Short- and long-term outcomes of gestational diabetes and its treatment on fetal development

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Abstract
Globally the prevalence of gestational diabetes mellitus (GDM) is rising mainly due to the increase in maternal obesity. A number of different methods to screen for and diagnose GDM have been described although consensus on the preferred methods does not yet exist. GDM has significant short- and long-term health risks for the mother, developing fetus and the children born to mothers with GDM. Short-term risks for the fetus include macrosomia (excessive birthweight), shoulder dystocia, birth trauma, and hypoglycaemia in the immediate postpartum period. Long-term risks for offspring born to mothers with GDM include increased rates of childhood and adulthood obesity and an increased cardiometabolic risk. A number of pharmacological treatments for GDM have been identified, these include insulin and oral glucose-lowering drugs metformin and glibenclamide. Whilst these oral glucose-lowering drugs show similar short-term childhood outcomes to insulin there is increasing evidence that these drugs may have adverse long-term outcomes on children and adults exposed to the drugs in utero. Future research on treatments for GDM should include long-term follow-up of children exposed to glucose lowering medication in utero to determine the long-term cardiometabolic risk in the offspring born to mothers with GDM.

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder of pregnancy, which is defined as new onset hyperglycaemia in women without overt diabetes prior to pregnancy and which resolves postnatally.1 The timing of onset of GDM can vary during pregnancy but it is typically diagnosed at 24 to 28 weeks gestation. The prevalence of GDM overall is increasing but accurate prevalence is difficult to record as it is influenced by the diagnostic criteria employed and the characteristics of the population. A number of different diagnostic criteria have been described (Table 1) with the prevalence being shown to be 2.4 times higher when the International Association of Diabetes in Pregnancy Study Group (IADPSG)2 criteria are used compared to the 1999 World Health Organisation (WHO) Criteria3 (this has now been replaced by the WHO 2013 guidelines).4 In 2012, the landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study including 25,505 women who underwent an oral glucose tolerance test with blood sampling at baseline and both one and two hours post the 75 g oral glucose load was published.5 This study found the prevalence of GDM to vary between 9% and 26% (mean 18%) in the 15 centres from the nine different countries involved (using a diagnostic criteria of pre-existing diabetes of >5.8 mmol mmol/l for the fasting plasma glucose and >11.1 mmol/L for the 2-hour plasma glucose, the average glucose values at which the odds of birthweight, Cord C-peptide and percentage body fat reached 1.75 times the estimate odds of these outcomes at mean glucose values based on the fully adjusted logistic regression models from HAPO). Regardless of the diagnostic criteria used the prevalence of GDM is also increasing.
worldwide due to an increase in maternal obesity, maternal age, and physical inactivity.6

As well as there being no consensus on the preferred diagnostic criteria of GDM, the screening criteria and timing of antenatal screening also differs depending on the guideline employed. Early screening is generally undertaken in the first trimester to exclude pre-existing diabetes in women who are at high risk. How this ‘risk’ is defined depends on the guideline used. The different guideline screening recommendations are summarized in Table 1. Some of the guidelines use risk factors for GDM as a screening method7,8 whilst others use risk factors for diabetes mellitus (DM) as a screening method for GDM.1,9 There is also no consensus on the best early screening tool used for GDM: fasting plasma glucose, random plasma glucose, HbA1c and an oral glucose tolerance test (OGTT) have all been described in national and international guidelines.1,2,7-9 Screening for GDM in later pregnancy is generally performed with an OGTT conducted between 24 and 28 weeks' gestation with the results of the screening test also being used to make the diagnosis. This 2-hour 75-g OGTT is endorsed by a number of national guidelines (Table 1) including the National Institute of Clinical Excellence in the UK.8 A two-step glucose challenge test (to screen for GDM) followed by an OGTT (to diagnosis GDM) for those with positive results is the screening and diagnostic method recommended by the American College of Obstetricians and Gynaecologists.10

The pathogenesis of GDM is defined by the inability of the maternal pancreas to respond to the increased insulin requirements of pregnancy.11 Pregnancy is a state of insulin resistance which results in a need for an increase in insulin secreted from the pancreatic beta cells. Pregnancy hormones (human placental lactogen, prolactin, progesterone and oestrogen) create a re-orientation of maternal metabolism from glucose to lipid utilization in order to facilitate glucose supply for the developing fetus.12 In normal pregnancy, the maternal pancreas responds to this change by increasing the amount of insulin secreted in order to maintain normal blood glucose levels. Post-partum the maternal insulin sensitivity quickly returns to normal.13 Women with GDM have increased insulin resistance compared to women without GDM and this resistance is likely to be present prior to pregnancy and to persist across pregnancy.11 The reduction in insulin sensitivity, combined with an inadequate response from the pancreatic beta cells to increase the insulin production results in maternal hyperglycaemia.

GDM is important to diagnose and treat in pregnancy because of its adverse short and long-term maternal and fetal outcomes. For the mother, short term complications of GDM include an increase in the risk of serious perinatal complications such as gestational hypertension, caesarean section,12 pre-eclampsia and shoulder dystocia.14-16 Long-term maternal complications of GDM include a high likelihood of recurrence of GDM in a subsequent pregnancy (estimated to be as high as 48% in a recent meta-analysis)17 and an increased risk of the mother developing type 2 diabetes in later life (50% of women who have GDM will develop type 2 diabetes within 5 to 10 years, which is a 7-fold increased risk over women without GDM)18,19 The adverse outcomes of GDM for the fetus are the focus of this review and discussed in detail below.

Management of GDM aims to reduce the risk of adverse maternal and fetal outcomes by reversing hyperglycaemia. The landmark ACHOIS (Australian Carbohydrate Intolerance Study in Pregnancy)20 study was the first study to show a reduction in maternal and fetal morbidity with the introduction of medical interventions for GDM. GDM should be managed by a multidisciplinary team with endocrine and obstetric clinical input as well as diabetes specialist nurses and dieticians. Maternal education is key to good glycaemic control in women with GDM though there remains debate and uncertainty about the most appropriate method and frequency of home glucose monitoring and whether more frequent monitoring by continuous glucose monitoring will have additional benefits.21 Lifestyle intervention comprising of dietary modification, physical activity and weight management is the first line treatment for GDM. If hyperglycaemia persists despite lifestyle intervention, pharmacological therapy can be introduced. Drug treatment for GDM includes glucose lowering agents metformin and glibenclamide (also known as glyburide) and insulin.22 There has also been interest in the use of non-pharmacological agents such as myo-inositol, which is an isomer of inositol and occurs endogenously and is found in natural dietary sources such as fruits, vegetables, nuts and cereals. Whilst there is some evidence that myo-inositol can lower blood glucose, there remain a lack of data on clinically relevant outcomes.23 Results of ongoing trials are awaited. Postnatally, women with GDM are advised to stop any pharmacological treatment they had been taking for GDM because of the rapid return of insulin sensitivity. However, because of the increased risk of developing type 2 diabetes in later life, they should be offered screening in the postnatal period. There is again a lack of consensus on the mechanism of screening employed in the

What is already known about this topic?

- The prevalence of GDM is increasing and set to continue to rise due to the global increase in maternal obesity
- Short-term fetal outcomes of GDM include increased risk of birth trauma, macrosomia and hypoglycaemia
- Long-term fetal outcomes of GDM include increased rates of childhood and adulthood obesity and an increased cardiometabolic risk

What does this study add?

- There remains a question over the long-term outcomes of GDM, particularly in the context of glucose-lowering drugs such as metformin
- Future studies should include follow-up of children exposed to glucose-lowering drugs to determine the future cardiometabolic risk
postnatal period (HbA1C or a fasting glucose \(^8\)) but most national guidelines recommend that some form of postpartum screening should be performed between 4 weeks and 6 months postnatal and then on an annual basis.

## 2 | SHORT-TERM IMPACT OF GDM ON FETAL DEVELOPMENT

As well as being associated with adverse maternal outcomes, GDM is associated with adverse fetal outcomes which were demonstrated definitively in the landmark HAPO study published in 2008.\(^14\) Maternal hyperglycaemia is associated with fetal macrosomia (excessive birth weight usually defined as greater than 4 kg) which in turn is associated with an increased risk of shoulder dystocia and birth trauma.\(^24\) Maternal GDM can also lead to fetal hypoglycaemia in the immediate postpartum period when the newborn is still hyperinsulinaemic and this may in turn lead to an increase in neonatal unit admission.\(^14,24\) GDM is also known to be associated with an increased risk of respiratory distress in the newborn infant which again can lead to an increase in neonatal unit admission.\(^14,25\)

Most GDM guidelines recommend elective birth (induction of labour or elective caesarean section) in women with GDM around the estimated date of delivery and before this if there are any maternal or fetal complications.\(^8\) In women with pre-existing diabetes, elective birth is recommended at an earlier gestation (normally from 37 weeks’

### TABLE 1 | Screening and diagnostic thresholds for GDM

| Organisation | Screening | Diagnostic thresholds | Fasting mmol/l (mg/dl) | 1 hour mmol/l (mg/dl) | 2 hours mmol/l (mg/dl) |
|--------------|-----------|-----------------------|------------------------|----------------------|------------------------|
| IADPSG\(^2,a\) | All women or high-risk women, Decision based on background frequency of glucose intolerance in local population | 75 | ≥5.1 (92) | ≥10.0 (180) | ≥8.5 (153) |
| WHO\(^3,b\) | Screening should be determined by individual countries based on prevalence of glucose intolerance in local population | 75 | ≥5.1 (92) | ≥10.0 (180) | ≥8.5 (153) |
| NICE\(^8,c\) | ≥1 risk factor for GDM: • BMI >30 kg/m\(^2\) • Previous macrosomic baby ≥4.5 kg • Previous GDM • First-degree relative with diabetes mellitus (DM) • Family origin with high prevalence of DM | 75 | ≥5.6 (101) | | ≥7.8 (140) |
| SIGN\(^7,d\) | ≥1 risk factor for GDM: • BMI >30 kg/m\(^2\) • Previous macrosomic baby ≥4.5 kg • Previous GDM • First-degree relative with diabetes mellitus (DM) • Family origin with high prevalence of DM | 75 | ≥5.1 (92) | ≥10.0 (180) | ≥8.5 (153) |
| ADA\(^1,e\) | Women with ≥1 risk factor for DM: • First-degree relative with DM • High-risk race or ethnicity • History of cardiovascular disease • Hypertension (140/90 mmHg or taking antihypertensives) • High-density lipoprotein <35 mg/dL, triglycerides >250 mg/dL • Polycystic ovarian syndrome (PCOS) • Physical inactivity • Other clinical conditions association with insulin resistance (eg, acanthosis nigricans) | 75 | ≥5.1 (92) | ≥10.0 (180) | ≥8.5 (153) |
| Diabetes Canada\(^9\) | All pregnant women without known pre-existing DM | 75 | ≥5.3 (95) | ≥10.6 (190) | ≥9.0 (162) |

\(^a\)International Association of Diabetes and Pregnancy Study Groups.
\(^b\)World Health Organisation.
\(^c\)National Institute for Health and Care Excellence.
\(^d\)Scottish Intercollegiate Guidelines Network.
\(^e\)American Diabetes Association.
gestation to 38 + 6 weeks’ gestation) to reduce the risk of perinatal death, although it remains uncertain whether GDM is associated with an increased risk of perinatal death as the evidence is conflicting. A large cohort study conducted in France of over 50,000 births demonstrated an increased risk of perinatal mortality of up to 30% in infants born at term to mothers with GDM compared to mothers without diabetes. When the analysis was conducted excluding those births thought to be complicated by pre-existing diabetes (defined by the presence of glucose lowering medication given to women in the year following delivery) the increased risk of perinatal death was only present in women with diet-controlled GDM. In contrast, a population cohort study from Canada of over 1 million women showed a reduction in perinatal mortality in mothers with GDM (relative risk [RR] 0.63, 95% confidence intervals [CI] 0.43-0.94) and a population cohort study from Sweden (n = 1,260,297 women) demonstrated no difference in perinatal mortality in women with GDM compared to the nondiabetic population (odds ratio [OR] 0.80, 95% CI 0.58-1.10). Current guidelines therefore recommend elective delivery to reduce the risk of maternal and fetal morbidity but not to reduce the risk of perinatal mortality except in the case of pre-existing diabetes.

The association between GDM and fetal anomaly also remains uncertain. There is clear evidence of an association between pre-existing diabetes and congenital anomaly with women with pre-existing diabetes having double the amount of congenital anomalies than would be expected in a nondiabetic population, however the evidence for GDM is conflicting. The Canadian study discussed above demonstrated an increased risk of congenital anomaly in the pregnancies complicated by GDM compared to non-diabetic pregnancies (absolute risk 37.5 per 1000 births in GDM vs 29.04 per 1000 births in the nondiabetic population) however it is important to note that this study may have included women with pre-existing type 2 diabetes mellitus thus potential overestimating the rate of congenital anomalies. Another smaller study of 5500 women with GDM demonstrated no differences in rates of congenital anomaly in babies born to mothers with GDM compared to normal glucose tolerance (2.3% vs 1.5% respectively, P > .05). No increased screening for congenital anomaly is currently recommended for women with GDM.

### 3 | LONG-TERM IMPACT OF GDM ON FETAL DEVELOPMENT

Long-term fetal outcomes of GDM include increased rates of obesity and an increased cardiometabolic risk in both childhood and adulthood. The HAPO study found an increase in neonatal cord c-peptide levels (a marker of insulin resistance) above the 90th percentile and neonatal adiposity in pregnancies complicated by GDM which were both positively correlated with maternal hyperglycaemia. The follow up of the HAPO study (4160 children) found that across the maternal glucose spectrum (fasting, 1 and 2 hour measurements after glucose load) higher levels of maternal glucose positively correlated with higher childhood glucose and insulin resistance in the offspring. This reduction in insulin sensitivity in offspring of mothers with GDM had also been demonstrated earlier in smaller studies. Further the HAPO follow up study (4832 children) demonstrated a significantly increased odds of obesity at age 10 to 14 years in offspring of pregnancies complicated by untreated maternal GDM compared to no GDM (OR 1.58, 95% CI 1.24-2.01, P < .001) after adjustment for maternal body mass index (BMI). Children born to mothers with GDM were also more likely to have a sum of skinfolds >85th percentile (OR 1.57, 95% CI 1.27-1.95, P < .001), body fat percentage > 85th percentile (OR 1.35, 95% CI 1.08-1.68, P = .007) and waist circumference > 85th percentile (OR 1.34, 95% CI 1.08-1.67) compared to children born to mothers without GDM.

Population studies have demonstrated that these changes displayed in childhood are likely to be sustained into adulthood. A population study from Denmark of over 1.7 million births found followed up over a 30 year period found that offspring born to mothers with GDM had an increased risk of disease of the circulatory system (Hazard Ratio [HR] 1.3, 95% CI 1.1 to 1.6 based on the international classification of Disease-10 “diseases of the circulatory system” [rheumatic fever, hypertensive disease, ischaemic heart disease, disease of pulmonary circulation, other forms of heart disease, cerebrovascular disease and diseases of arteries, veins and other diseases of the circulatory system]). A study from Finland demonstrated that adults (n = 916, mean age 24.1 ± 1.3 years) born to mothers with GDM had increased rates of insulin resistance and an increased atherogenic lipid profile compared to adults born to mothers without GDM after adjustment for offspring adiposity. Ongoing adult follow up studies will provide further insights into the long-term consequences of in-utero exposure to maternal GDM especially in terms of cardiometabolic outcomes.

### 4 | SHORT- AND LONG-TERM IMPACT OF TREATMENT OF GDM ON FETAL DEVELOPMENT

Pharmacological treatments of GDM aim to reduce maternal hyperglycaemia and hence reduce maternal and fetal morbidity. In the United States, Canada, Australia and many European Countries the first-line drug treatment for GDM after failure of lifestyle interventions is insulin. Insulin has been used safely in pregnancy for many years as it does not cross the placenta and the FDA has sufficient evidence to classify the risk of insulin use as “low” in pregnancy. A Cochrane review reported limited evidence to support one type of insulin regimen over another however there is growing evidence that insulin analogues are likely to be a safe alternative to human insulin in pregnancy. Although considered safe to use in pregnancy, insulin also has significant disadvantages as it can cause maternal hypoglycaemia, increase weight gain and requires education in administration and the inconvenience of multiple injections. Therefore, in the management of GDM oral glucose-lowering agents have received much clinical and research interest.
Glibenclamide/glyburide is an oral glucose lowering agent. Transplacental transfer is highly variable, but concentrations in new borns are usually very low. It has been shown in a large randomized controlled study to have similar rates of short-term adverse perinatal outcomes compared to insulin (proportion of macrosomia was 7% in the glibenclamide group vs 4% in the insulin group and admission to the NNU was 6% in the glibenclamide group vs 7% in the insulin group). However, there is paucity of evidence regarding the longer-term childhood outcomes of the use of glibenclamide in pregnancy. Glibenclamide is not commonly used in the management of GDM in the UK as a pilot randomized study showed insulin was superior for add-on therapy with metformin. Insulin was also associated with lower episodes of hypoglycaemia compared to glibenclamide.

In the UK, the oral lowering agent metformin is the first-line pharmacological therapy for the treatment of GDM and has also been recommended for use in GDM by the USA Society for Maternal-Fetal Medicine. Metformin has been shown to be beneficial for the mother in terms of controlling glucose and limiting gestational weight gain however there has been concern regarding the longer-term adverse outcomes for the offspring. Metformin crosses the placenta and has similar concentrations in fetal and maternal circulations and thus has the potential to affect the developing feto-placental unit. A large randomized controlled trial of metformin vs insulin for the treatment of GDM (MiG trial) showed no increased in short term adverse outcomes of metformin use compared to insulin (proportion of perinatal complications [composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, Apgar score < 7 or prematurity] was 32% in the metformin group vs 32.2% in the insulin group, RR 1.0 [95% CI 0.90-1.10]). Metformin was also more acceptable to women than insulin and thus metformin has been established as a first line pharmacological therapy for management of GDM. Although, the MiG trial was not powered to look at longer-term outcomes in the offspring, follow up studies have been conducted. A meta-analysis including data from the MiG follow-up studies and published in 2019 examined long-term outcomes of children exposed to metformin vs insulin for the treatment of GDM. Metformin-exposed children were found to have lower average birthweights compared to children exposed to insulin (mean difference −107.7 g, 95% CI -182.3, −32.7, \(P = .005\)). However, in the neonatal phase infants exposed to metformin were significantly heavier than those exposed to insulin (mean difference 440 g, 95% CI 50-830, \(P = .03\)) and in mid-childhood (aged 5-9) metformin exposed children were had a higher BMI compared to insulin-exposed children (mean difference 0.78 kg/m², 95% CI 0.23, 1.33, \(P = .005\)) and tended to be heavier (mean difference 1.13 kg 95% CI -0.19, 2.45). A further offspring follow-up study of the use of metformin in pregnancy, this time for the treatment of polycystic ovarian syndrome (PCOS) as opposed to GDM, had similar results to the meta-analysis described above. In this 5 to 10 year follow up study (141 children of the PregMet trial, children exposed to metformin had a higher BMI compared to the placebo group (difference in means = 0.41, 95% CI 0.03-0.78, \(P = .03\)).

In summary metformin exposure in utero appears to alter the growth trajectory postnatally of the offspring compared to insulin or placebo. Further studies are required to understand the significance of this growth trajectory change, in particular with regard to longer-term cardiometabolic risk in the children of mothers with GDM to determine if this increased risk continues into adulthood.

5 | CONCLUSIONS

GDM remains the most common metabolic disturbance during pregnancy and hence constitutes a significant global health burden. Despite this, there are considerable uncertainties and variations in clinical guidelines for GDM screening, diagnosis and management. Increasing evidence suggests GDM has significant short and long-term complications for both the mother and the offspring. Several treatment options are available for GDM and are discussed here but there is paucity of evidence regarding the long-term outcomes of these treatment strategies. Future research is needed to understand the cardiometabolic risk in offspring of mothers with GDM.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

No additional data available

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