Drugs for gestational diabetes

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Summary

The prevalence of gestational diabetes is increasing in Australia. Non-pharmacological intervention with dietary measures and exercise is the mainstay of therapy in most cases, but insulin is increasingly necessary to achieve adequate glycaemic control in some women. Basal-bolus insulin is the optimal management strategy, but therapy needs to be individualised. Although there is mounting evidence for the efficacy and safety of metformin, the lack of long-term follow-up data has prevented it from being recommended by most experts in the field. Women with gestational diabetes need long-term follow-up because of their increased risk of type 2 diabetes.

Key words: hypoglycaemic drugs, insulin, metformin, pregnancy.

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Introduction

Gestational diabetes is defined as an intolerance to glucose that is first diagnosed or has its onset during pregnancy. It is estimated to affect almost 5% of pregnancies in Australia and between 3% and 9% worldwide. Its prevalence increases with age, from 1% in women aged 15–19 years to 13% in those aged 44–49 years.[1] Other risk factors for developing gestational diabetes include being overweight or obese, having a family history of type 2 diabetes or a personal or family history of gestational diabetes or glucose intolerance, being from an Aboriginal or Torres Strait Islander background or belonging to certain ethnic groups (for example Polynesian, Middle Eastern, Indian or other Asian origin).[2] Although gestational diabetes does not affect perinatal mortality, it does increase morbidity, including the risk of shoulder dystocia, nerve palsies and neonatal hypoglycaemia. Maternal outcomes are also affected, with a higher incidence of pre-eclampsia and caesarean section (particularly with poor glycaemic control) in mothers who develop gestational diabetes.[3]

Diagnosis

Universal screening for gestational diabetes has been recommended in Australia since 1998. A fasting glucose challenge test should be performed at 26–28 weeks gestation. If abnormal, this is followed by a formal two-hour 75 g oral glucose tolerance test. Criteria for diagnosis are presented in Table 1. For women at risk of gestational diabetes, a glucose tolerance test can be performed at any stage during pregnancy. However, as placental production of diabetogenic hormones tends to increase throughout the second and third trimesters, a normal glucose tolerance test in the early part of pregnancy does not exclude the development of gestational diabetes later on. A second oral glucose tolerance test should therefore be performed at the standard 26–28 weeks of gestation even if an earlier test was normal.

New recommendations for screening and diagnosis are currently under consideration, but have yet to be adopted or approved by expert groups in gestational diabetes. It is likely, however, that the glucose challenge test will be removed from the screening process, so that a diagnosis of gestational diabetes will be made if the blood glucose is abnormal when fasting, or one or two hours after a 75 g glucose load (see Table 1).

Blood glucose targets

Once diagnosed, all women need to be educated about the possible implications of gestational diabetes (both fetal and maternal) and be taught how to perform home blood glucose monitoring. Finger-prick testing should be performed four times

Table 1

Current and possible future diagnostic criteria for gestational diabetes

	Test	Venous plasma glucose – for diagnosis
Current practices	screen: non-fasting 50 g glucose challenge	1 hour ≥ 7.8 mmol/L (requires confirmatory testing)
	confirmatory testing: fasting 75 g glucose tolerance	one of either: ■ fasting ≥ 5.5 mmol/L or ■ 2 hour ≥ 8.0 mmol/L
Potential new criteria[13]	fasting 75 g oral glucose tolerance	any one of three: ■ fasting ≥ 5.1 mmol/L ■ 1 hour ≥ 10.0 mmol/L ■ 2 hour ≥ 8.5 mmol/L

a day (before breakfast and two hours after each meal). Target blood glucose concentrations, shown in Table 2, need to be explained.

The results of the Hyperglycemia and Adverse Pregnancy Outcomes trial have demonstrated that the risks associated with maternal hyperglycaemia are on a continuum above the normal blood glucose concentration and treatment targets might be lowered in the future to reflect this.[4] As yet, a consensus on where these targets will be set has not been established.

Non-pharmacological interventions

All women with gestational diabetes should receive advice from a dietitian with specific knowledge in the area and dietary intervention should be initial therapy for most women. Dietary advice needs to be individualised, taking into account factors such as the patient's body mass index (BMI) and overall nutritional requirements.[2] Care should be taken to avoid excessive caloric restriction, as this can result in ketonuria and adverse pregnancy outcomes.[5] Moderate intensity exercise, such as a brisk walk for 30 minutes each day, can decrease insulin resistance and should be encouraged.[6]

Insulin

Insulin therapy remains the mainstay of pharmacotherapy and its use is becoming increasingly prevalent. In 2005–06, about 30% of confinements with gestational diabetes were treated with insulin, with women in older age groups requiring it in about 40% of cases.[1] Insulin should be considered when blood glucose concentrations (Table 2) exceed recommended targets on two or more occasions within one week. The indication for starting insulin is stronger if there is evidence of macrosomia or increased fetal abdominal circumference.[2]

All women started on insulin need education regarding storage of insulin, correct injection technique as well as recognition and treatment of hypoglycaemia. The assistance of a diabetes educator with this can be invaluable.

Insulin therapy needs to be individualised and is dependent upon the patient's blood glucose concentrations, her weight and her wishes. The regimen is determined by whether the blood glucose is elevated when fasting, after a meal, or both.

Elevated fasting glucose

If the fasting glucose is elevated, but postprandial levels are within the recommended target range, a single bedtime injection of intermediate-acting insulin (for example insulin isophane) will often suffice. A starting dose of 4–12 units is reasonable. If postprandial hyperglycaemia occurs later in the pregnancy, mealtime injections of rapid-acting insulin may need to be introduced.

Postprandial hyperglycaemia

Occasionally, women may have elevated postprandial blood glucose with normal fasting levels. Dietary intervention can be useful in this situation. However, should this prove inadequate, mealtime injections of rapid-acting insulin (for example insulin aspart, insulin lispro) can be introduced. Starting doses of 4–8 units with each meal are reasonable. Soluble human insulin is an alternative, but has the disadvantage of needing to be injected 30 minutes before eating.

Table 2

Target blood glucose concentrations in gestational diabetes

	Blood glucose (mmol/L)
Fasting capillary	< 5.5
Postprandial capillary	< 7.0 (2 hours) < 8.0 (1 hour)

Fasting and postprandial hyperglycaemia

A basal-bolus insulin regimen (mealtime rapid-acting insulin and bedtime intermediate-acting insulin) is generally preferred as it provides the patient with greater flexibility in diet and exercise. Twice-daily mixed insulin (for example insulin aspart/protamine or lispro/protamine) is an alternative, particularly if the patient is reluctant to inject four times per day or might find it too difficult.

Dosing

Larger doses of insulin are reserved for those with higher BMI or blood glucose readings significantly above target. Smaller doses might be appropriate for women with a slighter build. The dose can be titrated every two to three days as required, with increments of 2–4 units (no greater than 20% dose increase) until targets are met or the patient develops excessive hypoglycaemia (more than two to three times per week or any episode of severe hypoglycaemia).

It remains unclear if maternal hypoglycaemia adversely affects the fetus. If there are concerns, it tends to be in women with pre-existing diabetes in the first trimester of pregnancy (during organogenesis)[7] and not in those with gestational diabetes.

Insulin doses may be anticipated to rise throughout the third trimester as a result of increasing maternal insulin resistance. This tends to reach a plateau at 36–38 weeks.

Insulin analogues

There is currently little evidence to support the use of other insulin analogues (for example insulin glargine, insulin detemir) in pregnancy, although their use is increasing.

Metformin

There is increasing evidence for the use of metformin in pregnancy. The Metformin in Gestational Diabetes (MiG) trial, an open-label randomised controlled trial comparing metformin with insulin, was conducted throughout Australia and New Zealand.[8] It showed the efficacy and safety of metformin in the second and third trimesters with no difference in perinatal complications between treatments. Not surprisingly, patients

preferred oral metformin to insulin injections. Almost half of the patients taking metformin also required insulin to achieve treatment targets. There does not appear to be an increase in the risk of congenital malformations, even when the fetus is exposed to metformin in the first trimester.

Although this is promising, there is no long-term follow-up of children born to mothers who took metformin during pregnancy. The use of metformin in pregnancy is therefore not currently endorsed by regulatory authorities or professional bodies, including the Australian Diabetes in Pregnancy Society. Although no adverse effects have been demonstrated, metformin does cross the placenta, leading authorities to be very cautious in their recommendations. Nonetheless, metformin is used for the treatment of gestational diabetes in many centres around Australia and New Zealand, but has found much less favour in Europe and the USA.

Metformin could be considered for use in patients who have failed non-drug therapies and who either refuse or are unable to take insulin. The mother should be educated about the potential risks, benefits and areas of uncertainty so that an informed decision can be made.

Sulfonylureas

Glibenclamide has the most evidence for use in pregnancy. Unlike the older sulfonylureas, glibenclamide does not appear to cross the placenta to a significant degree. There does not appear to be an increase in fetal complications, but, like metformin, it is currently not recommended for widespread use in pregnancy because of a lack of long-term follow-up of children exposed to glibenclamide *in utero*.

There is little evidence for the safety or efficacy of other sulfonylureas in pregnancy and their use is not recommended.

Other drugs

There are few data about the safety or efficacy of acarbose, thiazolidinediones or incretin mimetics and enhancers in pregnancy. Currently these drugs are not recommended and their use in pregnancy should be considered experimental.

Follow-up and prognosis

Gestational diabetes resolves postpartum in more than 90% of women. In general, all insulin and oral hypoglycaemic drugs are ceased immediately postpartum with ongoing blood glucose monitoring until discharge from hospital. If concentrations return to normal, which occurs in the overwhelming majority of cases, a repeat glucose tolerance test should be performed 6–8 weeks postpartum to ensure that the patient does not have overt type 2 diabetes.

The long-term risk for developing type 2 diabetes is increased over sevenfold in women who develop gestational diabetes compared with those who have a normoglycaemic pregnancy.[9] Women with a pre-pregnancy BMI of more than 27 kg/m^2, those of advancing maternal age and those who required insulin for glycaemic control in pregnancy are at particularly increased risk.[10] It is important to counsel women about these issues and the need to continue with dietary measures, regular exercise and attempts at achieving and maintaining a normal body weight long into the future. Both intensive lifestyle intervention and drug therapy (metformin) may be useful to decrease the risk of these patients developing type 2 diabetes.[11]

There are no evidence-based guidelines for long-term follow-up of mothers with gestational diabetes. Australian guidelines recommend a glucose tolerance test at least every two years,[2] while others believe that a fasting glucose test one to two yearly is sufficient. A more intensive follow-up regimen would be rational if the patient has evidence of impaired glucose tolerance or impaired fasting glucose on early postnatal testing, a strong family history of type 2 diabetes, or if there are other major risk factors such as marked obesity or polycystic ovary syndrome.

Children and adolescents whose mothers had gestational diabetes seem to be at higher risk of developing features of metabolic syndrome compared with mothers who do not have diabetes. Although unproven, it is likely that these children will also have a higher risk of developing type 2 diabetes as adults.[12]

Conclusion

Gestational diabetes is increasing in Australia. Appropriate screening, diagnosis and management is important, not only to improve perinatal and maternal outcomes, but also because it may help to decrease the incidence of type 2 diabetes in the future. Insulin remains the mainstay of pharmacotherapy, but there is increasing use of oral hypoglycaemic drugs (particularly metformin) in Australia and New Zealand.

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Further reading

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Conflict of interest: none declared

Your questions to the PBAC

Avoiding wastage with insulin prescribing

The Pharmaceutical Benefits Scheme (PBS) provides affordable medicines to all Australians. However, increasing costs of medications are threatening it.

New means of cost-effective and cost-minimising interventions are always needed to ensure sustainability and viability of the scheme.[1] A practical and simple approach of saving is to change the PBS listing of insulin prescribed for gestational diabetes and users of low-dose insulin who will not necessarily go through the normal quantity of insulin provided to them. The standard quantity of insulin supplied by the PBS is five boxes of five individually packed units. This amount is usually excessive for patients using small doses of insulin who are prescribed other antidiabetic medicines.

A new listing of a single box of five individually packed units made available to these groups of patients will significantly save costs to the PBS and promote the quality use of medicines to the consumer as well as the prescribers.

By avoiding wastage of medications and educating prescribers about the need to restrict supply of excess unnecessary medications, resources could be freed up for other government-funded health expenditures.[2]

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PBAC response:

Thank you to Dr Khalil for the suggestion to add a differential PBS listing for insulin. The maximum quantity and number of repeats allowed for items subsidised on the PBS are recommended by the Pharmaceutical Benefits Advisory Committee (PBAC). In general, for drugs which are usually taken on a long-term basis – such as for the management of diabetes – the PBAC recommends a maximum quantity sufficing for about one month's therapy at average doses. The PBAC believes that this requirement is equitable since it is applied across most therapeutic classes of drugs intended for long-term use.

Although a maximum quantity is set out in the PBS listing, there is flexibility to vary the quantity prescribed for patients taking doses that are higher or lower than usual. It is the responsibility of the doctor to ensure that individual patients are prescribed the appropriate quantity. If a prescriber feels the maximum quantity (or number of repeats) should be increased for a particular patient, he or she has the option of completing an Authority PBS Prescription Form with Medicare Australia either by telephone or in writing. This situation usually arises where higher than normal dosages are required. If, as in the case raised by Dr Khalil, a lesser quantity is sufficient for the patient's needs, then this lower quantity may be prescribed. It is not necessary to prescribe the stated maximum quantity as PBS prescriptions and repeats can be for any amount up to the maximum quantity.