Gestational diabetes

Glynis Ross
MBBS, FRACP, is Visiting Medical Officer, Department of Endocrinology, Royal Prince Alfred Hospital, and Senior Staff Specialist in Endocrinology, Bankstown-Lidcombe Hospital, Sydney, New South Wales. gpross@bigpond.net.au

BACKGROUND
Gestational diabetes (GD) affects 5–10% of pregnant women in Australia. Long term follow up studies show that most women with GD will progress to type 2 diabetes. The Australian Carbohydrate Intolerance in Pregnant Women study (ACHOIS) has addressed the issue of whether identifying and treating GD reduces perinatal morbidity in offspring.

OBJECTIVE
This article discusses the evidence from ACHOIS and outlines the diagnosis and management of GD.

DISCUSSION
Gestational diabetes is associated with serious adverse perinatal effects. These can be reduced with diagnosis and appropriate treatment. Women at very high risk of GD should undergo diagnostic testing with a 75 g glucose tolerance test (GTT) as soon as feasible after the initial booking visit. If they do not meet the current criteria for GD, they should be re-tested at 24–28 weeks gestation. More frequent testing may be appropriate in women with multiple high risk factors. Gestational diabetes is managed initially by dietary modification, physical activity and close glucose self monitoring. Insulin therapy is commenced when glycaemic goals cannot be met on dietary adjustment alone or if there is evidence of excessive fetal growth. Women who had GD should have a GTT 2–4 months postpartum. Ongoing GTT is then needed (annually if IGT, every 2–3 years when glucose tolerance has been normal).

Gestational diabetes (GD) is one of the most common medical disorders complicating pregnancy with 5–10% of pregnant women affected in Australia at present. The increasing prevalence is due, among other factors, to the rise in both maternal age and weight at the time of conception as well as the increasing number of Australian women from ethnic groups in which type 2 diabetes is more common.

Gestational diabetes is defined as 'carbohydrate intolerance of varying degrees of severity with onset or first recognition in pregnancy'.[1] Gestational diabetes has been long accepted as being predictive of future diabetes in the mother. There has been a lack of agreement as to whether identifying and treating GD reduces perinatal morbidity in offspring.

A recent study, mainly conducted in Australia, has shown that GD is associated with serious adverse perinatal effects that can be reduced with diagnosis and appropriate treatment. The Australian Carbohydrate Intolerance in Pregnant Women study (ACHOIS)[2] was a randomised controlled trial conducted in 18 centres. Women with risk factors for GD or with an abnormal 50 g glucose challenge test (GCT) were subjected to a 75 g oral glucose tolerance test (GTT) at 24–34 weeks gestation. Women with a fasting plasma glucose <7.8 mmol/L and a 2 hour glucose of 7.8–11.0 mmol/L were eligible for the study (*Table 1*).

One thousand eligible women were then randomised to an intervention group (n=490) or a control group (n=510). Women in the intervention group were given 'standard' GD management with dietary advice, self blood glucose monitoring and, if necessary, insulin therapy aiming to keep premeal plasma glucose concentrations <5.5 mmol/L and 2 hour postprandial glucose <7.0 mmol/L. Women in the control group were given routine obstetric care without these interventions. The rate of 'serious adverse perinatal outcomes' (including stillbirth, neonatal death, shoulder dystocia, bone fracture, nerve palsy) was lower (1.4%) in the intervention group than in the control group (4.4%). There were five deaths in the control group but none in the intervention group. There were fewer large for gestational age infants born to the intervention group (13.4%) than to the control (21.9%) group. There was no increase in the caesarean section rate (*Table 2*).

Should all pregnant women be screened for GD?

ACHOIS has provided evidence that there is benefit in identifying and treating GD. The Australasian Diabetes in Pregnancy Society (ADIPS) recommends universal screening for GD.[3] Most patients in ACHOIS were relatively 'low risk' for GD and would not have been identified if screening had been undertaken purely on women with classic accepted risk factors.

However, at the initial antenatal visit, women should still be assessed for high risk factors for GD. High risk factors will alter the timing of testing as well as the testing process and include:

- ethnicity (Aboriginal, Pacific Islander, south Asian, southeast Asian, Arabic) (*Table 3*)
- maternal age >35 years (*Table 4*)
- family history of diabetes (especially parents, siblings)
- previous GD
- previous large baby (>90th centile, >4000 g at term)
- maternal obesity (BMI >27 in Asian or Aboriginal women, >30 in other women)
- polycystic ovarian syndrome
- previous poor obstetric history.

How should women be tested for GD?

There remains no agreement on the best strategy or glycaemic criteria for diagnosing GD. It is uncertain as to what degree of hyperglycaemia on a GTT is 'abnormal' as available data do not demonstrate a clear cut off of glycaemia above which there is increased perinatal morbidity.

The Hyperglycaemia and Adverse Perinatal Outcome (HAPO) study[4] is a large multinational multicentre study involving 25 000 women who had GTT in pregnancy. Women with fasting plasma glucose >5.8 mmol/L or 2 hour level >11.1 mmol/L were excluded from the study as it was agreed they had hyperglycaemia of a degree that required treatment. The pregnancy outcomes for the other women will be analysed according to the levels of glycaemia on the GTT. Once the results are available (anticipated in 2007) currently used criteria for diagnosing GD will be reviewed.

Screening and diagnosis

Currently in Australia the most widely used screening and diagnostic criteria for GD are those of ADIPS[7] (*Table 5*). They were reached by consensus initially in 1991,[8] and recommendations expanded in 1998 following further discussions and data review.

Women at very high risk of GD should undergo diagnostic testing with a 75 g GTT as soon as feasible after the initial booking visit. If these women do not meet the current criteria for GD, they should be re-tested at 24–28 weeks gestation (see *Case history*). More frequent testing may be appropriate in women with multiple high risk factors.

All other women should have testing undertaken at 24–28 weeks gestation. These women may either proceed directly to a 75 g GTT or may be screened first with the 1 hour GCT. The 50 g GCT is associated with an 18% false negative rate when the usual 7.8 mmol/L cut off is used. The 50 g GCT however, is more acceptable to antenatal patients and more convenient when organising large numbers of antenatal patients in a busy clinic.

At any stage of the pregnancy, if there is clinical suspicion that diabetes may be present, prompt testing with 75 g GTT should be organised.

Table 1. ACHOIS classification of glucose tolerance status[2]

	Excluded from study	ACHOIS study population	Excluded from study
GTT	**Normal**	**IGT in pregnancy**	**Diabetes**
fBGL	<7.8 mmol/L	<7.8 mmol/L	≥7.8 mmol/L
2 hour BGL	<7.8 mmol/L	7.8–11.0 mmol/L	≥11.1 mmol/L

Table 2. ACHOIS perinatal outcomes[2]

	Intervention group (n=506)	Routine obstetric care group (n=524)
Stillbirth	0	3
Neonatal death	0	2
Shoulder dystocia	7 (1.4%)	16 (3.1%)
Nerve palsy	0	1
Mean birth weight	3335 g	3482 g
LGA (>90th centile)	13.4%	21.9%
Caesarean section	152 (31%)	164 (32%)
Elective	72 (15%)	61 (12%)
Emergency	80 (16%)	103 (20%)

Table 3. Prevalence of gestational diabetes according to ethnicity[5]

Ethnicity	GD prevalence %
Anglo-Celtic	3.0
Indian	16.7
Chinese	15
Arabic	7.3
Vietnamese	9.6
Aboriginal	10.1

Management

Diet

The diet should provide adequate nutrition for pregnancy. Carbohydrates should be distributed throughout the day over main meals and midmeal snacks. Limiting carbohydrates to 40% of the total caloric intake and having a higher proportion of carbohydrates of lower glycaemic index decreases postprandial glucose levels, reduces the need for insulin therapy, and may lead to a lower rate of large for gestational age babies. A greater restriction of dietary carbohydrate at breakfast may be needed because insulin resistance is greatest in the morning.

Exercise

Regular moderate intensity physical activity for about 30 minutes per day should be encouraged during pregnancy if there are no medical or obstetric contraindications, and may assist in blunting the postprandial blood glucose rise.

Table 4. Prevalence of gestational diabetes according to maternal age[6]

Age (years)	GD prevalence %
<20	1.0
20–24	1.8
25–29	2.5
30–34	4.1
35–39	6.5
40–45	9.8
>45	12.8

Case history

Jane is 36 years of age and of Anglo-Celtic descent. She has a number of risk factors for GD including advanced maternal age, strong family history of type 2 diabetes (both parents, three grandparents), obesity (BMI 31), polycystic ovaries, and a previous baby born weighing 4270 g. In her first pregnancy she was not tested for GD. Her son was born at term by emergency caesarean section because of fetal distress and failure to progress in labour. He spent 24 hours in the neonatal nursery with mild respiratory distress.

As Jane is at very high risk for GD she is tested in her second pregnancy soon after her booking visit with a 75 g GTT, which was normal. However, she was found to have GD (fasting BGL 5.6 mmol/L, 2 hour postload BGL 9.9 mmol/L) at 28 weeks gestation. Within 2 weeks of diagnosis, she was commenced on insulin as her BGL were above target despite dietary adjustments and daily walks. By delivery at 38.5 weeks (elective caesarean section due to previous caesarean section) Jane was requiring a total of 470 units of insulin per day. Baby Lara weighed 3850 g at birth and had no neonatal problems. Jane's GTT at 3 months postpartum was normal. At her postpartum visit Jane wants to discuss her risk for developing GD in any subsequent pregnancy and asks about her risk for getting diabetes in the future.

Self blood glucose monitoring

Self monitoring of blood glucose levels (BGL) should be organised. The minimum goals recommended by ADIPS are:

- fasting capillary BGL <5.5 mmol/L
- 1 hour postprandial capillary BGL <8.0 mmol/L
- 2 hour postprandial BGL <6.7 mmol/L.

Tighter ranges, while still avoiding hypoglycaemia, may be appropriate if there is evidence of accelerated fetal growth. Reported BGL should be checked periodically against the memory in the blood glucose meter as many women are anxious to provide 'pleasing' results. Meter BGL should be compared with laboratory BGL occasionally to assess meter accuracy. HbA1c levels may provide some reassurance that the reported BGL reflect the level of actual glycaemia. The A1c in well controlled GD would generally be expected to be well within the normal nonpregnant range.

Insulin

Insulin therapy is commenced when glycaemic goals cannot be met on dietary adjustment alone. It should also be considered if there is evidence of excessive fetal growth. The type and dose of insulin should be tailored to the individual patient's requirements. Human insulin has generally been recommended. The newer rapid acting insulin analogues lispro (Humalog) and aspart (NovoRapid) appear to be safe in pregnancy, and the limited number of studies and case reports, and extensive clinical experience so far, suggest they are more effective in controlling postprandial hyperglycaemia with less hypoglycaemia than regular human insulin. At this stage, longer acting insulin analogues have generally not been recommended. There are only a few case reports on the use of insulin glargine in pregnancy and no reports on insulin detemir in pregnancy.

Most women with GD require premeal short or rapid acting insulin. A smaller number require prebed intermediate acting insulin. A small percentage of women with GD are very insulin resistant and require large (>500 units/day) doses of insulin.

Are oral hypoglycaemic agents safe in management of GD?

The use of oral hypoglycaemic agents in pregnancy is still not generally accepted practice. Further studies on the safety and efficacy of glibenclamide and metforminin in GD are needed before their usage is recommended.

Older sulphonylureas crossed the placenta, stimulated the fetal pancreas and caused fetal hyperinsulinaemia. Glibenclamide is a second generation sulphonylurea and little crosses the placenta. In a clinical trial, 404 women

with GD were randomised to either glibenclamide or insulin, mostly in the second half of pregnancy.[9] There did not appear to be any difference in pregnancy outcomes.

There is considerable interest in the use of metformin in GD. Metformin does cross the placenta; teratogenesis does not appear to occur. ADIPS stated in 2004 that metformin should not yet be used routinely in pregnancy but there may be occasions to consider metformin (eg. refusal of insulin therapy, high insulin requirement) following appropriate discussion with the patient regarding risks and benefits.[10] In Australia, the prospective MiG trial is underway looking at pregnancy outcomes in women with GD treated with metformin compared to women with GD treated with insulin.[11]

Recommended timing and mode of delivery

The optimum timing of delivery is debated. Indications for earlier delivery at 38 weeks include poor glycaemic control or anticipated macrosomia especially when the estimated fetal weight is >4500 g. ACHOIS has raised the question as to whether the lower perinatal mortality rate in the 'treatment' group was partly due to the slightly earlier delivery. The mode of delivery should be determined on obstetric grounds.

Long term considerations

Long term follow up studies show that most women with GD will progress to diabetes, usually type 2 diabetes. A meta-analysis indicated that women who have had GD have a six times increased rate of developing diabetes.[12] Only 3–10% of women will have diabetes within the first year following delivery,[13] with another 10–20% having impaired glucose tolerance. However, about 50% will have diabetes within 10 years of the pregnancy.

Factors associated with earlier development of diabetes include ethnicity, earlier gestational age at diagnosis, insulin requirement in pregnancy, and weight gain subsequent to the pregnancy. Further pregnancies may influence the rate of subsequent diabetes.

Aggressive treatment of insulin resistance in women who had GD may preserve B-cell function and reduce the development of type 2 diabetes. The Diabetes Prevention Program (DPP) in the USA included women with previous GD and showed that intensive lifestyle modification (diet, regular exercise, weight control) led to a 58% reduction in the development of type 2 diabetes in adults with IGT.[14] This study also showed metformin reduced the risk of diabetes but to a lesser degree. The TRIPOD[15] and PIPOD[16] studies showed that troglitazone and pioglitazone reduced the rate of development of diabetes in women with previous GD.

Table 5. ADIPS criteria and method for screening and diagnosis of gestational diabetes[7,8]

Screen: 50 g glucose challenge test (GCT)

Abnormal if 1 hour venous BGL ≥7.8 mmol/L

- Dietary preparation (eg. 3 day diet/fasting) is not required
- Should be done in the morning
- Patient to be seated for the duration of the test
- Give 50 g glucose load (should be consumed within 5 minutes)
- Blood glucose meters are not to be used
- Take venous blood 1 hour after glucose load – time accurately
- Send specimen to laboratory as soon as possible

Note: 18% false negative rate if cut off is 7.8 mmol/L. If the BGL cut off is lowered to reduce the false negative rate, there would be a marked increase in the number of women with abnormal GCT needing a diagnostic GTT. Consideration can be given to omit the GCT and do a full 75g GTT on all women because of this problem. If clinical suspicion of GD but GCT is normal, organise 75 g GTT

Diagnosis: 75 g glucose tolerance test (GTT)

Gestational diabetes if fBGL ≥5.5 mmol/L, or
2 hour BGL ≥8.0 mmol/L (1 or 2 abnormal readings)

- 3 day preparation – high carbohydrate diet (most people eat >150 g carbohydrate per day on their usual diet)
- Fast for 8–12 hours before test, usually from 10 pm (only water may be consumed)
- No smoking on the morning of the test (from 12 midnight until test is completed)
- Should start in the morning before 9.30 am
- Patient to be seated for the duration of the test
- Baseline venous blood glucose level
- Give 75 g glucose load (should be consumed within 5 minutes)
- Blood glucose meters are not to be used
- Take venous blood at 1 hour and 2 hours after the glucose load – time accurately
- Send specimens to laboratory as soon as possible

Recommendations for follow up – women

Women who have had GD should have a GTT 2–4 months postpartum. Ongoing GTT is then needed (annually if IGT, every 2–3 years when glucose tolerance has been normal). All women should be counselled about the importance of a healthy diet, regular exercise, weight control and follow up GTT. They should be aware of symptoms suggestive of hyperglycaemia. Appropriate family planning should be discussed.

Women who are lean and do not have strong risk factors for type 2 diabetes should be assessed regarding possible evolving autoimmune (type 1) diabetes (eg. GAD, IA2 antibodies). About 2% of women presenting as 'GD' either have clinically evident new onset type 1 diabetes or are positive for two or more auto-antibodies that have been associated with development of type 1

diabetes within a few years of delivery;[17] although this prevalence may be as high as 10% in ethnic groups where type 1 diabetes is more common.[18]

Long term considerations – offspring

The offspring of women with GD are at increased risk of obesity, glucose intolerance and diabetes in late adolescence and early adulthood. Intrauterine exposure to higher glucose and insulin levels may affect the development of adipose tissue and pancreatic beta cells.[19–21]

Resources

- Martin FIR. The diagnosis of gestational diabetes. Med J Aust 1991;155:112
- Hoffman L, Nolan C, Wilson JD, et al. The Australasian Diabetes in Pregnancy Society. Gestational diabetes mellitus: management guidelines. Med J Aust 1998;169:93–7
- Simmons D, Walters BNJ, Rowan JA, McIntyre HD. Metformin therapy and diabetes in pregnancy. Med J Aust 2004;180:462–4
- McIntyre HD, Cheung NW, Oats JJN, Simmons D. Gestational diabetes mellitus: from consensus to action on screening and treatment. Med J Aust 2005;183:8
- ADIPS website at www.adips.org provides guidelines and information on gestational diabetes and pregestational diabetes for both women and health professionals. There is also a discussion forum.

Conflict of interest: none declared.

References

1. Metzger BE, Coustan DR. The Organising Committee. Summary and recommendations of the 4th International Workshop Conference on Gestational Diabetes Mellitus. Diabetes Care 1998;21(Suppl 2):161–7.
2. Crowther CA. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–86.
3. McIntyre HD, Cheung NW, Oats JJN, Simmons D. Gestational diabetes mellitus: from consensus to action on screening and treatment. Med J Aust 2005;183:288.
4. HAPO Study Cooperative Research Group. The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study. Int J Gynaecol Obstet 2002;78:69–77.
5. Yue DK, Molyneaux LM, Ross GP, Constantino MI, Child AG, Turtle JR. Why does ethnicity affect prevalence of gestational diabetes? The underwater volcano theory. Diabet Med 1996;13:748–52.
6. Stone CA, McLachlan KA, Halliday JL, Wein P, Tippett C. Gestational diabetes in Victoria: incidence, risk factors and outcomes. Med J Aust 2002;177:486–91.
7. Hoffman L, Nolan C, Wilson DJ, Oats JJN, Simmons D. The Australasian Diabetes in Pregnancy Society. Gestational diabetes mellitus: management guidelines. Med J Aust 1998;169:93–9.
8. Martin FIR. The diagnosis of gestational diabetes. Med J Aust 1991;155:112.
9. Langer O, Conway D. Berkus M, Xenakis E, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134–8.
10. Simmons D, Walters BNJ, Rowan JA, McIntyre HD. Metformin therapy and diabetes in pregnancy. Med J Aust 2004;180:462–4.
11. Hague WM, Davoren PM, Oliver D, Rowan J. Metformin may be useful in gestational diabetes [letter]. BMJ 2003;326:762–3.
12. Cheung NW, Byth K. Population health significance of gestational diabetes. Diabetes Care 2003;26:2005–9.
13. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes. Diabetes Care 2002;25:1862–8.
14. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2000;346:393–403.
15. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic ß-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high risk Hispanic women. Diabetes 2002;51:2796–803.
16. Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic ß-Cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes 2006;55:517–22.
17. Beischer NA, Wein P, Sheedy MT, Mackay IR, Rowley MJ, Zimmet P. Prevalence of antibodies to glutamic acid decarboxylase in women who have had gestational diabetes. Am J Obstet Gynecol 1995;173:1563–9.
18. Jarvela IY. Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age. Diabetes Care 2006;29:607–12.

afp CORRESPONDENCE email: afp@racgp.org.au