Gestational diabetes

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Abstract

One in six live births occur in women with diabetes mellitus, of which the most common type, accounting for approximately 87.5% of all diabetes in pregnancy, is gestational diabetes mellitus (GDM). Maternal hyperglycaemia is one of the principle determinants of maternal–fetal complications in pregnancy in GDM. In particular, hyperglycaemia is most commonly associated with increased rates of instrumental and/or operative delivery, pre-eclampsia, increased adiposity, macrosomia and infant birthweight >90th percentile. Large for gestational age infants have an increased risk of birth complications, including shoulder dystocia and stillbirth. Maternal hyperglycaemia is also one of the factors most amenable to treatment during pregnancy. For most women with GDM, dietary and lifestyle modifications are sufficient to achieve glycaemic targets and optimal pregnancy outcomes. This chapter summarizes the latest evidence-based recommendations for the screening, diagnosis and treatment of pregnancies complicated by GDM. It considers the International Association of Diabetes and Pregnancy Study Groups and the National Institute for Health and Care Excellence guidelines. The evidence in support of dietary interventions for antenatal management and treatment options for postpartum care are reviewed.

Keywords Diabetes; gestational diabetes mellitus; hyperglycaemia in pregnancy; large for gestational age; macrosomia; MRCP; pregnancy

Key points

- Treatment of diabetes mellitus in pregnancy reduces the risk of perinatal complications, including pre-eclampsia, pregnancy-induced hypertension, caesarean delivery, large for gestational age babies and neonatal adiposity in women with gestational diabetes mellitus (GDM)
- There is inadequate evidence to recommend universal screening for GDM across all countries. Screening should be tailored to the clinical and economic needs of the region
- Continuous glucose monitoring provides a direct measure of fetal exposure to maternal blood glucose concentrations and will be used increasingly in research and in clinical practice
- The potential benefits of oral hypoglycaemic agents (metformin, glibenclamide) should be weighed against their uncertain long-term risks on the developing fetus

Introduction

In the UK, an estimated 700,000 pregnancies are affected by diabetes mellitus per year, and 87.5% of these are classified as gestational diabetes mellitus (GDM). Worldwide it is estimated that 1 in 6 live births occur in women with diabetes, causing challenges for low- and middle-income countries. For the mother, GDM is associated with increased risk of pre-eclampsia, delivery by caesarean section and later development of type 2 diabetes. Risks to the offspring include increased adiposity, macrosomia and birthweight that is large for gestational age (LGA). Although serious perinatal complications such as death, shoulder dystocia, bone fracture or nerve palsy are rare (1–4%), macrosomia (infant birthweight >4 kg) and LGA (birthweight >90th percentile) are common, affecting 10–20% of neonates born to women with GDM.

The World Health Organization (WHO) has previously defined GDM as any degree of hyperglycaemia (regardless of severity) with an onset or first recognition during pregnancy. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) now uses the term 'overt diabetes' to describe the phenomenon of severe hyperglycaemia appearing to mimic pre-existing diabetes.

For all pregnant women, hyperglycaemia should be considered as a continuous risk variable (like maternal weight and blood pressure measurements), rather than being dichotomized as normal or abnormal based on arbitrary diagnostic cut-offs. The recognition that the relationship between maternal blood glucose concentration and maternal–fetal outcomes is a continuum has, however, created controversy regarding appropriate diagnostic thresholds.

Pathophysiology

A normal pregnancy is characterized by a progressive increase in insulin resistance from the second trimester until delivery. It is attributed to a variety of factors, including increased secretion of human placental lactogen, growth hormone and cortisol during pregnancy. A combination of increased maternal adiposity and insulin resistance both contribute to hyperglycaemia in women with inadequate pancreatic β-cell function.

Implications of GDM for pregnancy outcomes

Women diagnosed with GDM are more susceptible to pre-eclampsia, caesarean section delivery, premature delivery and

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development of type 2 diabetes.[1] Serious perinatal complications such as death, fetal organomegaly, shoulder dystocia, bone fracture and nerve palsy are rare, complicating 1–4% of GDM pregnancies. However, perinatal complications such as macrosomia (infant birthweight >4 kg) and LGA infants are common, complicating 10–20% of these pregnancies. Macrosomic and LGA infants have an increased risk of longer term insulin resistance, cardiovascular disease, obesity and diabetes, with female offspring having a higher chance of developing GDM during future pregnancies.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study of >25,000 pregnant women confirmed that maternal glucose levels are directly associated with adverse pregnancy outcomes, independent of other risk factors such as maternal obesity.[1] The even larger Indian Gestational Diabetes Prevention and Control Project included >57,000 pregnant women. It also demonstrated that women with GDM had higher rates of pregnancy-induced hypertension, preterm and caesarean delivery, and antepartum and postpartum haemorrhage, with maternal and neonatal outcomes directly related to maternal blood glucose concentration.

Risk factors for the development of GDM[2]

Risk factors are:

- a past history of impaired glucose tolerance or GDM
- maternal body mass index (BMI) >30 kg/m^2
- a family history of diabetes (particularly in a first-degree relative)
- a previous LGA infant or infant >4.5 kg
- an ethnic origin associated with a high prevalence of type 2 diabetes (e.g. Indian, Pakistani, Bangladeshi, Middle-Eastern, Caribbean).

The risk of GDM is increased when multiple risk factors are present. Retrospective studies suggest increased risk in women with polycystic ovary syndrome, subfertility, long-term glucocorticoid use or conception via assisted reproductive technologies. However, 30–50% of affected women have no known risk factors.

Screening for GDM

Early identification and intervention to reduce fetal exposure to maternal hyperglycaemia can decrease perinatal morbidity, in particular macrosomia, shoulder dystocia and pre-eclampsia. However, whether screening should be universal or targeted at recognized high-risk groups remains controversial, and there remains a lack of uniformity within and between countries.

GDM screening can be a one- or a two-step process. In the two-step process, all women receive a 50 g 1-hour glucose challenge test (GCT). Those who screen positive (glucose >7.8 mmol/litre) are offered a 75 g oral glucose tolerance test (OGTT) to confirm the diagnosis. The one-step approach omits the GCT and women go straight to a 75 g 2-hour OGTT. A 2017 Cochrane review concluded that there was insufficient high-quality evidence to determine which was the superior GDM screening strategy.

Currently, most professional organizations (IADPSG, WHO, National Institute for Health and Care Excellence (NICE), Endocrine Society, Australasian Diabetes in Pregnancy Society) recommend the one-step approach at 24–28 weeks' gestation. The NICE guidelines also advise early screening, as soon as possible after pregnancy is confirmed, for women with previous GDM, either by self-monitoring of blood glucose (SMBG) or by a 75 g OGTT. The United States Preventive Services Task Force (USPSTF) found evidence supporting screening of asymptomatic pregnant women after 24 weeks of gestation but found there is insufficient evidence to assess the balance of benefits and harms of screening before 24 weeks, gestation.

Diagnosis of GDM

The NICE guidelines recommend that GDM be diagnosed if fasting glucose is ≥5.6 mmol/litre, or the 2-hour post-OGTT glucose is ≥7.8 mmol/litre. The IADPSG consensus panel recommends a lower fasting glucose of ≥5.1 mmol/litre, a 1-hour post-OGTT glucose of ≥10.0 mmol/litre or a 2-hour value of 8.5 mmol/litre.[3] The WHO and American Diabetes Association (ADA) support the IADPSG diagnostic criteria.

It is worth noting that different populations of women manifest different proportions of hyperglycaemia at each point of the OGTT. For example, the IADPSG's threshold for GDM (fasting glucose ≥ 5.1 mmol/litre) is reached by 25% of women with GDM in Hong Kong, yet in Barbados and the USA this figure was closer to 75%. The reasons for this may be partially explained by differences in maternal age, BMI and family history of diabetes in different populations, but the exact mechanism underlying this phenomenon remains unclear.

Monitoring hyperglycaemia in pregnancy

Management should be tailored to the personal preferences of the woman with GDM. In general, women are advised to carry out SMBG at least four times daily, most typically before breakfast and at 1–2 hours after each of the main meals.

The use of continuous glucose monitoring (CGM) has allowed far greater insights into maternal blood glucose concentration during pregnancy, in particular, to quantify overnight and postprandial glucose excursions. Newer glucose monitoring systems, which do not require SMBG, are becoming increasingly accurate, accessible and affordable. Evaluation of the use of the Abbott Diabetes Care FreeStyle Libre flash glucose monitoring system in pregnant women with diabetes found good agreement between the FreeStyle Libre system and SMBG.

Preliminary data suggest that CGM may also be useful not only as a research tool to better understand and quantify fetal exposure to maternal glycaemic excursions, but also to guide clinical management. Another study demonstrated potential for improved maternal–fetal outcomes, reporting less pre-eclampsia, fewer primary caesarean sections and fewer LGA infants among CGM users. As CGM becomes more affordable, it will probably play an increasing role in the detection and clinical management of GDM and as an outcome measure in clinical trials.

Non-pharmacological therapy

Women with GDM should aim for glucose levels below the following targets:

- fasting glucose <5.3 mmol/litre
- 1-hour postprandial glucose <7.8 mmol/litre

- 2-hour postprandial glucose <6.4 mmol/litre.

The initial treatment for GDM is dietary modification, aiming for the best glucose control safely achievable, adequate gestational weight gain and fetal well-being.[2] The recommended caloric intake for women is outlined in Table 1. Diet and lifestyle changes are effective for approximately two-thirds of women with GDM. Data from a landmark trial in a multiethnic population confirmed the effectiveness of lifestyle modification for improving obstetric and neonatal outcomes (Table 2) but lacked detailed dietary information.[4]

A recent systematic review concluded that all dietary interventions are moderately effective at improving maternal blood glucose concentration and reducing neonatal birthweight outcomes.[5] However, the quality of the published trials does not support any single diet (e.g. low fat, low carbohydrate, Mediterranean, total energy restriction, low glycaemic index) as being most effective. Further well-designed dietary intervention studies in GDM are needed, particularly in low- and middle-income countries where the global health consequences of GDM are most significant.[5]

NICE also recommends 30 minutes of moderate exercise per day for women with GDM.[2] Weight loss during pregnancy is generally not recommended, but whether this remains true for obese women is disputed. For women with a pre-pregnancy BMI >30 kg/m^2, energy restriction to reduce the amount of weight gained can be achieved by restricting caloric intake to approximately 30% below the recommended Dietary Reference Intake for women during pregnancy.

Recommended caloric intake during pregnancy

Weight classification during pregnancy	Recommended intake
Underweight	Up to 40 kcal/kg/day or 167 kJ/kg/day
Ideal weight	30 kcal/kg/day or 126 kJ/kg/day
Overweight	22–25 kcal/kg/day or 92–105 kJ/kg/day
Obese	*Minimum of* 1800 cal*/day to prevent ketosis*
Morbidly obese	12–14 kcal/kg/day or 50–59 kJ/kg/day

Based on recommendations from the ADA guidelines on GDM, 2004.

Table 1

Oral anti-hyperglycaemic agents

Metformin is recommended as a potential second-line therapy for women unable to achieve glucose targets with 1–2 weeks of diet and lifestyle changes.[2] A Cochrane review concluded that there were insufficient clinical data comparing metformin with other agents, such as glibenclamide and acarbose, to draw meaningful conclusions as to which agent is clinically superior.

However, a systematic review comparing metformin with glibenclamide found that glibenclamide is inferior to both insulin and metformin with respect to neonatal and obstetric outcomes in GDM. When compared with glibenclamide, metformin was associated with less macrosomia (risk ratio 0.33, confidence interval 0.13–0.81)), lower birthweight (pooled mean difference −209 g (confidence interval, −314 g to −104 g)), fewer LGA infants (pooled risk ratio 0.44 (confidence interval, 0.21–0.92)) and less maternal weight gain (pooled mean difference −2.06 kg (confidence interval −3.98 kg to −0.14 kg). Caution is warranted when prescribing either metformin or glibenclamide as both agents cross the placenta, and their long-term effects on a developing fetus are largely unknown.

Insulin therapy

The decision to commence insulin treatment is typically based on the level of maternal glycaemic control that has been achieved after 1–2 weeks of diet and lifestyle changes.[2] Overnight intermediate or long-acting insulin is given if fasting glucose concentrations remain above target, with fast-acting insulin analogues given before the main meals as required. Given the controversial nature of the use of oral agents that cross the placenta (including

Effects of treatment of mild GDM on maternal and perinatal morbidity

Variable	Treatment	Control	Relative risk (97% CI)	*p*-value
Maternal outcomes				
Caesarean delivery (%)	26.9	33.8	0.79 (0.64–0.99)	0.02
Pre-eclampsia or pregnancy-induced hypertension (%)	8.6	13.6	0.63 (0.42–0.96)	0.01
Weight gain (kg)	2.5 ± 4.5	5.0 ± 3.3		<0.001
BMI at delivery (kg/m^2)	31.1 ± 4.5	32.3 ± 5.2		<0.001
Neonatal outcomes				
Shoulder dystocia (%)	1.5	4	0.37 (0.14–0.97)	0.02
Birthweight (g)	3302 ± 502	3408 ± 589		<0.001
Birthweight >4000 g (%)	5.9	14.3	0.41 (0.26–0.66)	<0.001
Birthweight ≥90th percentile (LGA) (%)	7.1	14.5	0.49 (0.32–0.76)	<0.001
Fat mass (g)	427 ± 198	464 ± 222		0.003
Birthweight ≤10th percentile (SGA) (%)	7.5	6.4	1.18 (0.7–1.99)	0.49

SGA, small for gestational age.

Table 2

metformin and glibenclamide), the ADA and the American College of Obstetricians and Gynecologists (ACOG) recommend insulin as the preferred agent for treating GDM with suboptimal control achieved with diet and lifestyle modifications alone.

Prevention of type 2 diabetes

GDM increases a woman's risk of developing GDM in subsequent pregnancies, as well as overt type 2 diabetes, particularly within 5 years of diagnosis. LGA infants and higher maternal pre-pregnancy weight increase the risk of recurrent GDM. The Nurses' Health Study found that women with GDM also have an increased risk of developing cardiovascular disease in later life (hazard ratio (HR) 1.30, 95% confidence interval (CI) 0.99 −1.21). The risks were highest among those who later progressed to type 2 diabetes (HR 3.71, 95% CI 1.79−7.67).

GDM is also a risk factor for developing type 1 diabetes in the postpartum period, particularly in women who have particular human leucocyte antigen alleles such as DR3 and DR4. It is worth noting that lean women who develop diabetic ketoacidosis during pregnancy and postpartum hyperglycaemia may have pre-existing unrecognized type 1 diabetes rather than GDM.

To follow up women with GDM, NICE recommends offering women a fasting plasma glucose test 6−13 weeks postpartum to exclude diabetes, with glycated haemoglobin levels being a suitable, but less ideal alternative for women who cannot tolerate a fasting specimen. Moreover, breastfeeding reduces the risk of both maternal and paediatric rates of diabetes.

Annual screening for overt diabetes using fasting glucose should also be recommended.[2] Given that BMI and waist circumference are the strongest anthropometric measurements associated with an increased risk of developing type 2 diabetes after a diagnosis of GDM, women should be advised to maintain a healthy weight. However, there is a paucity of high-quality, randomized trials supporting the use of dietary and lifestyle modifications in preventing the development of GDM in obese women.

Future directions

Whether interpregnancy dietary and/or pharmacological interventions can mitigate these risks and reduce the recurrence of GDM and/or progression to type 2 diabetes warrants high-quality randomized controlled trials. Given that most obese women do not develop GDM, further research is needed to develop more effective tools for early detection and treatment of GDM in women at risk of developing the condition. ◆

KEY REFERENCES

1 Metzger B, Lowe L, Dyer A, et al. Pregnancy outcome (HAPO) study cooperative research group. *N Engl J Med* 2008; **358:** 991−2002.

2 National Institute for Health and Care Excellence. Gestational diabetes: risk assessment, testing, diagnosis and management. 2017 (accessed 24 April 2018), https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2.

3 Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33:** 676−82.

4 Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *New Engl J Med* 2009; **361:** 1339−48.

5 Yamamoto JM, Kellett JE, Balsells M, et al. Gestational diabetes mellitus and diet: a systematic review and meta-analysis of randomized controlled trials examining the impact of modified dietary interventions on maternal glucose control and neonatal birth weight. *Diabetes Care* 2018; **41:** 1346−61.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 35-year-old South Asian woman presented for antenatal care at 12 weeks' gestation. She had had gestational diabetes mellitus in her previous pregnancy.

What is the most appropriate next step in her management?

A Perform a glucose challenge test immediately as she has not been fasting
B Perform an HbA_{1c} measurement to check for overt diabetes
C Perform a 75 g oral glucose tolerance test (OGTT) at 24−28 weeks' gestation
D Perform a 75 g OGTT or 1 week of self-monitoring of blood glucose immediately
E Perform a random laboratory blood glucose test every 2−4 weeks

Question 2

A 28-year-old woman presented with her first pregnancy. She had no family history of diabetes and was not overweight. A 75 g oral glucose tolerance test (OGTT) had been performed at 24 weeks' gestation. The results were 4.5 mmol/litre fasting and 8.6 mmol/litre at 2 hours after the OGTT.

What is the next most appropriate action?

A Initiate insulin therapy immediately
B Repeat the OGTT as this might be a false-positive result
C Perform an HbA_{1c} measurement to screen for overt diabetes
D Do nothing because her normal fasting glucose means her pregnancy is low risk
E Diagnose gestational diabetes mellitus

Question 3

A 24-year-old woman was pregnant with her first child. At 30 weeks she was found to have a raised fasting plasma glucose. She was commenced on 2 weeks of substantial dietary modifications.

Investigations at 32 weeks

- Fasting plasma glucose 6.0–7.3 mmol/litre (3–6)
- Ultrasound scan was consistent with fetal growth acceleration

What is the most appropriate next step in her management?

A Start treatment with an intermediate or long-acting insulin before bedtime
B Continue diet and lifestyle for another 1–2 weeks
C Start treatment with glibenclamide before bedtime
D Advise a bedtime snack (e.g. a glass of milk) to exclude overnight hypoglycaemia
E Start metformin, glibenclamide and insulin before bedtime