Gestational diabetes: modern approaches to diagnosis and management

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Most women in Australia are screened during pregnancy for gestational diabetes. However, how this is performed is currently under active review. If the new criteria from the International Association of Diabetes and Pregnancy Study Groups are adopted in Australia, it will increase the number of women diagnosed with gestational diabetes significantly and will therefore have major workload implications.

Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It involves at least two distinct entities described below.

- The first is the common, mild abnormality in glucose tolerance (henceforth gestational diabetes) induced by the insulin resistance of pregnancy, usually identified by routine screening between 24 and 28 weeks of gestation.
- The second abnormality is less common but, for the individual, much more important. This abnormality is pre-existing diabetes, undiagnosed before conception.

With the increasing frequency of type 2 diabetes in women of childbearing age, undiagnosed type 2 diabetes is more common (in some ethnic groups) than the infectious diseases for which screening is routine. This entity, 'overt diabetes in pregnancy', will become a separate diagnostic criterion.[1] Of course not all women diagnosed with overt diabetes in pregnancy will have type 2 diabetes. Unfortunately, there is no agreement on how this entity should be diagnosed. However, every GP seeing women at the commencement of their pregnancy should have a screening strategy to detect undiagnosed diabetes. At a very minimum, the question 'Could this women have undiagnosed diabetes?' should be entertained.

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study clearly demonstrated a positive, continuous association of maternal plasma glucose levels during an oral glucose tolerance test (OGTT) performed between 24 and 32 weeks of gestation with the frequency of a number of pregnancy outcomes, including macrosomia, fetal adiposity and fetal hyperinsulinaemia.[2] Two randomised controlled trials have demonstrated that treating gestational diabetes improves several fetal and maternal outcomes.[3,4]

The varying diagnostic thresholds for gestational diabetes are arbitrary on a continuum of glycaemia. The new International Association of Diabetes and Pregnancy Study Groups (IADPSG)[1] recommended diagnostic criteria, which have not yet been adopted widely in Australia, base the arbitrary thresholds on the risk of fetal

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Key points

- **Gestational diabetes is common and the prevalence is increasing, almost certainly related to the increase in maternal obesity.**
- **Gestational diabetes is associated with adverse pregnancy outcomes for both mother and baby, which can be reduced by appropriate management of gestational diabetes (level 1 evidence).**
- **Management of gestational diabetes usually involves education, advice about diet and exercise, and insulin therapy if the home monitored blood glucose levels are above target. The evidence base for any specific dietary therapy is not strong.**
- **Women with a history of gestational diabetes are at increased risk of developing type 2 diabetes. This risk can be reduced by appropriate diet, exercise and pharmacological interventions (level 1 evidence).**
- **Women with a history of gestational diabetes are at increased risk of cardiovascular disease. This risk and the risk of developing type 2 diabetes need to be appropriately monitored.**

macrosomia derived from the HAPO data (see Table 1). A National Institutes of Health consensus conference on diagnosing gestational diabetes will take place 29 to 31 October, 2012. Attendance on the web can be arranged via http://prevention.nih.gov/cdp/conferences/2012/gdm/default.aspx.

Prevalence

A population study revealed that 5.1% of singleton pregnancies in NSW were complicated by gestational diabetes in 2001.[5] The prevalence appears to be increasing.

Risk factors

Certain ethnic groups are at much greater risk of developing gestational diabetes. These groups include Aboriginal and Torres Strait Islanders, Pacific Islanders, and women from the Indian subcontinent, East Asia and the Middle East. These same ethnic groups are also at increased risk of undiagnosed type 2 diabetes. Additional risk factors for gestational diabetes are any maternal characteristic that increases insulin resistance or is associated with increased insulin resistance (see the box on page 8 listing these characteristics).

Guidelines approved by ADIPS

The council of the Australasian Diabetes in Pregnancy Society (ADIPS) has recently approved the consensus guidelines for the testing and diagnosis of women with gestational diabetes in Australia. These are available at http://www.adips.org/images/stories/documents/2012_adips_guidelines.pdf. The guidelines will be discussed among the broader membership of ADIPS and then other interested parties. Assuming they are accepted widely, there will then be an implementation process, which will require some time and patience. Such a change is unlikely to be widespread before late 2013.

Aetiology

Pregnancy is a very insulin-resistant state. The insulin resistance is the result of the physiological changes of pregnancy. The dominant factors are thought to be placental hormones and adipokines. Gestational diabetes occurs when the maternal pancreas is unable to increase insulin secretion to a sufficient degree to compensate for this insulin resistance. This inability of the pancreas to deal with insulin resistance also explains the postpartum risk of type 2 diabetes. If women become insulin resistant again postpartum, glucose intolerance will recur.

Insulin resistance will also recur in the next pregnancy. The risk of gestational diabetes after one pregnancy with gestational diabetes varies from 30 to 70% and in part depends on the changes in maternal age (long duration between pregnancies is worse), fitness and weight. After two gestational diabetes pregnancies the risk of recurrence is up to 95%.[6,7]

Why is maternal hyperglycaemia bad? The Pedersen hypothesis

Maternal glucose crosses the placenta. This results in a tendency to fetal hyperglycaemia and causes the fetal pancreas to produce more insulin to maintain normoglycaemia. Fetal hyperinsulinaemia

Table 1. The diagnostic thresholds for diagnosing gestational diabetes with a 75 g OGTT*

Time	ADIPS (mmol/L)	IADPSG (mmol/L)
Fasting blood glucose level	≥5.5	≥5.1
One-hour blood glucose level	n/a	≥10.0
Two-hour blood glucose level	≥8.0†	≥8.5

* One or more of these values must be abnormal for a diagnosis of gestational diabetes.
† For Australia, not New Zealand where the value is 9 mmol/L.

ABBREVIATIONS: ADIPS = Australasian Diabetes in Pregnancy Society; IADPSG = International Association of Diabetes and Pregnancy Study Groups; OGTT = oral glucose tolerance test.

Risk factors for pre-existing or gestational diabetes

- Personal or family history of diabetes and/or gestational diabetes
- Ethnicity
- Maternal age (particularly ≥40 years)
- Overweight, especially if BMI >35 kg/m^2 or physical inactivity
- Previous macrosomia baby
- Polycystic ovary syndrome
- Use of certain medications (e.g. corticosteroids)

is believed to directly cause the fetal complications of diabetes in pregnancy, such as macrosomia, adiposity, increased birth weight and neonatal hypoglycaemia.[8] The Pedersen hypothesis has been strongly supported by the HAPO study, which confirmed fetal hyperinsulinaemia as a consequence of maternal hyperglycaemia.[2]

Screening

Screening early for pre-existing diabetes

Screening for undiagnosed diabetes at the first visit early in pregnancy is recommended but without agreement on how this should be performed.[1] There is a widely recognised need to separate undiagnosed pre-existing diabetes and gestational diabetes.

The author's personal opinion is that women at high risk of having pre-existing diabetes in early pregnancy should undergo a formal 75 g OGTT at their first visit, unless a random plasma glucose level is diagnostic of diabetes. It may be that in the future, glycated haemoglobin will become part of routine antenatal blood testing to detect pre-existing diabetes (but not gestational diabetes as the sensitivity is poor).

Screening later for gestational diabetes

Most women in Australia are screened during pregnancy for gestational diabetes. However, how this is performed is currently under active review (see the box on page 7; the recommendations are available at: http://www.adips.org/images/stories/documents/2012_adips_guidelines.pdf). Screening is offered to all low-risk women and is currently performed with a 50 g glucose challenge test at 24 to 28 weeks of gestation, followed by a formal 75 g OGTT if the challenge test is abnormal.[9]

Screening tests for gestational diabetes should only be administered to low-risk asymptomatic groups. Women identified at higher risk of having glucose intolerance should proceed directly to the diagnostic 75 g OGTT. However, the new IADPSG guidelines recommend universal testing of all women with the diagnostic 75 g OGTT, omitting the 50 g glucose challenge test.[1]

Diagnostic criteria

The current Australasian Diabetes in Pregnancy Society (ADIPS) and the new IADPSG diagnostic criteria for gestational diabetes are shown in Table 1. If the IADPSG criteria are adopted in Australia, it will increase the number of women diagnosed with gestational diabetes significantly and have major workload implications.[10] It has provoked a lively debate.

Initial management

Initial management of patients with gestational diabetes, which is supported by two randomised controlled trials, is patient education, including dietary education, and home glucose monitoring.[3,4] Many centres also include advice regarding exercise. Women are then followed and additional therapy or intervention is initiated if home monitored blood glucose levels rise above predefined thresholds (apart from obvious dietary 'errors'). These thresholds are discussed below.

Dietary therapy

Broadly speaking, the principles of dietary therapy are appropriate caloric intake (portion size) spread throughout the day (six small meals per day) with an emphasis on low-glycaemic index foods. However, the evidence base for dietary therapy in gestational diabetes is not large. Overly restrictive diets may result in ketonaemia, which occurs more easily in pregnancy and may be associated with adverse outcomes.

It would seem logical and advantageous to advise all pregnant women about a healthy diet early in pregnancy and to define the appropriate weight gain goals (see Table 2).[11] However, it is unclear whether this reduces the risk of gestational diabetes diagnosed later in pregnancy.

It is not clear from the existing data whether the macronutrient composition of the diet (carbohydrate, protein, fat content) contributes to gestational diabetes. Interestingly, many women with gestational diabetes and apparently good glycaemic control and women with obesity but without hyperglycaemia have infants with macrosomia. The role in this process of pregnancy-induced hypertriglyceridaemia, which is also influenced by dietary fat intake, is unclear but there is emerging evidence to suggest it is very important.[12-14] More information is likely to become available over the next few years.

Managing weight gain

A large proportion of our population is now overweight or obese.[15] Obesity is itself associated with macrosomia and adverse pregnancy outcomes, even without recognised hyperglycaemia. In the past 20 years there has been a tendency to ignore the amount of weight gain during pregnancy. The American Institute of Medicine has revised its guidelines for weight gain during pregnancy (see Table 2).

A recent systematic review of weight gain during pregnancy found a strong association of excessive gestational weight gain with increased birth weight and an increased proportion of large-for-gestational-age infants.[16] Conversely, it also found a strong association of inadequate gestational weight gain with decreased birth weight and an increased proportion of small-for-gestational-age infants, suggesting that appropriate weight gain needs to be tailored to the individual woman.

In the general community, 'diet' is frequently taken to mean dietary restriction, and some women will severely restrict their intake in response to a diagnosis of gestational diabetes or in response to hyperglycaemia documented in home blood glucose monitoring.

Exercise

Exercise in early pregnancy might delay or prevent the onset of gestational diabetes. Exercise in women with gestational diabetes has been shown to reduce postprandial rise in blood glucose level and may reduce the need for insulin therapy.[17-19] This exercise does not have to be strenuous.

In practice, pregnancy, and particularly late pregnancy after diagnosis of gestational diabetes, is not the time to start a new vigorous exercise program. However, women who have been exercising regularly should be encouraged to continue this (unless there are obstetric contraindications). Women who are not active can be encouraged to walk gently after meals to help control postprandial hyperglycaemia.

Pharmacological intervention

Indications for therapy

There is ongoing discussion regarding the ideal glucose level during pregnancy, especially pregnancy complicated by gestational diabetes. The guidelines, which have now been approved by ADIPS (see: http://www.adips.org/images/stories/documents/2012_adips_guidelines.pdf), suggest the following:

- fasting blood glucose level of ≤5.0 mmol/L
- one-hour postprandial blood glucose level of ≤7.4 mmol/L
- two-hour postprandial blood glucose level of ≤6.7 mmol/L.

These targets, based on self-measured capillary blood glucose levels, may be adopted widely in Australia although they are based on expert opinion and observational studies. The two randomised controlled trials, which demonstrated benefit, had higher glycaemic targets.[3,4] In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial, the targets were:

- fasting blood glucose level of <5.5 mmol/L
- two-hour postprandial blood glucose level of <7.0 mmol/L at 35 weeks' gestation or less
- two-hour postprandial blood glucose level of <8.0 mmol/L at more than 35 weeks' gestation.

In the ACHOIS trial, the incidence of serious perinatal outcomes was reduced from 4 to 1% and the incidence of macrosomia from 21 to 10%.[3] The incidence of maternal pre-eclampsia was 18% in the control group and 12% in the intervention group.

In the American Fetal Medicine Units Study, which was very similar to the ACHOIS trial in design, active management reduced mean birth weight, neonatal fat mass, the frequency of large-for-gestational-age infants (from 14.5 to 7.1%), macrosomia (>4 kg; from 14.3 to 5.9%), shoulder dystocia (from 4 to 1.5%) and Caesarean delivery (from 33.8 to 26.9%).[4] Maternal pre-eclampsia and gestational hypertension (combined) were reduced from 13.6 to 8.6%.[4]

The targets in this study were:

- fasting blood glucose level of <5.3 mmol/L
- two-hour postprandial blood glucose level of <6.7 mmol/L.

There is no randomised controlled trial evidence for the one-hour target, which is

Table 2. Recommended weight gain in pregnancy*[11]

Pre-pregnancy body mass index (kg/m²)	Total weight gain (kg)	Rate of weight gain 2nd and 3rd trimester (mean rate [range] kg/week)
Underweight (<18.5)	12.5–18	0.51 (0.44–0.58)
Normal weight (18.5–24.9)	11.5–16	0.42 (0.35–0.50)
Overweight (25.0–29.9)	7–11.5	0.28 (0.23–0.33)
Obese (>30.0)	5–9	0.22 (0.17–0.27)

* Assumes a weight gain of 0.5 to 2 kg in the first trimester.
Adapted from the American Institute of Medicine weight gain in pregnancy guidelines (Institute of Medicine. Weight Gain During Pregnancy: Re-examining the Guidelines. The National Academies Press, Washington DC, 2009).[11]

derived from a small number of observational studies in normal pregnancy. There has been no assessment of the risk/benefit ratio of treating to this target.

Whatever thresholds are used, if they are not being achieved, intervention is required. If diet and exercise have been optimised and there is still inadequate glycaemic control, pharmacological therapy is indicated.

Insulin use and safety

Insulin is the standard pharmacological agent to control hyperglycaemia in pregnancy. Hyperglycaemia in women with gestational diabetes usually occurs postprandially. It seems logical therefore to use a short-acting insulin with the meals that result in hyperglycaemia, provided the woman is able to anticipate those types of meals and administer insulin before the meal. Insulin lispro and insulin aspart are widely used in pregnancy and there is little concern as to their safety.[20]

Fasting and preprandial hyperglycaemia occur less commonly (this will change if the new fasting treatment target of ≤5.0 mmol/L is adopted) and require long-acting insulin. Isophane insulin has been widely used and is considered safe in pregnancy. The long-acting insulin analogues have been, to date, examined only in observational or retrospective reports in relatively small numbers of women with gestational or pregestational diabetes. A randomised trial of insulin detemir in women with type 1 diabetes during pregnancy will report shortly.

Oral agents

Oral hypoglycaemic agents are not currently recommended for routine use in pregnancy, despite the growing popularity of, and push for, metformin therapy. Metformin crosses the placenta, exposing the fetus to direct effects of the drug. A large randomised, non-inferiority trial, the Metformin in Gestational Diabetes Trial, has shown promising results during pregnancy.[21] However, early follow up of the children demonstrated differences in fat distribution, the significance of which is not clear, despite the claims of the authors that this is potentially beneficial.[22]

Glibenclamide is widely used in the USA but not as frequently in Australia. It has been associated with an increased risk of neonatal hypoglycaemia.

Long-term implications

Maternal

Women with a history of gestational diabetes are at significant risk of further glucose intolerance. The prevalence of type 2 diabetes increases with time, and in the two longest studies, one of which is from Victoria, the increase is linear.[23]

The rate of conversion to type 2 diabetes averages 1.5 to 2% a year. This risk is higher in women with more severe gestational diabetes no matter how that is measured (i.e. insulin use, degree of hyperglycaemia, etc). If the average age of a pregnancy complicated by gestational diabetes is 33 years, some simple calculations indicate that one-third of women diagnosed with type 2 diabetes before age 60 years could have been identified by their history of gestational diabetes.

Women with previous gestational diabetes are also at high risk of cardiovascular morbidity and mortality, independent of the risk of type 2 diabetes.[24] This is less well known. This risk may be in addition to the risks associated with obesity, the metabolic syndrome and family history, which are more common in women with a history of gestational diabetes (i.e. previous gestational diabetes may be an independent cardiovascular risk factor).

We now have strong evidence from at least two randomised controlled trials that type 2 diabetes can be prevented in high-risk populations, including women with a history of gestational diabetes[25] (and see http://diabetes.niddk.nih.gov/dm/pubs/preventionprogram/). We also have strong evidence from multiple trials that controlling dyslipidaemia and hypertension reduces cardiovascular morbidity and mortality. It therefore seems incumbent on us to provide appropriate follow up and treatment for these women. At the present time we do not do this well.

The follow up of women with a history of gestational diabetes is an important public health issue. Most women with gestational diabetes register with the National Gestational Diabetes Register – a part of the National Diabetes Services Scheme. This register will now prompt follow up and provide health-related advice to reduce the risk of developing diabetes.

Children

Untreated hyperglycaemia in pregnancy results in obesity and glucose intolerance or frank diabetes in the offspring. Fetal adiposity is a strong predictor of these adverse long-term outcomes.

Although there are excellent data that treating gestational diabetes reduces fetal adiposity, as yet we do not have clear evidence that treatment of gestational diabetes prevents these long-term consequences. However, it would seem obvious that the children would benefit from following a healthy diet and having an active lifestyle.

Summary

Using current diagnostic criteria, the prevalence of gestational diabetes is increasing. A change in diagnostic criteria may result in a further increase. The health system is already struggling to cope with the number of women diagnosed with gestational diabetes and any increase can only worsen this problem.

For this reason, most centres already manage women in group settings and this is likely to continue. More resources will be needed but it is also likely that we will need to modify our approaches to the management of these women.

We need better tools and risk calculators to stratify women diagnosed with gestational diabetes so that those with the greatest risk can be identified and managed more aggressively. We also need a better public health system for organising the follow up of women previously diagnosed with gestational diabetes. The National Gestational Diabetes Register is a first step. **ET**

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: Associate Professor McElduff has received honoraria for speaking from both Eli Lilly and Novo Nordisk.

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