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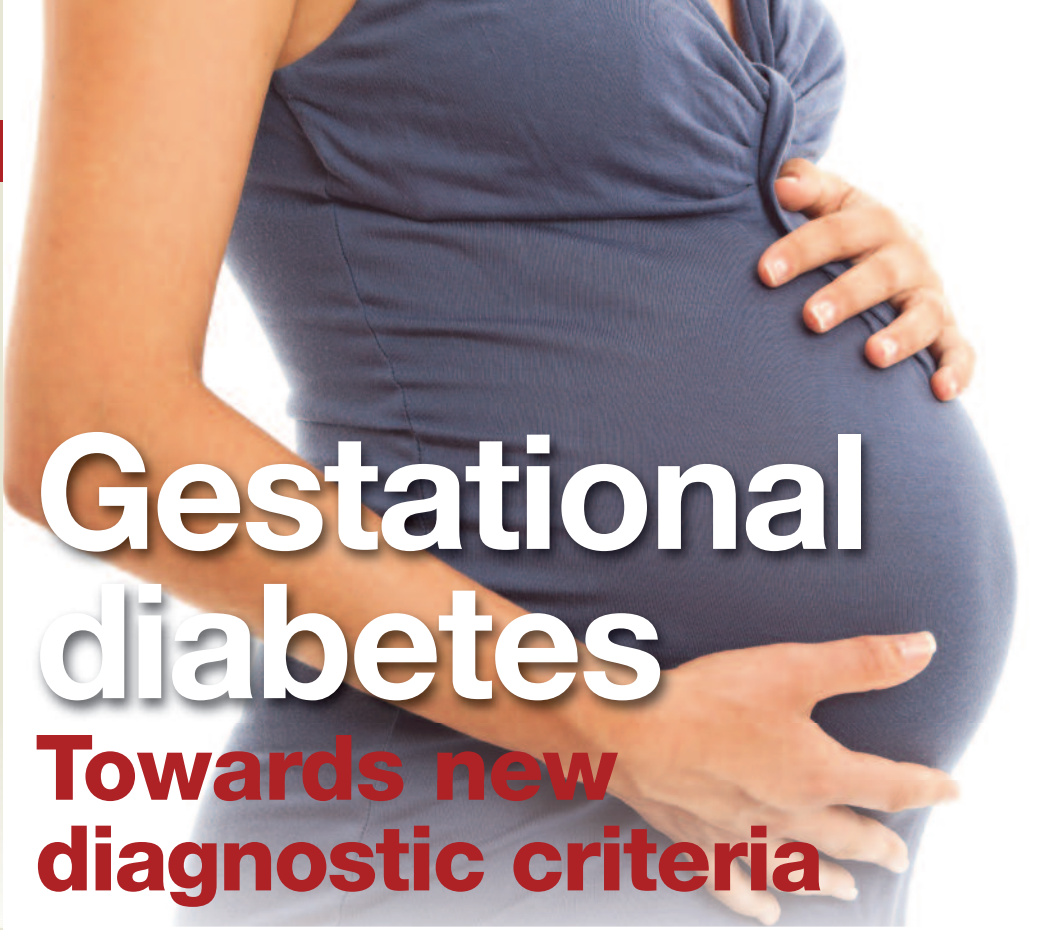

Gestational diabetes

Towards new diagnostic criteria

Key points

- The Australasian Diabetes in Pregnancy Society has been revising its guidelines for the testing and diagnosis of gestational diabetes. Ongoing controversy over diagnostic criteria is delaying a unified approach to the condition within Australia.
- Gestational diabetes is associated with adverse maternal and neonatal outcomes at even lower blood glucose levels than previously recognised.
- Universal testing with a one-step 75 g two-hour oral glucose tolerance test at 24 to 28 weeks of gestation is recommended.
- Treatment ideally involves a multidisciplinary approach focusing on patient education, dietary modification and lifestyle intervention. Medication should be initiated when treatment targets are not achieved by diet alone.
- General practitioners play a crucial role in detecting undiagnosed pre-existing diabetes in high-risk women before or in early pregnancy, and ensuring timely post-partum follow up and risk factor modification to reduce the risk of future diabetes.

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The Australasian Diabetes in Pregnancy Society (ADIPS) has been revising its consensus guidelines for the testing and diagnosis of gestational diabetes but these have not yet been translated into a unified approach to the condition in Australia. Controversy over the diagnosis of gestational diabetes persists internationally. Key practice points for general practitioners arising from the revised guidelines are reviewed.

Gestational diabetes mellitus refers to abnormal glucose tolerance with onset or first recognition during pregnancy. It is a common complication of pregnancy and is associated with significant maternal and neonatal morbidity. The rising prevalence of gestational diabetes parallels the increasing incidence of obesity and type 2 diabetes in women of childbearing age in Australia. The country's multiethnic population and advancing maternal age, both of which are well established risk factors, also contribute to the burden of gestational diabetes.

The Australasian Diabetes in Pregnancy Society (ADIPS) has been revising its consensus guidelines for the screening and diagnosis of women with gestational diabetes in Australia (including treatment targets), largely endorsing the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[1,2] The revised criteria for diagnosis will further increase the prevalence of gestational diabetes in Australia. Women with gestational diabetes will therefore comprise a substantial proportion of the patient cohort in general practice and as such, general practitioners need an understanding of the key issues surrounding screening, diagnosis and management of gestational diabetes as well as strategies to prevent future diabetes.

However, controversy continues to surround

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RISK FACTORS FOR GESTATIONAL DIABETES[1]

- Previous gestational diabetes
- Previously elevated blood glucose level
- Ethnicity:*
  - Asian (including Indian)
  - Aboriginal and Torres Strait Islander
  - Pacific Islander
  - Maori
  - Middle Eastern
  - African
- Maternal age over 40 years
- Family history of diabetes
- Obesity (BMI greater than 30 kg/m^2)
- Previous macrosomia (birthweight more than 4500 g)
- Polycystic ovarian syndrome
- Iatrogenic: glucocorticoids and antipsychotic medication

* Women in ethnic groups that have a high incidence of type 2 diabetes.

the IADPSG and ADIPS guidelines. Indeed, the recent ADIPS guidelines have not yet been endorsed by the Australian Diabetes Society, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists or the Royal College of Pathologists of Australasia. Ongoing discussion is currently underway between these organisations.

It was anticipated that the recent March 2013 National Institutes of Health (NIH) consensus development meeting in the USA on the diagnosis of gestational diabetes might have aided the development of a national consensus in Australia. Ultimately, however, the NIH panel concluded there was insufficient evidence to adopt the IADPSG diagnostic criteria, citing concerns over the expected increase in prevalence of gestational diabetes with attendant cost and intervention, without sufficient evidence of a corresponding proportional improvement in outcomes. Nevertheless, a unified approach to gestational diabetes within Australia is essential.

This article highlights key practice points for general practitioners arising from the revised ADIPS guidelines. These guidelines are available on the ADIPS website (http://www.adips.org/downloads/ADIPS%20consensus%20guidelines%20GDM%20140213.pdf). The revised guidelines recommend a change in the thresholds for the diagnosis of gestational diabetes and a lowering of treatment glucose targets (see page 50).[1]

PREVALENCE

The Australian Institute of Health and Welfare (AIHW) reports an overall incidence of gestational diabetes in Australia of 4.9%.[3] However, this underestimates the incidence of gestational diabetes in areas with a significant multiethnic population, as women born overseas are twice as likely to have gestational diabetes as other Australian women. For example, the incidence of gestational diabetes in south-western Sydney is as high as 10 to 12%.[4]

Lowering the fasting blood glucose level cut-off in the revised ADIPS diagnostic criteria for gestational diabetes will significantly increase the prevalence of gestational diabetes in Australia. Using these revised criteria, the overall incidence of gestational diabetes in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study cohort was 17.8%.[5] The new diagnostic criteria have increased the incidence of gestational diabetes in Wollongong (a predominantly Caucasian population) from 9.6 to 13%.[6] This is consistent with the reported incidence of gestational diabetes in the Newcastle and Brisbane HAPO study centres of 15.3 and 12.4%, respectively.[5] This increased incidence is expected to translate into an increase in workload of greater than 30%.[4]

CLINICAL SIGNIFICANCE OF GESTATIONAL DIABETES

Maternal complications

Short-term

- Pre-eclampsia
- Gestational hypertension
- Obstetric intervention
  - induction of labour
  - caesarean section

Long-term

- Gestational diabetes recurrence in subsequent pregnancies
- Future diabetes (usually type 2)
- Hypertension

Neonatal complications

Short-term

- Stillbirth
- Macrosomia
- Birth trauma:
  - shoulder dystocia
  - bone fracture
  - nerve palsy
- Hypoglycaemia
- Hyperbilirubinaemia
- Respiratory distress syndrome

Long-term

- Type 2 diabetes and obesity (even as early as childhood and adolescence)

PATHOPHYSIOLOGY AND RISK FACTORS

Gestational diabetes occurs when the maternal pancreas is unable to compensate for increased insulin resistance in pregnancy. Insulin resistance arises from placental secretion of counter-regulatory hormones such as growth hormone, corticotrophin-releasing hormone, placental lactogen and progesterone, and is exacerbated by maternal weight gain. Generally, insulin resistance progressively increases during pregnancy and is most pronounced late in the third trimester.[7] Risk factors for gestational diabetes are outlined in the box on this page.[1]

The presence of risk factors for gestational diabetes, especially if multiple factors are present, should prompt general practitioners to assess women for gestational diabetes in early pregnancy. If an early oral glucose tolerance test (OGTT) is used for this purpose and the result is normal, the OGTT should be repeated at the usual time, around 24 to 28 weeks of gestation.

WHY DOES GESTATIONAL DIABETES MATTER?

Increased maternal and neonatal risk

The HAPO study showed continuous positive association between maternal blood glucose levels and adverse maternal and neonatal outcomes at lower blood glucose thresholds than those reflected in previous gestational diabetes diagnostic criteria.[8] As maternal glucose rises, there is a higher rate of caesarean section, pre-eclampsia, large for gestational age babies and neonatal hypoglycaemia. These results, supported by other large recent studies, were the basis for the revised IADPSG recommendations for the diagnosis and classification of gestational diabetes, subsequently endorsed by ADIPS.[1,2]

The clinical significance of gestational diabetes is summarised in the box on page 47.

Treatment of gestational diabetes is effective

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated that treatment of gestational diabetes reduces the incidence of macrosomia, perinatal complications and pre-eclampsia.[9] Moreover, treatment of mild gestational diabetes (defined as a fasting glucose level below 5.3 mmol/L) is associated with reduced rates of macrosomia, caesarean section and gestational hypertension.[10]

These studies provide some support for the proposed lowering of the gestational diabetes diagnostic criteria, as they suggest that identifying and treating patients with even mild hyperglycaemia can improve pregnancy outcomes.

A window into the future

Gestational diabetes represents an inability to adapt to significant metabolic stress (i.e. pregnancy). Thus a diagnosis of gestational diabetes provides an invaluable opportunity to identify women at increased risk of future diabetes and initiate appropriate interventions. There is strong evidence that lifestyle changes can prevent or delay the progression of type 2 diabetes in many of these women.[11]

PROPOSED CHANGES TO DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES

Universal testing

Universal testing for gestational diabetes at 24 to 28 weeks of gestation is still recommended in Australia.[1]

Early testing

Early testing in pregnancy aims to detect women with previously undiagnosed pre-existing diabetes, as these women require prompt clinical review and intervention as well as more intensive surveillance both during pregnancy and postpartum. Early testing with a 75 g OGTT is strongly recommended in women at high risk of diabetes, and should be undertaken at the first antenatal visit.[1] Consideration should also be given to screening all women at the first antenatal visit with a fasting or random blood glucose level. However, this issue remains contentious. Unless blood glucose levels are clearly diagnostic of diabetes, these women should still proceed to an OGTT at 24 to 28 weeks of gestation for confirmation of gestational diabetes.

Glycosylated haemoglobin (HbA_{1c}) measurements are not a useful diagnostic alternative to an OGTT for gestational diabetes.[12] An HbA_{1c} value greater than 6.5% (48 mmol/mol) in early pregnancy may be useful in identifying pre-existing undiagnosed diabetes, but currently no Medicare rebate is available in Australia for the diagnostic use of HbA_{1c}.

Overt diabetes during pregnancy

The key aim of the revised IADPSG recommendations for early screening is to identify women with undiagnosed pre-existing diabetes from the outset, as distinct from women with glucose abnormalities related to pregnancy alone. The former are referred to as having 'overt diabetes during pregnancy', defined as:

- fasting blood glucose level equal to or greater than 7.0 mmol/L
- random blood glucose level equal to or greater than 11.1 mmol/L, or
- HbA_{1c} equal to or greater than 6.5% (48 mmol/mol).

It is important to note that overt diabetes during pregnancy is not synonymous with type 1 or type 2 diabetes, and therefore these women must be tested postpartum to confirm their glucose tolerance status. Nevertheless, women with overt diabetes during pregnancy should be managed similarly to those with pre-existing diabetes, with increased antenatal surveillance and diligent postpartum follow up.

The ADIPS consensus guidelines differ from the IADPSG criteria on this concept – ADIPS have not endorsed this term, arguing that it leads to complexity and confusion. Instead, ADIPS recommends that antenatal surveillance of these women should primarily be guided by clinical judgement. ADIPS concurs with the need for postpartum reassessment.[1]

Routine OGTT at 24 to 28 weeks of gestation

Unless a diagnosis of gestational diabetes, type 1 or type 2 diabetes has already been made, all pregnant women should undergo a one-step 75 g two-hour OGTT at 24 to 28 weeks of gestation to screen for gestational diabetes.[1] The glucose challenge test is no longer recommended as a screening test for gestational diabetes because of its lack of sensitivity and specificity.

TABLE 1. ADIPS DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES[1]

OGTT time-point	BGL (mmol/L)
Fasting	≥5.1
One-hour	≥10.0
Two-hour	≥8.5

ABBREVIATIONS: ADIPS = Australasian Diabetes in Pregnancy Society; BGL = blood glucose level (venous plasma); OGTT = 75 g oral glucose tolerance test.

TABLE 2. ADIPS TREATMENT TARGETS IN GESTATIONAL DIABETES[1]

Self-monitoring of blood glucose time-point	BGL target (mmol/L)
Fasting	≤5.3
One-hour postprandial*	≤7.4
Two-hour postprandial*	≤6.7

ABBREVIATIONS: ADIPS = Australasian Diabetes in Pregnancy Society; BGL = blood glucose level.
* After commencement of meal.

New diagnostic criteria for gestational diabetes

The recently revised ADIPS consensus guidelines change the threshold blood glucose levels for diagnosis of gestational diabetes. They propose a lowering of the fasting blood glucose cut-off level, an increase in the two-hour cut-off level on OGTT and the introduction of a one-hour cut-off level. The updated diagnostic criteria are shown in Table 1.[1] Only one abnormal blood glucose level is required to diagnose gestational diabetes.

Controversies

Agreement on early pregnancy assessment for gestational diabetes has not been reached. One-step testing of women for gestational diabetes (with no preceding glucose challenge test) will greatly increase the number of OGTTs needing to be performed, and lowering the diagnostic criteria will also lead to more women being diagnosed with gestational diabetes in Australia. The increased workload in the face of limited resources will inevitably require cautious restructuring of current gestational diabetes services while avoiding adverse impacts on the quality of care and glycaemic control achieved. Arguably, further stratification of risk and alternative diagnostic strategies may be required.

Despite these concerns, a recent cost-effectiveness analysis of implementing the revised IADPSG recommendations in Israel found that the diagnostic OGTT approach was actually cost-saving. The savings derived from a combination of delaying future type 2 diabetes and preventing perinatal complications.[13]

MANAGEMENT OF GESTATIONAL DIABETES

Multidisciplinary team

The main objective in the management of women with gestational diabetes is to reduce maternal and neonatal complications associated with even mild levels of hyperglycaemia. Ideally, management should focus on patient education, facilitated by a multidisciplinary team including a diabetes educator, dietitian, endocrinologist and obstetric care provider.

The role of general practitioners within this multidisciplinary team is likely to expand in the face of a rising prevalence of gestational diabetes, and may be particularly important in smaller centres and remote and rural areas.[1]

Self-monitoring of blood glucose levels

Lower treatment targets based on self-monitoring of blood glucose have been proposed in the recently revised ADIPS consensus guidelines, and are summarised in Table 2.[1]

Women with gestational diabetes should monitor their blood glucose levels with blood glucose meters, usually four times daily, at least initially. The authors prefer fasting and one-hour peak postprandial levels, but two-hour postprandial levels are more commonly used.[14]

Dietary advice

Dietary intervention is the mainstay of treatment for women with gestational diabetes. A gestational diabetes diet should consist of 2000 to 2500 kcal per day. The recommended total carbohydrate intake is between 150 and 180 g per day, with an even distribution of preferably complex carbohydrates/lower glycaemic index food across three meals and three snacks to minimise significant postprandial glycaemic excursions.[15]

Caloric or carbohydrate restriction should be avoided as this increases ketosis and the risk of small-for-gestational-age infants. Restriction should be suspected if there is evidence of ketonuria, low postprandial blood glucose levels or weight plateau or loss during pregnancy, and any of these findings should prompt further dietary education and closer monitoring of the woman.

Physical activity

Exercise improves insulin sensitivity and reduces the risk of gestational weight gain. Regular moderate intensity exercise, such as walking for 20 to 30 minutes three or four times weekly, may be appropriate in the absence of any contraindication to exercise.[16] Walking for 10 to 15 minutes after meals can be beneficial in reducing the postprandial glucose peak.

GESTATIONAL DIABETES: KEY MANAGEMENT POINTS FOR GENERAL PRACTITIONERS

Pre-pregnancy counselling (all women)

- Diabetes risk assessment – consider OGTT
- Achieve ideal weight prior to conception
- Avoid excessive weight gain during pregnancy (optimal total weight gain during pregnancy, 7 to 16 kg for most women and 5 to 9 kg for obese women)

Postpartum OGTT (women with gestational diabetes)

- Ensure postpartum OGTT is performed in a timely fashion
- Repeat OGTT two to three-yearly for most women, annually for high-risk women

Regular follow up and risk factor modification

- Healthy, balanced diet
- Regular exercise

ABBREVIATION: OGTT = 75 g two-hour oral glucose tolerance test.

Insulin

Women with gestational diabetes should be reviewed regularly for ongoing support and to assess their diet and glycaemic control. Patterns of glycaemia are more important than isolated off-target blood glucose levels. If blood glucose levels are tending to be high at any one time-point despite appropriate diet and post-meal activity, targeted insulin therapy should be initiated. This is generally undertaken under specialist supervision and requires frequent review for insulin dose titration tailored to the woman's individual pattern of blood glucose abnormality.

Metformin

The use of metformin in the treatment of women with gestational diabetes remains controversial because of concerns regarding possible long-term effects of placental transfer of metformin to the fetus. The Metformin in Gestational Diabetes: the Offspring Follow-Up (MiG TOFU), a two-year follow-up study to the Metformin in Gestational Diabetes (MiG) trial, found that children exposed to metformin had increased subcutaneous fat (localised to the arm) compared with children whose mothers were treated with insulin alone.[17] Longer follow-up studies are needed for definitive assessment of the long-term effects of metformin.

If metformin is used as the initial treatment for gestational diabetes, the authors consider it should be reserved for women who do not have markedly elevated glucose levels on the diagnostic OGTT. Many women treated with metformin still require insulin therapy to achieve the recommended blood glucose treatment targets.

Obstetric management

Serial ultrasonographic assessment of fetal growth (particularly measures of fetal abdominal circumference looking for disproportional growth) may be useful in guiding the intensity of glycaemic control in women with gestational diabetes.[18]

The optimum timing of delivery remains controversial, but can involve induction of labour at 38 to 40 weeks of gestation. Women with gestational diabetes require intensive monitoring of blood glucose levels during labour, and an intravenous insulin–glucose infusion may be required to achieve normoglycaemia.

Insulin therapy should be ceased immediately postpartum, and neonates should be monitored for hypoglycaemia, respiratory distress and jaundice. Women who required insulin treatment in pregnancy should have their blood glucose level checked at least on day three postpartum to ensure blood glucose levels have returned to normal.

POSTPARTUM FOLLOW UP: ROLE OF THE GP

Women with significantly abnormal blood glucose levels in early pregnancy may have pre-existing type 2 diabetes and require regular self-monitoring of blood glucose in the immediate postpartum period in addition to a diagnostic OGTT six to 12 weeks postpartum.[7] Up to one-third of women with gestational diabetes will have type 2 diabetes or impaired glucose tolerance postpartum, but only 50% are ever formally tested.[19]

Women with gestational diabetes are at significant risk of recurrence of gestational diabetes in future pregnancies, with reported rates between 30 and 84%.[20] Moreover, gestational diabetes is associated with a sevenfold increased risk for developing type 2 diabetes, with a lifetime risk of around 50%.[21] Thus, women with gestational diabetes are required to undertake regular testing for diabetes (repeat OGTTs every two to three years; annually for high-risk women) and should be encouraged to maintain a healthy lifestyle, with a balanced diet and regular exercise.

Key management points for general practitioners caring for women with gestational diabetes are listed in the box on this page.

CONCLUSION

The evolving revised ADIPS consensus guidelines for testing and diagnosis of women with gestational diabetes in Australia change the thresholds for diagnosis and treatment of gestational diabetes. These changes reflect increasing evidence that links gestational diabetes to multiple adverse maternal and fetal outcomes even at low levels of maternal hyperglycaemia. However, ongoing controversy nationally and internationally over gestational diabetes diagnostic criteria has delayed the adoption of the revised guidelines.

The diagnostic criteria for gestational diabetes proposed in the new guidelines,

in conjunction with rising obesity, a multiethnic population and advancing maternal age, will greatly increase the prevalence of gestational diabetes in Australia. This in turn will significantly impact on clinical workload, requiring additional resource allocation and/or possible risk stratification. Accordingly, implementation of the revised ADIPS guidelines should only be undertaken after appropriate planning. The expected impact of the revised ADIPS guidelines will vary depending on local population characteristics and current testing practices.

General practitioners play a crucial role in early identification of gestational diabetes and undiagnosed pre-existing diabetes, thereby reducing maternal and neonatal morbidity. Further, a diagnosis of gestational diabetes provides a critical opportunity to highlight women at risk of future diabetes, enabling general practitioners to engage in targeted monitoring and early lifestyle interventions in the postpartum period. This can not only reduce maternal risk but also potentially lower their offspring's future risk of obesity and abnormal glucose tolerance. MT

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