The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy

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ABSTRACT

- Strict control of blood glucose levels should be pursued before conception and maintained throughout the pregnancy (glycohaemoglobin [HbA_{1c}] level as close as possible to the reference range).
- Before conception:
  - high-dose (5 mg daily) folate supplementation should be commenced;
  - oral hypoglycaemic agents should be ceased; and
  - diabetes complications screening should take place.
- Management should be by a multidisciplinary team experienced in the management of diabetes in pregnancy.
- Blood glucose monitoring is mandatory during pregnancy, and targets are: fasting 4.0–5.5 mmol/L; postprandial < 8.0 mmol/L at 1 hour; < 7 mmol/L at 2 hours.
- A first trimester nuchal translucency (possibly with first trimester biochemical screening with pregnancy-associated plasma protein A and β-human chorionic gonadotropin) should be offered.
- Ultrasound should be performed for fetal morphology at 18–20 weeks, if required, for cardiac views at 24 weeks and for fetal growth at 28–30 and 34–36 weeks.
- Induction of labour or operative delivery should be based on obstetric and/or fetal indications.
- Level 3 neonatal nursing facilities may be required and should be anticipated when birth occurs before 36 weeks, or if there has been poor glycaemic control.
- Insulin requirements fall rapidly during labour and in the puerperium. At this time, close monitoring and adjustment of insulin therapy is necessary.

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The management of pregnancy in women who have type 1 or type 2 diabetes mellitus remains challenging. The St Vincent declaration of 1989 set a 5-year target to reduce adverse pregnancy outcomes in women with type 1 diabetes mellitus (T1D) to a level equal to that of women without diabetes.[1] However, there is evidence from many countries that this target has not been met.[2-7] There is often a lack of awareness of the dangers posed by diabetes for pregnancy, particularly with type 2 diabetes mellitus (T2D), which is increasingly common and often undiagnosed before pregnancy. Despite these very significant problems, there is a paucity of comprehensive published guidelines for the management of pregestational diabetes.

The Australasian Diabetes in Pregnancy Society (ADIPS) formed a working group comprising diabetes educators, endocrinologists and obstetricians to formulate guidelines appropriate for Australia. The background details to these guidelines are available at <www.adips.org>, and this article is a summary. These guidelines were formulated following literature searches through MEDLINE and further review of references in the articles examined. However, in many areas, there was no level 1 evidence,[8] and the combined experience and expertise of the writing group was drawn upon to arrive at the consensus guidelines.

Management of women with diabetes before conception

Information and counselling should be provided to all women of reproductive age with diabetes so that they are aware of the problems of diabetes in pregnancy, the potential dangers inherent in unplanned pregnancy, and the benefits of prepregnancy counselling. The risks include increased perinatal mortality and malformation rates. These matters should be raised at each annual review of diabetic status, or more frequently if required. A meta-analysis has demonstrated a significantly lower prevalence of major congenital anomalies in offspring of women who attended for prepregnancy counselling (relative risk, 0.36; 95% CI, 0.22–0.59; absolute risk, 2.1% v 6.5%).[9] The importance of this pre-conception counselling and review cannot be overestimated.

Diabetes-specific measures

A multidisciplinary team experienced in the management of diabetes in pregnancy has been shown, in many countries,[10,11] to

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provide superior obstetric and fetal outcomes relative to appropriate local comparators. This team should consist of people with an interest and experience in managing diabetes in pregnancy. The team should consist of an obstetrician, an endocrinologist (or a physician experienced in diabetes care during pregnancy), a diabetic educator and a dietitian.[10,11]

Specific issues to be discussed by the management team include the clear benefits of optimal metabolic control before conception in reducing the risk of miscarriages, congenital malformations, perinatal mortality and other complications, and the benefits of taking folic acid 5 mg daily for the prevention of neural tube defects.[12] Vitamin B_{12} levels should be measured in women taking metformin.

The optimal glycaemic targets should be made clear. At present, the minimum standard set by the National Diabetes in Pregnancy Advisory Council is to achieve and maintain a target glycohaemoglobin (HbA_{1c}) level of < 1% above the reference range (generally < 7%).[13] However, there is evidence that the level of HbA_{1c} should be maintained within the reference range if possible,[5,7] while avoiding hypoglycaemia, and this is to be encouraged. This should be achievable in most patients with T2D, but may not be possible in women with T1D. Women should not actively attempt pregnancy or embark on assisted reproductive treatment until the best available glycaemic control has been achieved.

The pre-conception review should include a reassessment of diabetes education with the goal of ensuring adequate self-management skills, including sick day care and hypoglycaemic management; diet, including suggestions for dealing with morning sickness; and the physical activity regimen.

Diabetes complications review

Formal assessment for diabetes complications, particularly retinopathy and nephropathy, is essential. Medical practitioners should advise women with diabetic complications of the risks they may encounter during pregnancy. Because of the risk of progression, some of these complications are contraindications to pregnancy.

Retinopathy: The eye examination should be conducted through dilated pupils by a person experienced in retinal examination. Pre-existing retinopathy may progress more rapidly in pregnancy.[14] Therefore, retinopathy that requires laser therapy should be treated before pregnancy.

Nephropathy: Screen for nephropathy with an overnight or 24 hour urine sample to quantify the albumin excretion rate. Failing this, an albumin/creatinine ratio on an early morning specimen is an alternative screening test. If the albumin/creatinine ratio is > 3.5 mg/mmol, a timed sample should be collected. Patients with pre-existing microalbuminuria are more likely to develop pre-eclampsia.[15] If renal function is significantly impaired (creatinine, > 0.2 mmol/L), there is an increased risk of progression to dialysis during pregnancy, so this should be considered a contraindication to pregnancy.[16] A third of such patients may die within 16 years.[17] The implications should be discussed with the woman planning pregnancy.

Macrovascular disease: Evidence of macrovascular disease should be sought through detailed history and examination, and investigated if suspected. Pre-existing heart disease, including coronary heart disease, requires cardiological review before conception. Significant coronary artery stenosis should be treated before pregnancy.

Autonomic neuropathy: The presence of autonomic neuropathy resulting in gastroparesis, orthostatic hypotension or hypoglycaemic unawareness may severely complicate the management of diabetes in pregnancy.

Other related issues

Thyroid function should be measured for women with T1D,[18] as abnormalities in these women are common and may adversely affect pregnancy outcomes. The possibility of other coexistent autoimmune disease (eg, coeliac disease) in women with T1D should be considered.

Management during pregnancy

General management

Women with diabetes should be managed by a specialised multidisciplinary team. In certain situations (eg, isolated communities) some aspects of ideal pregnancy management may not be possible.

Medical

Routinely review women (possibly by telephone in some instances) every 1–4 weeks during the first 30 weeks and then every 1–2 weeks until delivery, depending on diabetes control and the presence of diabetic and obstetric complications. The assessment should include a review of glycaemic control. Self-monitoring of blood glucose is mandatory. It is recommended that tests be performed fasting and 1–2 hours after meals. In addition, some testing before meals or overnight may be useful, particularly in people with T1D. The blood glucose targets are: fasting and preprandial 4.0–5.5 mmol/L, and postprandial < 8.0 mmol/L at 1 hour or < 7 mmol/L at 2 hours. A basal bolus regimen of insulin generally provides the best opportunity for good glycaemic control. Insulin pump therapy is a suitable alternative where there is local experience. The HbA_{1c} level should be monitored every 4–8 weeks and kept within the normal range. (Note that the HbA_{1c} level is normally lower in pregnancy, but most laboratories do not report a reference range specific to pregnancy.) Serious or sustained ketonuria should be avoided. Pregnant women with T1D are more prone than usual to ketoacidosis.

Women should be monitored for signs or progression of diabetic complications, particularly retinopathy and proteinuria. Formal eye review should be at least 3-monthly if baseline retinopathy is present, if there is a rapid improvement in glycaemic control, or if there has been a long duration of pre-existing diabetes.[19] Proteinuria should be assessed by dipstick at regular intervals, and quantitated where appropriate. The diabetes complications review should be repeated at the first antenatal visit if conception has been delayed.

Insulin requirements: what to expect

Hypoglycaemia, especially overnight, is more frequent from the 6th to 18th weeks of gestation, and insulin doses may need to be decreased.[20] The physiological insulin resistance of pregnancy increases in the late second trimester, and may continue to increase after that time. Insulin requirements may increase substantially. Insulin requirements can fall after 32 weeks.[21] Any fall greater than 5%–10% should lead to an assessment of fetal wellbeing and a search for medical conditions that can lead to loss of counter-regulatory control (eg, adrenal insufficiency). In the absence of abnormalities on fetal monitoring, a fall in insulin requirement

does not correlate with adverse fetal outcome and is not in itself an indication for delivery.[21]

Tight glycaemic control needs to be balanced against the risk of hypoglycaemia. Maternal deaths due to hypoglycaemia have been reported.[22] It remains unclear if hypoglycaemia can adversely affect fetal development.[22] Modest maternal hypoglycaemia down to 2.5 mmol/L does not appear to affect fetal wellbeing.[23]

Unsatisfactory glycaemic control

If there is unsatisfactory metabolic control, potential sources of the problem (such as diet, intercurrent illness, concurrent medication, stress, exercise and lifestyle) need to be explored. Treatment needs to be reviewed and adjusted. Occasionally, it may be necessary to admit the woman to hospital to optimise glycaemic control.

Medications for diabetes control and associated conditions

Insulin analogues: There is increasing use of the newer rapid acting insulin analogues during pregnancy. Two reviews have concluded that, on current evidence, lispro and aspart are not teratogenic, nor are they associated with adverse effects in pregnancy.[24,25] Nevertheless, their use in pregnancy should be discussed with the woman. There is little published experience with glargine (Lantus, Aventis Pharma Pty Ltd), the new long-acting insulin analogue. A recent review draws attention to the increased mitogenic potential of this agent and urges caution in pregnancy.[25]

Oral hypoglycaemic agents: The gold standard for pharmacological hypoglycaemic therapy in pregnancy is insulin. Oral hypoglycaemic agents are not recommended because there is limited information regarding their safety in pregnancy. A meta-analysis suggested that the oral agents do not cause an increased risk of congenital malformations.[26] Therefore, they could be considered safe from this limited point of view. However, the authors of that review called for more data with oral agents in well-controlled diabetes. ADIPS has recommended that metformin therapy not be used routinely in women with pregnancies complicated by diabetes. Nevertheless, when the potential harm from metformin therapy is likely to be outweighed by its benefits, it could be considered. Such situations include refusal of the patient to use insulin.[27] When pregnancy occurs while a woman is taking oral agents, the medication should not be stopped immediately; rather, an urgent referral to the physician member of the management team is indicated for careful transfer to insulin therapy to avoid hyperglycaemia in the critical early period of gestation.

Anti-hypertensive medication: Anti-hypertensive therapy in pregnancy has been reviewed by the Australasian Society for the Study of Hypertension in Pregnancy, and guidelines formulated.[28] There is considerable evidence supporting the use of methyldopa, oxprenolol, clonidine, labetolol, prazosin and nifedipine in pregnancy. Angiotensin-converting enzyme (ACE) inhibitors should be avoided in pregnancy as they are hazardous for the fetus in the third trimester, and of unproven safety in the first.[29] If a woman has severe or difficult to control hypertension, it may be acceptable, after informed discussion, to continue the ACE inhibitor, ceasing it as soon as pregnancy occurs. The effect of angiotensin 2 receptor blockers in pregnancy is unknown, but it is expected that it would be similar to that of ACE inhibitors.

Lipid-lowering medication: Fetal malformations have been documented in pregnancies where statins were continued in the first trimester.[30] They are contraindicated in pregnancy.

Obstetric management

Regular routine obstetric review is based on a high-risk pregnancy. Normal fetal growth and indices for fetal and maternal welfare should be maintained. Midtrimester maternal serum screening for aneuploidy is less reliable in the presence of diabetes. Consideration should be given to the use of first trimester screening using nuchal translucency at 12–13 weeks, with β-human chorionic gonadotropin and pregnancy-associated plasma protein A measured at 10–13 weeks where resources are available.[31] Because of the need for accurate dating, a first trimester ultrasound examination should be performed even when aneuploidy screening is not desired.

Ultrasound examination for fetal morphology should be offered at 18–20 weeks. In selected cases, repeat morphology scanning at 24 weeks may help to better define cardiac structures. Further examinations to assess fetal growth should be performed at 28–30 weeks and repeated at 34–36 weeks. The latter will help to determine the timing and route of delivery. Further ultrasound examination, including umbilical artery Doppler flow measurements, may be indicated in the presence of other abnormalities. Formal testing of fetal wellbeing (eg, cardiotocography, umbilical Doppler blood flow studies or biophysical profile) is not necessary in an otherwise uncomplicated pregnancy before 36 weeks gestation.

Medications used in management of premature labour

Some pharmacological agents, administered when a premature delivery is likely, may lead to significant hyperglycaemia and risk of ketoacidosis in women with diabetes.[32,33] These include β-sympathomimetic agents (eg, salbutamol) given to suppress uterine contractions (tocolytics) and corticosteroids given to enhance fetal lung maturity. Following administration of salbutamol, there may be a rapid rise in blood glucose level.[32,33] Therefore, alternative tocolytic agents such as nifedipine are recommended. Following administration of corticosteroid, the rise in blood glucose level usually starts about 6–12 hours later, and may persist for up to 5 days.[33]

In this setting, it is important to maintain good glycaemic control to reduce any further metabolic stress on the fetus, with blood glucose level monitored every 1–2 hours until glycaemic control has stabilised and insulin requirement returned to baseline. There should be a local protocol to proactively manage the anticipated hyperglycaemia.[32,33]

Type 2 diabetes in pregnancy

A recent survey of 10 teaching hospitals by ADIPS has found that, in pregnancies complicated by pre-existing diabetes, T2D is at least as common as T1D.[2] T2D in women of reproductive age is particularly common among Aboriginal and Torres Strait Islander peoples, Maori and people from Pacific islands, Asia and the Middle East. With the increasing prevalence of T2D among women of reproductive age, some specific issues need to be considered.

The treatment targets and screening for complications are as for T1D. Some women with diet-controlled T2D may require no pharmacological hypoglycaemic treatment during early pregnancy. Insulin is usually required later in pregnancy. Oral hypoglycaemic agents are generally not recommended in pregnancy. Exceptions to this practice should only be made after review by the specialised management team. Women with pre-existing impaired glucose tolerance or impaired fasting glycaemia should be managed as if

they had gestational diabetes from the time of confirmation of pregnancy.

The risk of congenital anomalies among women with T2D is similar to that among women with T1D.[2,3] T2D should not be considered a more "benign" form of diabetes. It is often accompanied by obesity and other features of the metabolic syndrome, which carry their own increased perinatal risk.[34,35]

Management during delivery

A plan for insulin management during delivery and in the immediate post-partum period should be documented in advance, and communicated to all parties, including the patient.

Delivery

Delivery should be at term for women with pre-existing diabetes unless obstetric or medical factors dictate otherwise (eg, fetal macrosomia, polyhydramnios, poor metabolic control, pre-eclampsia, intrauterine growth restriction). Vaginal delivery is preferable unless there is an obstetric or medical contraindication. Where the estimated birthweight exceeds 4250–4500 g, the risk of shoulder dystocia warrants consideration of elective caesarean section.[36]

The need for induction of labour or assisted delivery should be based on obstetric and fetal indications. The need for access to specialised neonatal intensive care should be based on fetal risk. The need for level 3 neonatal nursing facilities should be anticipated when birth occurs before 36 weeks, or if there has been poor metabolic control.

Protocol for diabetes management during labour

Women should continue their regular diet, insulin and blood glucose monitoring until in labour. During active labour, the blood glucose level should be measured every 1–2 hours, and should be kept within the range of 4–7 mmol/L.

Guidelines for management of diabetes in labour vary widely. There is no evidence to prove one method superior to others. A locally accepted protocol should be in place.

Protocol for the management of diabetes during caesarean section

Elective caesarean section should be scheduled first on the morning list, and the usual dose of intermediate insulin given the night before. Long-acting insulins may require a dose reduction to avoid hypoglycaemia in the post-partum period. Women with T1D may require an insulin/dextrose infusion because of the prolonged fasting.

An emergency caesarean section will require a flexible approach to ensure glycaemic stability and prevent hypoglycaemia immediately post partum.

Post-partum management

A management plan should be developed before discharge, including specific contact details in case any problems with glycaemic control occur following discharge.

Type 1 diabetes

Insulin requirements fall rapidly after delivery. Close monitoring and restabilisation will be necessary in the first few weeks post partum. The primary treatment goal in the post-partum period is to avoid hypoglycaemia. Specific advice should be given about nocturnal hypoglycaemia and its management. New mothers should be reassured that a short-term relaxation of tight control is justified to reduce the risk of hypoglycaemia. Women should be made aware that breastfeeding may accentuate hypoglycaemia.

Type 2 diabetes

In many women, diet alone will achieve good glycaemic control after delivery. If treatment is required, insulin is recommended if breastfeeding. The World Health Organization states that oral hypoglycaemic agents are not contraindicated,[37] although metformin does pass to the child.[38] They recommend monitoring the baby for hypoglycaemia. However, several members of this panel believe that this exposure is unwarranted in most situations.

Contraception

It is important to discuss contraception before discharge from hospital. There is no evidence that any of the present contraceptive methods is contraindicated in women with diabetes. All available options should be discussed with the woman and her partner.

Neonatal management

This area was not addressed by the panel.

Implications for the offspring

Diabetes during pregnancy has far-reaching implications for the child in infancy and in later life. There is good evidence that an adverse intrauterine environment, independent of any genetic determinant, is a factor in later metabolic disturbances in the offspring of a diabetic mother. Studies have shown that obesity, impaired glucose tolerance and T2D are more prevalent in children and adults when diabetes was present during their fetal development.[39] This is assumed to be due to maternal hyperglycaemia during pregnancy, and emphasises the importance of good glycaemic control during pregnancy. Attention to long-term healthy lifestyle practices for the whole family may minimise the risk of diabetes in other family members.

Competing interests

David McIntyre has received speaker fees from Novo Nordisk Australia, Lilly Australia and Alphapharm, and has received assistance to attend meetings from Novo Nordisk Australia, Aventis and Lilly Australia.

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