion

Pregnancies with GDM are associated with an increased risk of maternal and neonatal complications, compared to non-diabetic pregnancies, regardless of the treatment they require to maintain euglycaemia including dietary modification, oral hypoglycemic drugs such as metformin or insulin therapy. There is a linear association between the risk of adverse outcomes and the severity of GDM with those on insulin treatment demonstrating an increased association with complications compared to those that have milder disease requiring only dietary modification. Even pregnancies with a milder GDM requiring dietary modification have a higher risk of adverse outcomes compared to those without diabetes. Further research should be undertaken to investigate whether earlier screening for GDM would identify a cohort of pregnancies that would potentially benefit from earlier and more effective treatment, thus mitigating the association with adverse outcomes and whether treatment of milder disease would improve perinatal outcomes.

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## Data availability statement

Data is available from authors upon request.

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