Screening, complications and treatment of gestational diabetes

Michael Dennedy, Eoin O'Sullivan, Fidelma Dunne

Gestational diabetes (GD) is a condition of increasing incidence, largely as a result of a higher prevalence of maternal obesity. Women diagnosed with GD have a greater risk of adverse pregnancy and perinatal outcome and are also more likely to be diagnosed with type 2 diabetes in later life. Recent updated criteria for the diagnosis of gestational diabetes recommend its diagnosis at more modest degrees of hyperglycaemia during pregnancy. However, there is no consensus on how best to screen or diagnose this condition. Recent evidence suggests that treatment with metformin may be a safe alternative or adjunct to insulin. Additionally, active management of lower degrees of maternal hyperglycaemia improves gestational outcome. This article looks at screening guidelines, complications and treatment of GD.

Gestational diabetes (GD) is defined as glucose intolerance with onset of first recognition during pregnancy (American Diabetes Association, 2000). Its prevalence in the general population is 9% but it occurs with greater prevalence in obese women (6–12%) when compared with their lean counterparts (2–4%) (Solomon et al, 1997). This translates into a relative risk of 2.9 for mothers who have a BMI ≥30 kg/m^2 when compared with lean mothers (Solomon et al, 1997; Ehrenberg et al, 2002).

Weight loss and a healthy lifestyle reduce the risk of developing GD. Weight gain, particularly between pregnancies, significantly increases this risk. Given the current prevalence of obesity in women of reproductive age worldwide, GD and its complications present a significant multidisciplinary challenge in modern obstetric care (Solomon et al, 1997).

Screening and diagnosis of GD

Criteria for screening and diagnosis of GD were first formulated over 40 years ago. Original criteria related to the risk of developing type 2 diabetes in the first 8 years postpartum rather than relating to the risk of adverse pregnancy outcome (Metzger and Coustan, 1998). While newer guidelines for screening and diagnosis take into account the broader evidence relating to the complications of pregnancy associated with GD, there still remains a lack of consensus on whom to screen and how best to screen using an oral glucose tolerance test (OGTT) (HAPO [Hyperglycemia and Adverse Pregnancy Outcome] Study Cooperative Research Group et al, 2008; International

Article points

1. Gestational diabetes comprises a maternal profile of insulin resistance, hyperglycaemia and an adverse metabolic state, usually in the setting of raised BMI.
2. While the controversy regarding the merits of universal screening continues, many centres are now adopting the International Association of Diabetes and Pregnancy Study Group thresholds for the diagnosis of gestational diabetes.
3. Emerging evidence suggests that metformin is a well-tolerated oral antidiabetes agent for use during pregnancy.

Key words

- Gestational diabetes
- Hyperglycaemia
- Pregnancy
- Screening

Authors' details can be found at the end of this article.

Association of Diabetes and Pregnancy Study Groups Consensus Panel et al, 2010).

In the US, screening has traditionally taken a two-step approach. At 24–28 weeks' gestation, a 50 g oral glucose challenge test is performed and women who have a 1-hour glucose of >7.8 mmol/L are reassessed with a 3-hour 100 g OGTT. A woman who exceeds at least two of the thresholds at fasting, 1, 2 or 3 hours is deemed to have GD (American College of Obstetricians and Gynecologists [ACOG] Committee on Practice Bulletins – Obstetrics, 2001). In the UK, NICE recommends a 2-hour 75 g OGTT at 16–18 weeks' gestation in women with a history of GD and at 24–28 weeks if risk factors are present (Kmietowicz, 2008; National Collaborating Centre for Women's and Children's Health, 2008; Holt et al, 2010). This selective screening approach differs from the recommendation of universal screening by some authorities, such as ACOG. The recently published guidelines of the International Association of Diabetes and Pregnancy Study Group (IADPSG) suggest that an initial assessment consisting of fasting or random glucose should be performed at the first pre-natal visit (either in individuals with risk factors or universally depending on prevalence of diabetes and local practice), followed by a 2-hour 75 g OGTT at 24–28 weeks in all women not previously diagnosed with GD on initial assessment at first pre-natal visit (IADPSG Consensus Panel et al, 2010) (*Table 1*).

Arguments against universal screening include a lack of evidence for the benefit of such an approach, increased costs, and generation of maternal anxiety and increased caesarean section rates (Berger and Sermer, 2009). Proponents of universal screening highlight the fact that less women with GD would go undiagnosed and that identification and application of risk factors is cumbersome in routine practice.

While the controversy regarding the merits of universal screening continues, many centres are now adopting the IADPSG thresholds for the diagnosis of GD. The publication of the IADPSG recommendations (IADPSG Consensus Panel et al, 2010) will hopefully lead to an approach to diagnosing GD that is more streamlined and consensual. Differences will persist at practice level due to differences in local prevalence of diabetes and financial constraints.

Complications of gestational diabetes

Hyperglycaemia in pregnancy has long been associated with numerous maternal and perinatal complications. GD comprises a maternal profile of insulin resistance,

Page points

1. Mothers with gestational diabetes (GD) have an increased risk of pre-eclampsia, pregnancy-induced hypertension, the risk for hypertensive disease of pregnancy being raised almost four-fold.
2. GD is additionally associated with increased fetal death, particularly perinatal mortality, and offspring of women with GD have a higher odds of meconium aspiration, neonatal hypoglycaemia, neonatal jaundice and congenital abnormality, particularly orofacial and cardiovascular abnormalities.

hyperglycaemia and an adverse metabolic state, usually in the setting of raised BMI (Catalano et al, 1993). In fact, it is difficult to separate the pregnancy risks associated with GD from those associated with obesity and vice versa.

Numerous observational studies and meta-analyses have examined the adverse maternal pregnancy outcomes of GD and obesity. Mothers with GD have an increased risk of pre-eclampsia, pregnancy-induced hypertension, the risk for hypertensive disease of pregnancy being raised almost four-fold. Delivery-related complications are also increased with GD, including failed induction of labour and failure to progress with a consequent increase in delivery by caesarean section. Predictably, the odds for both antepartum and postpartum haemorrhage are also raised in association with GD (Heslehurst et al, 2007; 2008). In common with hyperglycaemic disorders in general, there is a higher rate of infection in mothers diagnosed with GD.

The association between maternal hyperglycaemia and birthweight is well established. One of the principal aims in treating diabetes during pregnancy has been to avoid large for gestational age (LGA) birthweight, macrosomia and the associated complication of shoulder dystocia (Pedersen, 1952; Heslehurst et al, 2008). However, GD is additionally associated with increased fetal death, particularly perinatal mortality, and offspring of women with GD have a higher odds of meconium aspiration, neonatal hypoglycaemia, neonatal jaundice and congenital abnormality, particularly orofacial and cardiovascular abnormalities. It is therefore, not surprising that these infants are more likely to require admission to the neonatal intensive care unit (HAPO Study Cooperative Research Group et al, 2008; Heslehurst et al, 2007; Stothard et al, 2009). Consequently, the focus of treatment for GD has shifted to take into account the broader range of associated complications.

Table 1. Current recommendations from NICE (National Collaborating Centre for Women's and Children's Health, 2008) and International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel et al (2010).

Diagnostic criteria	NICE	IADPSG
Screening	*Screening with 75g OGTT if:* BMI ≥30 kg/m^2 Previous macrosomic baby (≥4.5 kg) Previous diagnosis of GD Family history of diabetes (first-degree relative with type 2 diabetes) Family origin with high prevalence of diabetes: ● South Asian (India, Pakistan, Bangladesh) ● Black Caribbean ● Middle Eastern	Universal screening with 75 g OGTT
Diagnostic test	75 g OGTT	75 g OGTT
Thresholds:		
Fasting PG	>5.6 mmol/L	>5.1 mmol/L
1-hour PG	–	>10.0 mmol/L
2-hour PG	>7.8 mmol/L	>8.5 mmol/L
IGT	5.0–5.5 mmol/L	Diagnosis eliminated

GD=gestational diabetes; IGT=impaired glucose tolerance; OGTT=oral glucose tolerance test; PG=plasma glucose.

Results from the HAPO study series have shown that milder degrees of hyperglycaemia in GD were associated with persistent higher odds of chosen primary outcomes, which included LGA birthweight, primary caesarean delivery, neonatal hypoglycaemia and raised neonatal C-peptide concentrations. Secondary outcomes of pre-eclampsia, preterm delivery, shoulder dystocia, hyperbilirubinaemia and admission to a neonatal intensive care unit were also observed at relatively modest levels of hyperglycaemia (HAPO Study Cooperative Research Group et al, 2008; HAPO Study Cooperative Research Group, 2009). As a consequence of these findings, the IADPSG published recommendations for diagnosing and classifying GD and hyperglycaemia in pregnancy. These recommendations are based on fetal and maternal risk rather than on future risk of developing type 2 diabetes.

Treatment of gestational diabetes

Treatment of GD is initially by dietary modification, and if glycaemic targets are not achieved, insulin is usually added in the form of multiple daily injections. Randomised controlled trials have examined in greater detail the benefits of treating hyperglycaemia in GD. Intervention with diet or insulin (as necessary) in the Australian Carbohydrate Intolerance in Pregnant Women Study improved maternal glycaemic control, with associated reduction in the rates of serious perinatal complications, including death, shoulder dystocia, bone fracture and nerve palsy when compared with controls (Cheung et al, 2005).

The treatment of mild GD, using thresholds based on the findings of the HAPO investigators, reduced the frequency of LGA birthweight, macrosomia, shoulder dystocia and caesarean delivery (Landon et al, 2009). There were no neonatal deaths in the latter

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trial. The role of metformin as an agent in GD was studied by Rowan et al (2008), who demonstrated no difference in perinatal outcomes in those treated with metformin plus insulin (if required) compared with those treated with insulin alone. Women diagnosed with polycystic ovary syndrome, who commenced metformin to improve fertility, have also been reported to have fewer first trimester miscarriages when compared with those not taking metformin (Barbieri and Gargiulo, 2004). While not included in current guidelines for the treatment of GD, this emerging evidence suggests that metformin is a well-tolerated oral antidiabetes agent for use during pregnancy.

Studies examining the benefits of weight loss pre- and inter-gestationally have shown a lower incidence of GD in addition to fewer pregnancy complications when compared with obese or overweight, BMI-matched controls. (Dennedy and Dunne, 2010). ATLANTIC DIP (Diabetes in Pregnancy) was established in 2005 to audit clinical practice, determine prevalence, observe complications and guide future policy on the management of GD in Ireland. It is a partnership between five antenatal centres on the Atlantic coast covering a geographical area of approximately 150 km by 300 km and a population of 500 000 people. ATLANTIC DIP networks and shares information between participant centres using an electronic link via DIAMOND® (Hicom, Woking), a diabetes clinical information system for data collection. DIAMOND® is hosted at a central location as a secure service. Data captured in the peripheral clinics is consolidated in real time within the central DIAMOND® database and made available in anonymised form for analysis and reporting.

Under ATLANTIC DIP, universal screening for GD was offered to all women. In line with World Health Organization recommendations for the diagnosis of GD, a 75 g OGTT was performed at 24–28 weeks' gestation. A wide variety of maternal and fetal outcomes were prospectively gathered and comparisons were made between women with and without GD. Over 12 000 women were identified and invited to enrol in the study, of whom almost 5500 completed the study (Owens et al, 2010).

In this study, when IADPSG criteria for diagnosis of GD were applied, the prevalence increased from 9.5% to 12%. GD was also associated with a greater frequency of adverse pregnancy outcome when compared with women of normal glucose tolerance. However, within the "normal glucose tolerance" cohort, there was a strong association between raised maternal BMI and adverse pregnancy outcome. This association was not entirely independent of maternal glucose when measured during OGTT (Owens et al, 2010).

Conclusion

The reversal of all modifiable risk factors for adverse pregnancy outcome should be undertaken zealously by healthcare professionals in general. Therefore, it is imperative that measures are taken to first reduce the incidence of GD and second to screen for and diagnose this condition at the earliest opportunity. Evidence for complications of pregnancy arising from milder degrees of gestational hyperglycaemia is convincing. There is also irrefutable evidence for reversal of these complications with active management of hyperglycaemia.

The authors therefore advocate universal screening for diagnosis and management of GD, in line with updated IADPSG recommendations, as a measure that will help provide the best outcome for mother and offspring. Active involvement by primary care physicians is vital to increase awareness of the importance of screening (and treatment, if required), and maintenance of a healthy BMI. ■

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