Gestational diabetes

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Abstract

Maternal hyperglycaemia is associated with increased risk of adverse perinatal outcome, in particular, infant birth weight that is large for gestational age, increased infant fat mass, pre-eclampsia and preterm delivery, and an increased need for caesarean section. However, there is controversy regarding the diagnosis and treatment of specific levels of hyperglycaemia during pregnancy. This article summarizes the latest evidence-based recommendations for the diagnosis and classification of gestational diabetes mellitus (GDM). It considers the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations and epidemiological evidence from the landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study. It reviews the evidence in support of intensive treatment of hyperglycaemia in pregnancy and provides suggestions for post-partum management to delay and/or prevent progression to type 2 diabetes.

Keywords diabetes; gestational diabetes; hyperglycaemia in pregnancy; large for gestational age; macrosomia; pregnancy

What's new?

- There is ongoing controversy about universal versus selective screening for gestational diabetes mellitus (GDM). International guidelines advise universal screening for all pregnant women at 24–28 weeks' gestation using a 75-g oral glucose tolerance test (OGTT). Health economic analyses are currently awaited
- The current World Health Organization (WHO) and International Association of Diabetes and Pregnancy Study Groups guidelines for diagnosing GDM (fasting plasma glucose (FPG) ≥5.1, 1-hour ≥10.0, 2-hour ≥8.5 mmol/litre) may result in a two- to threefold increase in the number of women diagnosed with GDM compared with the previous WHO/National Institute for Health and Care Excellence criteria (FPG ≥7.0, 2-h ≥7.8 mmol/litre)
- Metformin appears to be safe and effective treatment in late gestation, with no adverse outcomes noted in offspring up to 2 years of age

Introduction

Diabetes mellitus is the commonest medical condition complicating pregnancy, affecting up to 5% of pregnancies in England and up to 25% of pregnancies in Asia.[1] Gestational diabetes mellitus (GDM) accounts for 87.5% of diabetic pregnancies. It is defined as 'any degree of glucose intolerance with onset or first recognition during pregnancy'.[2] Hyperglycaemia during pregnancy is associated with increased risk of pre-eclampsia, premature delivery, caesarean section delivery, and of the later development of overt (predominantly type 2) diabetes in the mother. Risks to the offspring include the perinatal and longer-term consequences of increased adiposity and birth weight that is large for gestational age (LGA).[3] Although serious perinatal complications such as death, shoulder dystocia, bone fracture or nerve palsy are rare (1–4%), macrosomia (infant birth weight >4 kg) and LGA are common, affecting 10–20% GDM offspring. LGA infants are themselves at increased longer-term risk of insulin resistance, obesity and diabetes, with female offspring having a higher chance of developing gestational diabetes during future pregnancy.[4]

Hyperglycaemia should be considered as a continuous risk variable for all pregnant women in a similar way to other continuous variables such as weight and blood pressure, rather than being dichotomized into distinct diagnoses based on arbitrary diagnostic criteria.[5] The recognition that the relationship between glycaemia and maternal–fetal outcome is a continuum has created controversy regarding appropriate diagnostic thresholds.

Risk factors for developing GDM

- Body mass index greater than 30 kg/m^2
- Previous large for gestational age (LGA) infant over 4.5 kg
- Gestational diabetes in a previous pregnancy
- Family history of diabetes (first-degree relative)
- Ethnic origin with high prevalence of type 2 diabetes (e.g. South Asian (in particular Indian, Pakistani and Bangladeshi), Black Caribbean, Middle Eastern)

Retrospective analyses also suggest increased rates of GDM with advancing maternal age and in women who have a history of infertility, polycystic ovary syndrome or conception using assisted reproductive technologies.[6–8] However, although these factors increase the risk of GDM, 30–50% of affected women have no known risk factors.

Screening for GDM

Whether screening for GDM should be universal or targeted at high-risk groups remains controversial. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel,[9] supported by the World Health Organization[10] and the Australasian Diabetes in Pregnancy Society advise universal screening of pregnant women at 24–28 weeks' gestation using a 2- or 3-hour 75-g oral glucose tolerance test (OGTT), and earlier screening for women at high risk of GDM. While the OGTT represents the gold standard diagnostic test for GDM, a non-fasting 1-hour 50-g glucose challenge test (GCT), recommended by the 2013 National Institutes of Health (NIH) consensus group,[11] is a cheaper and less burdensome initial alternative, and widely used in clinical practice. In the NIH-recommended protocol, women with a positive GCT should have an OGTT before GDM is diagnosed (known as the two-step approach). The American Diabetes Association recommends

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universal screening using either the IADPSG or NIH strategy.[12] A recent Cochrane review found insufficient evidence to make a recommendation regarding universal GDM screening or specific screening protocols for GDM.[13]

Guidelines published by the National Institute for Health and Care Excellence (NICE) in 2008,[14] currently under review, recommend screening only high-risk women and suggest that, before deciding, women should be informed that:

- most women respond to diet and lifestyle changes and only 10–20% require insulin and/or oral medication
- undiagnosed GDM is associated with a small risk of birth complications such as shoulder dystocia
- diagnosed GDM may lead to increased monitoring and planned intervention during pregnancy/labour.[7]

Epidemiology: Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study

The objective of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study was to clarify the maternal glucose concentration threshold associated with adverse perinatal outcome.[15] It was a landmark multinational, multicultural, epidemiological study in which 25,000 women had a 75-g oral glucose tolerance test (OGTT) performed during the third trimester. OGTT results were available to women and health professionals only when overt diabetes was diagnosed (fasting plasma glucose >5.8 mmol/litre or a 2-hour value of >11.1 mmol/litre). Primary outcomes were birth weight over the 90th percentile (LGA), delivery by caesarean section, neonatal hypoglycaemia and cord C-peptide over the 90th percentile (a marker of fetal hyperinsulinaemia). Secondary outcomes were pre-eclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinaemia and neonatal care admission. The key finding was of a continuous linear relationship between maternal hyperglycaemia (on fasting, 1-hour and 2-hour post-OGTT values) and increased frequency of primary or secondary outcomes. Importantly, this association was independent of other risk factors, including maternal obesity, and did not differ between countries or centres.

Diagnosis of GDM

The IADPSG recommendations for the diagnosis of GDM are based on findings from the HAPO study[9] (Table 1). Widespread adoption of these criteria is likely to increase the number of women diagnosed with GDM by two- to threefold. However, these criteria are associated with adverse maternal and neonatal outcomes,[16–18] and although the cost implications are significant, so too is the opportunity for intervention to reduce maternal and fetal complication rates. Nevertheless, this benefit may not apply in all contexts; a recent epidemiological study in a Chinese population found that implementation of the IADPSG criteria doubled the prevalence of GDM, but that women in whom GDM was diagnosed solely on the basis of IADPSG criteria were not at increased risk of complications.[19] Given the significant cost and resource implications of screening and treatment, particularly in resource-poor settings, context-specific health economic evaluation is important.

Treatment of maternal hyperglycaemia: evidence from randomized trials

'Near normoglycaemia' is the established goal for glycaemic management during pregnancy, and the associations established by HAPO support this. However, formal demonstration in intervention studies that treatment of GDM improves pregnancy outcomes, and investigation of what degree of hyperglycaemia warrants treatment and which treatments are most effective, are critical. This has been addressed by three large-scale, rigorously conducted, randomized controlled trials.

Treatment of severe maternal hyperglycaemia

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)[20] showed that women with GDM (75% White) treated with dietary advice and insulin had a reduced rate of serious perinatal complications (a composite primary outcome measure comprising infant death, shoulder dystocia, bone fracture and nerve palsy). However, the rates of serious complications were low (1% treatment versus 4% control group) and much attention

IADPSG criteria for GDM and overt diabetes in pregnancy[9]

Hyperglycaemia during pregnancy	
Gestational diabetes[a]	
Fasting plasma glucose	≥5.1 mmol/litre
1-hour plasma glucose	≥10.0 mmol/litre
2-hour plasma glucose	≥8.5 mol/litre
Overt diabetes in pregnancy	
Fasting plasma glucose	≥7.0 mmol/litre
Glycated haemoglobin (HbA_{1c})	≥6.5% (DCCT/UKPDS standardized)
Random plasma glucose	≥11.1 mmol/litre and confirmed by either fasting plasma glucose or HbA_{1c}

DCCT, Diabetes Control and Complications Trial; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; UKPDS, United Kingdom Prospective Diabetes Study.

[a] One or more of these values after a 75-g oral glucose tolerance test is consistent with GDM.

Table 1