Gestational diabetes

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Abstract

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia that is diagnosed for the first time in the second or third trimester of pregnancy. It occurs in one in seven pregnancies worldwide and is associated with increased risk of adverse perinatal outcome, in particular, infant birth weight that is large for gestational age, increased infant adiposity, preeclampsia and preterm delivery, and increased delivery by caesarean section. This review focuses on the controversy regarding screening and diagnosis of GDM following development of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines and the National Institute of Clinical Excellence (NICE) 2015 guidelines. It reviews the most recent research in to diet and exercise modification in prevention and management of GDM, pharmacological management and postpartum management to delay and/or prevent progression to type 2 diabetes.

Keywords blood glucose; diabetes; gestational diabetes; hyperglycaemia in pregnancy; large for gestational age; pregnancy; pregnancy complications; screening

Introduction

Gestational diabetes mellitus (GDM) is defined by the World Health Organisation as hyperglycaemia that is first recognised during pregnancy, or by the American Diabetes Association as "diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes". It is associated with increased risk to the mother of preeclampsia, preterm delivery, caesarean section delivery and later development of overt diabetes. Risks to the offspring include increased adiposity and large for gestational age (LGA) defined as infant birth weight, adjusted for sex and gestational age, that is above the 90th percentile. While the severe perinatal complications associated with LGA, including asphyxia and death are rare, LGA infants are at increased longer-term risk of insulin resistance, obesity and diabetes later in life, with female offspring having an increased chance of developing GDM during future pregnancy.

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Epidemiology

Gestational diabetes mellitus affects up to 5% of pregnancies in England and up to one in seven pregnancies worldwide. Recognised risk factors include obesity and family history of type 2 diabetes mellitus (T2DM) which are steadily increasing in the background maternity population. The National Institute of Clinical Excellence (NICE) recognise additional risk factors including maternal ethnicity, advanced maternal age, multiple pregnancy and previous history of GDM or macrosomia (birthweight $\geq$4.5 kg). NICE guidance recommends that women with any one of these risk factors should undergo further diagnostic testing for gestational diabetes mellitus (Table 1).

Screening

There has been a longstanding debate about which women should be screened for GDM, all women (universal screening) or only high risk women (selective screening). The importance of screening was highlighted in the MBRRACE UK Confidential Enquiry into Antepartum Stillbirth two decades ago. However despite this, along with screening being widely accepted by patients and cost-effective, women are not always screened. In 2015 the MBRRACE UK enquiry identified that out of 133 stillbirths, 69 (52%) women had one or more risk factors for GDM, but only 32 (46%) of women with risk factors were offered diagnostic testing. This discrepancy may not have been helped by the continued controversy between screening and diagnostic criteria, with no consensus among international bodies. The two main approaches of 'universal' and 'selective' screening and one step versus two step testing vary between clinics and across countries.

One versus two step GDM screening

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel supported by the World Health Organisation (WHO), the Australian Diabetes in Pregnancy Society (ADIPS) and the International Federation of Gynaecology and Obstetrics (FIGO) advise a universal diagnostic testing of all pregnant women at 24–28 weeks of gestation using a one-step approach of a 75 g oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) also recommends a 75 g OGTT at the same gestation, or alternatively a two-step 50 g glucose challenge test (GCT) followed by diagnostic 100 g OGTT for women who screen positive. The two step approach can result in short delays to diagnosis and onset of treatment. However, a recent study of more than 81,000 women described only minimal delays, on average 10 days after the initial screen. A

National Institute of Clinical Excellence screening criteria for gestational diabetes mellitus

- BMI above 30 kg/m^2
- Previous macrosomic baby weighing 4.5 kg or above
- Previous gestational diabetes
- Family history of diabetes (first-degree relative with diabetes)
- Minority ethnic family origin with a high prevalence of diabetes

Table 1

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benefit of the two-step approach is that women who screen negative to the 50 g GCT, do not have to undergo an OGTT.

Selective versus universal GDM screening

The UK NICE guidelines suggest one step selective screening using identifiable risk factors. Women's risk of developing gestational diabetes is assessed at a booking visit (Table 1) and only those with recognised risk factors are offered a 2-hour 75 g OGTT at 24–28 weeks' gestation. An exception is women with previous GDM, who are offered self-monitoring of blood glucose or an early 75-g two-hour OGTT, with a repeat 75-g two-hour OGTT at 24–28 weeks if the early OGTT is normal. Selective risk factor screening approaches miss women with no apparent risk factors meaning that a proportion of women with GDM will not be treated. The proportion of women missed varies between populations but can be up to 50%. Griffin et al. randomised 3742 Irish women to either a group screened for GDM if a risk factor was present, or to a universal screening group. Prevalence of GDM was 2.7% in the universal screening group compared to 1.45% in the risk factor screened group ($P < 0.03$). The universal screening group also had higher rates of spontaneous vaginal delivery and lower rates of macrosomia. The universal screening group were diagnosed approximately 3 weeks earlier than the risk-factor screened group (30 versus 33 weeks' gestation), which may have contributed to the differences in outcomes.

The American Congress of Obstetricians and Gynaecologists (ACOG) guidelines agree that all women should be screened, but suggest this could be performed by assessment of the patient's medical history, clinical risk factors or laboratory screening tests.

Gestation of GDM screening

The recommended gestation at which women are screened for GDM is 24–28 weeks' gestation. The U.S Preventive Services Task Force (USPSTF) found little evidence on the benefits and detriments of screening prior to 24 weeks' gestation. Sovio et al. investigated fetal growth in 4069 women who took part in the Pregnancy Outcome Prediction study in Cambridge, UK. In women who developed GDM, excessive growth of fetal abdominal circumference was identified between 20 and 28 weeks' gestation, preceding the diagnosis of GDM. Therefore screening at 28 weeks may be too late to prevent fetal overgrowth especially in overweight and obese women, who had increased abdominal circumference by 20 weeks' gestation. As the proportion of women with overweight and obesity increases the risks and benefits of earlier screening will need to be re-evaluated.

Random plasma glucose for GDM screening

A national survey from the UK identified that 52% of respondents used random plasma glucose (RPG) measurements to screen for GDM, despite not being supported in clinical guidelines. Meek et al. studied the use of random plasma glucose (RPG) to detect GDM in 17,736 births in the UK. Women were invited to have a random plasma glucose test at booking (typically 12–16 weeks' gestation) as part of their usual care. The RPG at booking was more predictive than maternal age or BMI for identifying women at high risk of GDM. Even though it cannot replace the oral glucose tolerance test for screening of GDM, it may be useful in prioritising those who would benefit from early OGTT or to exclude women who do not need further investigation. NICE do not recommend the use of fasting plasma glucose, random blood glucose, glucose challenge test, HbA1c or urinalysis for GDM screening.

Diagnosis

As for screening there is no international consensus on diagnostic criteria for gestational diabetes. The landmark Hyperglycaemia and Adverse Pregnancy Outcome study (HAPO) published in 2008 described the risks of adverse outcomes associated with various degrees of maternal hyperglycaemia. This was a multinational, multicultural study of 25,000 women who had a 75-g oral glucose tolerance test (OGTT) during their third trimester of pregnancy. Results indicated strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels, suggesting that maternal glycaemia and associated maternal–fetal outcomes is a continuum, as opposed to an association reached at a particular threshold.

Following the HAPO study, the International Association of Diabetes in Pregnancy Study Group (IADPSG) produced new guidelines in 2010 recommending lower fasting plasma glucose thresholds at 1-hour (≥5.1 mmol/mol), 2-hour (≥10.0 mmol/mol) and 3-hour (≥8.3 mmol/mol) after 75-g OGTT (Table 2). Implementation of the one-step IADPSG criteria in Madrid, was associated with a 3.5 fold increased prevalence of GDM but was considered to be both clinically and cost effective compared to the traditional two-step Carpenter Coustan approach. There were reduced rates of caesarean section, large for gestational age infants and infant admission to neonatal intensive care units.

The IADPSG diagnostic values have been adopted by the WHO and also by ADA who give the option of using either IADPSG criteria or diagnostic values using a two-step approach for diagnosing GDM. The National Institute of Clinical Excellence (NICE) produced new diagnostic guidelines for GDM in 2015 varying from those recommended by the WHO and IADPSG. NICE recommends a higher threshold for fasting glucose ≥5.6 mmol/mol and a lower 2-hour value ≥7.8 mmol/mol, with no diagnostic threshold at 1 hour post OGTT.

The IADPSG and NICE criteria were compared in a retrospective study of 25,543 births in the UK where originally 3848 OGTTs were performed. Retrospectively applying the 2015 NICE diagnostic and IADPSG criteria in these women, suggested that NICE criteria would have missed only a small number of women with GDM, who would have been detected using IADPSG criteria (0.5%). However, this group of women had a higher risk of having a large for gestational age infant, caesarean delivery and polyhydramnios compared with women with normal glucose tolerance. Women with the highest risk of having an LGA infant were those who "fell through the net", suggesting that the IADPSG criteria identify women at substantial risk of complications who would not be identified by NICE 2015 criteria. Alternatively, 261 women were identified as GDM positive using the 2015 NICE criteria, but negative using IADPSG, with 2-hour post OGTT glucose values between 7.9 and 9.9 mmol/litres. These women did not have increased risk of preeclampsia or large for gestational age but they had an increased risk of polyhydramnios, compared to the reference population.

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