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POSITION PAPERS

ADIPS 2020 guideline for pre-existing diabetes and pregnancy

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This is the full version of the Australasian Diabetes in Pregnancy Society (ADIPS) 2020 guideline for pre-existing diabetes and pregnancy. The guideline encompasses the management of women with pre-existing type 1 diabetes and type 2 diabetes in relation to pregnancy, including preconception, antepartum, intrapartum and postpartum care. The management of women with monogenic diabetes or cystic fibrosis-related diabetes in relation to pregnancy is also discussed.

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KEYWORDS
Australia, diabetes mellitus, high-risk pregnancy, New Zealand, postnatal care, practice guideline, preconception care, pregnancy, type 1 diabetes, type 2 diabetes

GUIDELINE DEVELOPMENT AND METHODOLOGY

This guideline is a consensus-based guideline, designed to provide practical guidance to clinicians. It was developed with a multidisciplinary writing team including obstetricians, endocrinologists, obstetric physicians, credentialled diabetes educators (CDE), midwives, lactation consultants and accredited practising dietitians (APD) with expertise in diabetes in pregnancy. It had input from both Australian and New Zealand clinicians. The writing group members were drawn from a variety of clinical backgrounds, including practitioners from metropolitan, regional and rural/remote settings. The guideline did not aim to meet the National Health and Medical Research Council standard for guidelines, and rating quality of evidence or strength of each recommendation was out of scope. There was no funding available and this work was completed on a purely voluntary basis.

The literature was reviewed, and each member of the writing group was assigned a section of the guideline to write. Sections were then reviewed by all members, and a consensus of expert opinion was achieved.

The guideline was reviewed by the Australasian Diabetes in Pregnancy Society (ADIPS) board, and then widely disseminated throughout Australia and New Zealand for stakeholder review, with feedback from 14 professional organisations and 17 ADIPS members (obstetricians, endocrinologists, midwives, dietitians). The guideline writing group would like to acknowledge the valuable and extensive feedback provided. Each item of feedback was reviewed by the writing group and a consensus decision was made in response to each item of feedback.

There are key areas that this guideline does not address:

1. Routine pregnancy care: This guideline specifically addresses issues of pre-existing diabetes and pregnancy. It does not include details of routine pregnancy care. Women with pre-existing diabetes and pregnancy require all the usual preconception, antenatal, peripartum and postnatal care that every other woman requires. This guideline is designed to supplement all the usual guidelines for regular pregnancy care for all women.
2. Social determinants of disease are important contributors to the excess burden of type 2 diabetes in Aboriginal and Torres Strait Islander, Maori and Pasifika women. The relationship between social determinants of disease and disease management is critically important. The complexity of these important issues is beyond the scope of this document and cannot be given due consideration in this already lengthy clinical guideline. The reader is encouraged to consider the important issues of cultural competence and trauma informed care for vulnerable women.
3. The unique needs of Indian, Asian and Middle Eastern women, refugees and other vulnerable and disadvantaged women with type 2 diabetes are also beyond the scope of this clinical guideline. However, the reader is encouraged to carefully consider the relationship between disadvantage, major life events, adverse childhood experiences and the management of chronic illness. High-quality therapeutic relationships, compassion and respect are fundamental.
4. Women-centred care, culturally safe care and other geographical nuances have not been outlined. ADIPS recommends that all local guidelines provide women-centred, family-centred and culturally safe care for all women, including women with pre-existing diabetes.
5. The relationship of clinical care for women with pre-existing diabetes and local healthcare systems: The writing group acknowledges that in different systems, there are different care providers, processes and funding models. Therefore, the writing group recommends that this guideline be translated into local care policies and care pathways, considering all relevant local and cultural factors.
6. Neonatal care: Neonates born to women with pre-existing diabetes are at increased risk of a range of health outcomes and require specialised care. This guideline focuses on the care of the mother, and the reader is encouraged to read specific neonatal guidelines and seek specialist neonatology advice to guide care of these infants.

INTRODUCTION

Pre-existing diabetes includes type 1 diabetes, type 2 diabetes and rarer forms of diabetes such as monogenic diabetes and cystic fibrosis-related diabetes. This guideline outlines the management of women with pre-existing diabetes in relation to pregnancy. Women with prediabetes (impaired fasting glucose and/or impaired glucose tolerance) should be managed as if they have gestational diabetes from conception and do not need to undergo a pregnancy oral glucose tolerance test (OGTT).[1,2] The management of gestational diabetes is not included in this guideline.

The overall prevalence of pre-existing diabetes in Australia has been reported as 0.6% of pregnancies. The Australian Institute of Health and Welfare (2010) reported a ten-fold higher rate of

pre-existing type 2 diabetes among Aboriginal than non-Indigenous Australian women.[3] In New Zealand, 2018 Ministry of Health statistics report that 1.12% of pregnancies were complicated by pre-existing diabetes, 0.36% type 1 diabetes, 0.75% type 2 diabetes and the remainder 'other specified type'. The prevalence of pre-existing diabetes in Australasia, particularly type 2 diabetes in pregnancy,[4,5] has been increasing, likely due to the increasing prevalence of obesity in women of childbearing age, earlier onset of type 2 diabetes, increasing maternal age and an increasing proportion of women from ethnic groups at high risk of type 2 diabetes. Women with type 1 diabetes are less likely to become pregnant than the general population with a lower standard fertility ratio (SFR) of 0.80 (95% CI 0.77–0.82).[6] The SFR is particularly low among women with retinopathy, nephropathy, neuropathy or cardiovascular complications (0.63, 0.54, 0.50, and 0.34, respectively).[6]

Adverse pregnancy outcomes correlate with glycaemia in women with pre-existing diabetes.[7] Across New South Wales, adverse pregnancy outcomes were substantially more common among those with pre-existing diabetes, including greater likelihood of neonatal hypoglycaemia (56.8-fold), maternal intensive care unit admission (9.1-fold), neonatal intensive care unit admission (5.5-fold), major infant morbidity or mortality (5.0-fold), caesarean before labour (4.8-fold) and large for gestational age (>90th centile, 4.9-fold).[4] Most women have neither achieved optimal glycaemia by conception, nor commenced folic acid therapy by the time of conception.[8] Adverse pregnancy outcomes and rates of suboptimal pregnancy planning are similarly high in New Zealand.[9] Barriers to achieving glycaemic targets and optimal pregnancy outcomes include:[10]

1. lack of pregnancy planning
2. lack of awareness, particularly among women with type 2 diabetes, of the potential risks associated with diabetes in pregnancy
3. failure to achieve optimal glycaemia prior to conception, in part due to a lack of regular contact with health professionals
4. difficulties in achieving and maintaining optimal glycaemia in pregnancy
5. variable attendance at antenatal appointments, in part due to the length of time required to see all members of the multidisciplinary team.

Ideally, women with pre-existing diabetes would have comparable pregnancy outcomes to women without diabetes.

TYPE 1 DIABETES AND TYPE 2 DIABETES: KEY PRACTICE POINTS (CHECKLIST)

Preconception

☐ Provide advice and education:
- o healthy eating / glycaemic index / carbohydrate content (refer: APD)
- o individualised weight management recommendation and healthy pre-pregnancy weight
- o folic acid 2.5–5 mg daily in total, taking multivitamin supplementation into account, commenced ideally 3 months prior to conception and continued until 12 weeks gestation
- o physical activity
- o self-monitoring of blood glucose (SMBG) frequency and targets (refer: CDE)
- o HbA1c target ≤6.5% (48 mmol/mol) without causing hypoglycaemia
- o continuous glucose monitoring (CGM) use and targets
  - ■ range: 3.5–7.8 mmol/L
  - ■ time in range: >70% (ie >16.8 h/day)
  - ■ time below range: <4% (1 h/day) at <3.5 mmol/L and <1% (15 min/day) at <3.0 mmol/L
  - ■ glycaemic variability (%CV): aim ≤36%
- o sick day management / ketone testing
- o hypoglycaemia management
- o driving advice
- o contraception until glycaemia optimised
- o advise improved maternal and neonatal outcomes with optimal glycaemia
- o routine preconception care, as applies to all women planning a pregnancy
- o routine vaccination advice

☐ Review medications:
- o review insulin doses and use of non-insulin glucose-lowering agents
- o record preconception insulin requirements
- o review and cease or replace medications not advised during pregnancy

☐ Screen for comorbidities and complications and manage / refer as appropriate:
- o blood pressure (BP)
- o coronary artery disease (CAD)
- o retinal disease
- o kidney disease
- o autonomic neuropathy
- o diabetic foot disease
- o thyroid disease
- o coeliac disease
- o mental health
- o dental health

☐ Arrange baseline investigations:
- o HbA1c (repeat every 2–3 months)
- o lipids
- o thyroid-stimulating hormone (TSH) and thyroid peroxidase (TPO) autoantibodies (for type 1 diabetes)
- o coeliac autoantibodies (for type 1 diabetes)

- o B12 (for type 1 diabetes, metformin use, vegetarian or vegan diet, bowel disorders, bariatric surgery, megaloblastic anaemia) and red blood cell folate
- o serum creatinine and estimated glomerular filtration rate (eGFR)
- o spot urine albumin : creatinine ratio (ACR)
- o routine pre-pregnancy investigations, as for all women planning a pregnancy

☐ Refer to appropriate specialist(s) / centre.

During pregnancy

☐ Complete preconception checklist if not yet performed
☐ Provide all usual antenatal care, as for all pregnant women
☐ Provide advice and education:
- o healthy eating in pregnancy (refer: APD)
- o physical activity and reduction in sedentary time in pregnancy
- o individualised weight gain recommendation
- o advise improved maternal and neonatal outcomes with optimal glycaemia
- o SMBG frequency and targets (refer: CDE)
- o CGM use and targets
- o HbA1c target
- o sick day management / ketone testing
- o hypoglycaemia management
- o driving
- o breastfeeding / consider referral to lactation consultant from 32 weeks gestation
- o neonatal considerations

☐ Assessment**:**
- o glycaemic monitoring:
  - ▪ review SMBG and/or CGM at each visit (every 1–2 weeks if on insulin)
  - ▪ HbA1c at least once each trimester
- o obstetric monitoring:
  - ▪ monitoring of maternal weight gain
  - ▪ regular assessment for fetal growth and well-being
  - ▪ serial fetal growth scans every 2–4 weeks from 28 weeks gestation
  - ▪ weekly cardiotocography (CTG) from 34 weeks gestation
- o medications:
  - ▪ if not done preconception, review medications not suitable for pregnancy
  - ▪ reassess insulin doses every 1–2 weeks or as required to achieve optimal glycaemia
- o pre-eclampsia prevention:
  - ▪ commence aspirin 100–150 mg daily with evening meal (unless contraindicated) from 12 weeks gestation and cease at 36 weeks gestation
  - ▪ commence calcium supplementation (total 1.5 g daily including dietary calcium) from 12 weeks gestation
  - ▪ check BP and urinalysis at each visit
- o screen for complications and manage / refer as appropriate:
  - ▪ retinal screening: first trimester (unless performed within 3 months prior to conception) and consider repeating in third trimester if no evidence of diabetic retinopathy on initial screen, or earlier if baseline retinopathy is detected as directed by ophthalmologist. Diabetic retinopathy requires specialist care.
  - ▪ renal screening: serum creatinine, and spot urine ACR or protein : creatinine ratio (PCR) each trimester. Increase to monthly monitoring if elevated creatinine or macroalbuminuria and arrange specialist review.

Postpartum

☐ Birth plan:
- o multidisciplinary planning should occur regarding timing and mode of birth
- o provide diabetes management plan for birth
- o arrange neonatal assessment and management
- o discuss effect of breastfeeding on blood glucose levels / insulin doses
- o discuss postpartum contraception plan.

☐ Encourage breastfeeding for maernal and infant benefits
☐ Review diabetes management (insulin / non-insulin glucose-lowering agents / healthy eating) in view of mode of infant feeding
☐ Provide advice and education:
- o advise SMBG frequency and targets or CGM targets (breastfeeding effect)
- o promote a healthy lifestyle
- o provide individualised weight target recommendation

☐ Discuss contraception plan / pregnancy planning prior to discharge from hospital
☐ Arrange regular contact with usual diabetes care providers
☐ Arrange diabetes follow-up (glycaemia, BP, lipids) at least biannually.

TYPE 1 DIABETES AND TYPE 2 DIABETES: PRECONCEPTION MANAGEMENT

Preconception care, including contraception advice, ideally should be provided to all women of reproductive age.[11] General preconception advice, including smoking cessation, alcohol intake and vaccinations, has been developed by The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).[12] For women with type 1 and type 2 diabetes, specific diabetes-related information should be discussed annually so that women are aware of the significance of diabetes in pregnancy.[13] Preconception care should empower women with diabetes to have a positive experience in pregnancy and reduce the risk of adverse outcomes for mother and baby.[14,15]

Preconception counselling

Contraception/family planning

Information and counselling should be provided to all women of reproductive age so they are aware of the risks associated with diabetes in pregnancy and the inherent risks of an unplanned pregnancy.[16–18] Adequate contraception should be discussed at each annual review. Women should be advised to continue using reliable contraception until stable and acceptable glycaemia is achieved and the woman is ready to become pregnant.[19–21] There are a number of reliable methods of contraception and the choice should be based on the woman's preference and any known risk factors.[14]

Referral to appropriate specialist centre

Prior to conception, women with diabetes should be referred to a multidisciplinary team which is experienced in the care of women with diabetes as this has been shown to improve pregnancy outcomes.[22] This team may consist of an obstetrician, endocrinologist/ diabetes physician, CDE, APD, lead maternity carer (NZ) and other health specialists as required.[23] In rural areas where distance is a barrier to antenatal attendance, the local healthcare team should contact the nearest expert diabetes in pregnancy multidisciplinary team for access to telehealth options.

Influence of pregnancy on glycaemia and diabetes complications

Pregnancy can affect glycaemia and diabetes complications. Pregnant women with diabetes are at increased risk of impaired awareness of hypoglycaemia, more frequent and severe hypoglycaemia particularly in early pregnancy, and diabetic ketoacidosis.[24] Pregnancy is associated with progression of diabetic retinopathy (DR). For women with severe retinopathy, hypertension, suboptimal HbA1c, and/or a rapid improvement in HbA1c, progression of DR can be rapid.[25–28] Pregnant women with normal serum creatinine have a low risk of loss of kidney function during pregnancy,[29] while women with serum creatinine >176 μmol/L and severe hypertension or urine PCR >300 mg/mmol (indicating nephrotic range proteinuria) and/or pre-existing cardiovascular disease (CVD) prior to pregnancy are at risk of permanent kidney damage and progression to dialysis.[30] For women with diabetes and chronic kidney disease, the risk of maternal and fetal complications is associated with the severity of chronic kidney disease and glycaemic levels.[28,31–33]

Influence of diabetes on pregnancy outcomes

Women with type 1 or type 2 diabetes have an increased risk of adverse pregnancy outcomes, including large or small for gestational age, maternal hypertensive complications, preterm birth, caesarean section, birth trauma, neonatal intensive care unit admission, and neonatal hypoglycaemia. Compared to women without diabetes, there is an increased risk of intrauterine fetal death or other major maternal or infant morbidity. Women with preconception diabetes complications are more likely to have a poor pregnancy outcome (odds ratio [OR] 2.6, 95% CI 1.3–4.9) compared with women without diabetes complications. Recurrent hypoglycaemia and severe hypoglycaemia during pregnancy are not obviously associated with poor pregnancy outcomes.[28] However, few studies have investigated the effect of maternal hypoglycaemia during pregnancy. There are risks associated with hypoglycaemia, such as reduced cognition both during and after the hypoglycaemic event, which may disrupt everyday activities such as driving. Recurrent hypoglycaemia increases the risk of impaired awareness of hypoglycaemia and subsequent risk of accidents and physical injury. Fear of hypoglycaemia may make it difficult to achieve and sustain optimal glycaemic levels.[34]

Assisted conception

Prior to any assisted conception attempts, women with diabetes should undergo appropriate preconception counselling and aim to optimise glycaemic levels.[35]

Pregnancy loss

Rates of early (<12 weeks gestation) spontaneous miscarriage are two- to three-fold higher in women with diabetes than in women without diabetes.[36] Pre-existing diabetes is associated with a substantially increased rate of total pregnancy loss, largely driven by hyperglycaemia.[37,38] Optimal glycaemic levels prior to conception reduce the rate of miscarriage and perinatal mortality.[36]

Congenital anomalies

Observational studies demonstrate an increased risk of diabetic embryopathy including congenital heart disease, anencephaly, microcephaly and neural tube defects, that is directly proportional to the HbA1c during the first 10 weeks of pregnancy.[39,40] Although these studies are confounded by other lifestyle behaviours, the quantity and consistency of data are convincing. A meta-analysis demonstrated a significantly lower prevalence of major congenital anomalies in offspring of women who attended specialist pre-pregnancy care (relative risk [RR] 0.36, 95% CI 0.22–0.59).[41] Achieving an HbA1c within range before and during early pregnancy confers the lowest possible risk of diabetes-related congenital anomalies, reducing the risk to the baseline population risk.

Folic acid supplementation

Women with diabetes have an increased risk of having a baby with a neural tube defect.[42] There are many controversies around folic acid supplementation, with clinical practice

extrapolated from studies not undertaken in women with pre-existing diabetes. In order to reduce the risk of a neural tube defect, ADIPS recommends that women with diabetes should be advised to commence folic acid 2.5–5 mg daily (data lacking on optimal dose) ideally three months prior to conception and continue until 12 weeks gestation.[42,43] Not commencing folic acid supplements prior to pregnancy is associated with an increased risk of adverse pregnancy outcomes (OR 2.2, 95% CI 1.3–3.9).[42] The evidence for continuing high-dose folic acid (5 mg daily) after 12 weeks gestation is concerning with some evidence of negative impact on child cognitive development at the age of 4–5 years.[44] Total daily doses of folic acid >5 mg are not recommended given the potential for harm.[44] Therefore, the total daily dose of folic acid should not exceed 5 mg, taking into account folic acid contained in other pregnancy supplements a woman may be taking.

Vitamin B12 status

Vitamin B12 status, along with red blood cell folate, should be assessed in women with type 1 diabetes given the association with pernicious anaemia,[45] and women with type 2 diabetes who have been taking metformin given the risk of B12 deficiency associated with its use.[46] Vitamin B12 and red blood cell folate should also be checked in those with a vegetarian or vegan diet, inflammatory bowel disorder, prior bariatric surgery, and megaloblastic anaemia.

Dental review

Pregnancy itself does not have a negative effect on oral health but may increase the risk of periodontal disease.[11] A multicentre randomised controlled trial (RCT) reported a prevalence of periodontal disease of 50% during pregnancy.[47] Some evidence suggests that periodontal disease is even more common in women with diabetes and obesity.[47] While treating periodontal disease is important for dental health, treating periodontal disease during pregnancy does not appear to improve obstetric or neonatal outcomes.[48–50] Women planning a pregnancy should consider a dental review prior to pregnancy. Dental and oral health treatment can also take place safely in pregnancy.[11]

Mental health review

The relationship between pre-existing diabetes and mental health disorders remains unclear.[51] However, given that both conditions are common in young women of reproductive age, screening for mental health disorders should be part of preconception care so that women do not enter pregnancy with an unrecognised mental health condition. Health professionals should be aware of the additional impact on mental and emotional health of planning for pregnancy and the intensive diabetes management required during pregnancy, and should support emotional well-being.[51,52] A targeted mental health review may be needed in high-risk women such as those who have previously had a mental health illness, post-bariatric surgery or if there are significant psychosocial stressors.

Preconception glycaemic monitoring

Self-monitoring of blood glucose

Women planning pregnancy should be provided with the knowledge and skills to achieve optimal glycaemia. SMBG is a key component of management prior to pregnancy.[19,28] Given that most women with diabetes require intensification of diabetes therapy in order to achieve optimal preconception glycaemic targets, women should be advised to increase the frequency of SMBG prior to pregnancy.[19] A combination of fasting, pre-meal, post-meal, prior to driving and overnight SMBG enables a more accurate assessment of glycaemia and medication requirements. Individualised targets for SMBG should be developed. For women with pre-existing diabetes who are planning pregnancy, ADIPS recommends a fasting and pre-meal SMBG target of <6.0 mmol/L and a post-meal SMBG target of <8.5 mmol/L (1-h post-meal) or <7.5 mmol/L (2-h post-meal), provided that these levels can be achieved without causing significant hypoglycaemia.

Hypoglycaemia management and sick day education should be provided prior to pregnancy, to prepare for potential intercurrent illness and/or nausea and vomiting in pregnancy. For women with type 1 diabetes who develop diabetes ketoacidosis (DKA) during pregnancy, the risk of fetal demise is higher than the baseline risk (2–3%).[53] All women with type 1 diabetes should be offered a meter with the capability for blood ketone testing. Women should be advised to check blood ketones if blood glucose levels are ≥15.0 mmol/L or if they are unwell.[28] Ketones of 0.6–1.5 mmol/L require a retest; >1.5 mmol/L requires contact with a healthcare provider.

Some blood glucose meters may not adequately address changes (eg haematocrit) in pregnancy, so meter technical specifications should be reviewed before use.[54]

Preconception HbA1c target

In order to establish the best possible glycaemia in early pregnancy, striving to achieve the HbA1c target preconception is vital and may take many months, during which time contraception is advised. For women who are actively trying to conceive, regular HbA1c every 2–3 months may improve glycaemia but may also induce maternal stress. Any reduction in HbA1c toward a target HbA1c of ≤6.5% (48 mmol/mol) will reduce the risk of congenital abnormality.[39] HbA1c targets need to be individualised, but should be as close to ≤6.5% (48 mmol/mol) as is safely possible for an individual, without significant weight gain or hypoglycaemia. HbA1c targets are generally more achievable in women with type 2 diabetes than in women

with type 1 diabetes. Women should be strongly advised against pregnancy or assisted conception if the HbA1c is >9.0% (75 mmol/mol). The congenital anomaly risk exponentially increases with increasing periconceptional HbA1c above this level.[39]

Continuous glucose monitoring

CGM in women with type 1 diabetes provides a detailed view of glucose levels over 24 h, which better demonstrates the variability of glucose levels compared with SMBG. CGM measures interstitial glucose, so there is a small time lag (~10 min) between the blood glucose and interstitial glucose. Currently, most CGM requires calibration with SMBG. CGM can be linked to a mobile phone, reading device or continuous subcutaneous insulin infusion pump (CSII, insulin pump). CGM linked to insulin pumps with a low-glucose suspend function is able to suspend insulin administration when a hypoglycaemic event is predicted.

Prior to pregnancy, a trial of CGM is useful for confirming glycaemic excursions and trends, particularly overnight, when more data are obtained compared with SMBG.

During pregnancy, CGM can predict and detect asymptomatic hypoglycaemia and post-prandial peaks which may not be detected by SMBG.[55–58] The correlation between CGM and reference values during pregnancy is acceptable, except when glycaemia changes rapidly.[55,59] CGM is particularly useful for pregnant women with unstable blood glucose levels, suspected/undetected hypoglycaemia, previous severe hypoglycaemia, fear of hypoglycaemia and impaired awareness of hypoglycaemia.

The Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial (CONCEPTT) used CGM as an adjunct to SMBG among pregnant women with type 1 diabetes and reported increased duration in target blood glucose range as well as improved neonatal outcomes including reduced rates of large for gestational age infants (OR 0.51, 95% CI 0.28–0.90), neonatal intensive care admissions lasting ≥24 h (OR 0.48, 95% CI 0.26–0.86) and neonatal hypoglycaemia (OR 0.45, 95% CI 0.22–0.89).[60] There is currently insufficient evidence to support the use of CGM in pregnant women with type 2 diabetes.

For women with type 1 diabetes, the CGM targets prior to pregnancy include:

- range: 3.5–7.8 mmol/L
- time in range: >70% (i.e. >16.8 h per day)
- time below range: <4% (1 h per day) at <3.5 mmol/L and <1% (15 min per day) at <3.0 mmol/L
- glycaemic variability (%CV): aim ≤36%.[61]

Access

In Australia, the federal government provides access to fully subsidised CGM through the National Diabetes Services Scheme (NDSS) for women with type 1 diabetes who are actively planning pregnancy, pregnant or immediately post-pregnancy. To be eligible for access, women with type 1 diabetes need to be assessed by an authorised health professional and meet certain criteria. More information about the CGM initiative and specific eligibility criteria are available at https://www.ndss.com.au/type-1-diabetes-pregnancy. CGM is not currently subsidised in New Zealand (as at 1 August 2020).

Flash glucose monitoring

Flash glucose monitoring measures the interstitial glucose via a one second scan ('flash') by the reader over a sensor that is worn on the upper arm. A single scan downloads the current glucose level and up to eight hours of previous glucose data. Flash glucose monitors are factory calibrated. However, the sensor needs to be scanned by the reader at least once every eight hours to download and store the previous eight hours of data. Confirmatory SMBG is required during times of rapidly changing glucose levels, apparent hypoglycaemia, if impending hypoglycaemia is reported or if the symptoms do not match the flash glucose monitor data. Confirmatory SMBG is also recommended prior to adjusting the insulin regimen. A small study showed good sensor accuracy for pregnant women with diabetes.[62]

Access

In Australia, flash glucose monitoring is also fully subsidised by the NDSS (from 1 March 2020) for eligible women. Find out more at https://www.ndss.com.au/cgm. In New Zealand, flash glucose monitoring is not currently subsidised by PHARMAC (as at 1 August 2020).

Review of medication

Review of medication with the woman planning pregnancy requires careful discussion around the risks and benefits of each medication in the preconception phase and at different time points of pregnancy. The potential adverse effects of a medication in pregnancy depend on the placental transfer of the medication and the stage of fetal development. Both Australia and New Zealand use the same categorisation system for prescribing medicines in pregnancy, which considers known risks in human or animal studies. The Therapeutic Goods Administration (TGA) database, available at https://www.tga.gov.au/prescribing-medicines-pregnancy-database, should be searched before prescribing any medication in pregnancy. Note that categories A to X are not linear in terms of risk but describe steps of knowledge ranging from extensive human data, through limited human but significant animal data, to limited/no data.[63] The Food and Drug Administration in the USA has moved away from a letter category system to a narrative risk summary. Additional pregnancy and lactation medication resources include Briggs *et al.*[64] and the Drugs and Lactation Database (Lactmed).[65] If you are not familiar with prescribing in pregnancy, seek specialist advice.

TABLE 1 Australasian Diabetes in Pregnancy Society recommendations for preconception medication review

- Preconception counselling includes discussion of maternal medications and review of pregnancy effects. Medications with known risks should be ceased prior to or as soon as pregnancy is detected, or substituted with pregnancy appropriate medications.
- The decision to continue insulin analogues that have little available safety data in pregnancy, and metformin, should be individualised, but neither medication should be ceased abruptly in early pregnancy due to the imperative to maintain euglycaemia. Cessation should depend on the risks and benefits of continuation. While metformin crosses the placenta, there has not been any evidence that it is teratogenic.
- Other non-insulin glucose-lowering agents should be ceased prior to or as soon as pregnancy is detected.
- RAS blockade should be ceased prior to a planned conception or as soon as pregnancy is detected and replaced with alternate blood pressure lowering agents. For women with diabetic kidney disease, the risks and benefits of RAS blockade cessation at various time points should be discussed. At the latest, RAS blockade should be ceased as soon as pregnancy is detected.
- Statins and other lipid-lowering therapy should be ceased prior to or as soon as pregnancy is detected.

When counselling, it is important to not only consider the pregnancy category of the medication, but also the specifics of the available data regarding its use in pregnancy, the pregnancy stage and the degree of potential maternal and/or fetal benefit or risk of the medication and/or from ceasing the medication. ADIPS strongly encourages reporting of pregnancy outcomes for medications used in pregnancy, particularly for newer drugs. ADIPS recommendations for preconception medication review are summarised in Table 1.

Insulin

Insulin is the first-line therapy for pharmacological management of hyperglycaemia in pregnant women with pre-existing diabetes. High-level evidence regarding the relative benefits of various insulin preparations and modes of insulin delivery is sparse. A 2017 Cochrane review could not draw any conclusions regarding the use of different insulin types or regimens in women with pre-existing diabetes.[66] A recent review summarised the evidence for the insulin analogues.[67]

Of the available rapid-acting insulin analogues, insulin aspart and insulin lispro appear safe for use in pregnancy,[68] although RCT data exist only for insulin aspart.[69] Insulin lispro does not cross the placenta except at high levels (single insulin lispro dose of >50 units).[70] Insulin aspart is not thought to cross the placenta at therapeutic concentrations.[71] There are no well-controlled clinical trials of insulin glulisine in pregnancy, and its use in pregnancy is not currently recommended.

The use of insulin detemir is supported by RCT data[72] and it does not cross the placenta.[73]

Insulin glargine has not been associated with increased fetal risk on the basis of observational studies and surveillance data;[74] however, it remains pregnancy category B3 due to the limited number of studies. Laboratory data show that insulin glargine does not cross the placenta to a significant degree at concentrations similar to clinical dosing, but does have low transfer at significantly supratherapeutic doses.[75] Toujeo Glargine U300 has not been tested in pregnancy and is, therefore, not recommended for use in pregnancy.

Insulin degludec has only two case reports of women with type 1 diabetes who conceived on insulin degludec, with no apparent issues.[67] Degludec is the subject of a current RCT (NCT03377699). It is not currently recommended for use in pregnancy.

The safety of insulin analogues in pregnancy and lactation is summarised in Table 2.

Neutral protamine Hagedorn (NPH, Isophane) insulin is exempted from TGA pregnancy classification, but has been used in pregnancy as the gold standard intermediate-acting preparation for many years.[76]

TABLE 2 Safety of insulin analogues in pregnancy and lactation

Insulin analogue	Pregnancy category	Does it cross the placenta?	Is it secreted in breastmilk?
Lispro	A*	Yes, at single doses> 50 units	Unknown
Aspart	A*	Unlikely at therapeutic concentrations	Unknown
Glulisine	B3†	Unknown	Unknown
Detemir	A*	Unlikely at therapeutic concentrations	Unknown
Glargine	B3†	Unlikely at therapeutic concentrations	Unknown
Degludec	B3†	Unknown	Unknown

*Category A – 'Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed'.[313]

†Category B3 – 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans'.[313]

Non-insulin glucose-lowering agents

The data for the use of metformin and sulfonylureas in pregnancy are primarily derived from the setting of gestational diabetes, which is often diagnosed later in pregnancy, after the first trimester. The generalisability of these data to women with type 2 diabetes, who usually require glucose-lowering agents throughout pregnancy, is unclear. Contributing to the data for early pregnancy use of metformin are studies of metformin in women with polycystic ovary syndrome who require fertility assistance and studies of metformin in women with obesity aiming to prevent gestational diabetes (unsuccessfully).[77–80]

Metformin

Metformin crosses the placenta but studies of its use in early pregnancy show no evidence of teratogenicity.[81] Data based on the use of metformin in polycystic ovary syndrome and gestational diabetes are relatively reassuring regarding safety in pregnancy and offspring development into early childhood.[82–85] There are recent data suggesting small increases in childhood weight and body mass index (BMI) in those exposed to metformin.[86,87] A meta-analysis suggested larger numbers are needed to explore this further.[88]

Metformin should be avoided in the setting of intrauterine growth restriction, pre-eclampsia, and inadequate weight gain in low BMI women.

An open-label study of metformin in pregnant women with type 2 diabetes showed 89% of women needed additional insulin therapy.[89] The MiTy study of metformin in women with type 2 diabetes from early pregnancy has recently been completed, with results pending (NCT01353391).[90]

Metformin, when taken in pregnancy, should not be stopped abruptly due to the known risks conferred by raised glycaemic levels. Cessation should be discussed and depends on the risks and benefits of continuation. Women should be advised that metformin crosses the placenta and that the long-term effects of *in utero* exposure to metformin on the offspring as they grow to adulthood are not known.

Lactation Metformin levels in breastmilk are low, with infants receiving <0.5% of mothers' weight-adjusted dose.[91] An observational study compared 61 nursing infants to 50 formula-fed infants whose mothers were taking 2.55 g metformin/day through pregnancy and lactation for polycystic ovary syndrome and reported no differences in weight or motor-social development at six months of age.[92] Metformin is considered compatible with breastfeeding, but the long-term effects are not known.

Sulfonylureas

These are not recommended for use in Australia and New Zealand. Glibenclamide is used internationally in gestational diabetes. However, the American Diabetes Association recommends insulin as first-line glucose-lowering therapy.[93]

In 2015, a study of cord blood levels of glibenclamide in 19 infants showed variable transplacental transfer, with most infants having cord blood levels <10 ng/mL, but 37% having levels higher than corresponding maternal levels.[94] In recent cohort studies of women with gestational diabetes, glibenclamide use was associated with increased risks of neonatal intensive care unit admissions, respiratory distress and macrosomia.[95,96] Furthermore, a systematic review and meta-analysis of RCTs of pharmacotherapy in gestational diabetes showed that, compared with insulin, glibenclamide was associated with increased birth weight, macrosomia and neonatal hypoglycaemia.[97] There are no studies investigating the use of sulfonylureas throughout pregnancy in women with type 2 diabetes.

Lactation Glibenclamide and glipizide have not been detected in breastmilk in dosing studies in a small number of women.[91,98]

Alternative glucose-lowering agents

Alternative glucose-lowering agents, including SGLT2 inhibitors, DPP4 inhibitors, acarbose and GLP-1 receptor agonists are not recommended for antenatal use in Australia and New Zealand. Minimal data in pregnancy and lactation are available, with only a few case reports available.

Antihypertensive agents

A detailed guideline for the use of antihypertensive agents in relation to pregnancy was developed by the Society for Obstetric Medicine of Australia and New Zealand (SOMANZ) in 2014 and endorsed by ADIPS.[99] This guideline is available at https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf.

Commonly used antihypertensive agents in pregnancy include methyldopa, labetalol and nifedipine. Alternative antihypertensive agents, including hydralazine, oxprenolol, prazosin, and clonidine, are used as third or fourth line.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in the second and third trimester. Use in that later period of pregnancy is associated with fetal anuria, oligohydramnios, renal tubule dysplasia and hypocalvaria. The teratogenicity of renin-angiotensin system (RAS) blockade-agents during the first trimester is less certain. Recent retrospective cohort studies reported an increased risk of fetal defects in women on RAS blockade compared to the normotensive population (RR 3.7, 95% CI 1.8–7.3[100] and OR 1.5, 95% CI 1.1–2.6[101]) but no difference in rates compared to other hypertensive women (RR 0.8, 95% CI 0.7–1.1[102] and OR 1.1, 95% CI 0.6–1.9[101]).

A subject of ongoing consideration is the known benefit of RAS blockade for renal disease in the setting of diabetes, the potential for women to have RAS blockade ceased months or longer prior to conception and the risk that this cessation may pose to their long-term renal outcomes.[103–107] The National Institute for Health and Care Excellence (NICE) guideline states that 'Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists should be discontinued before conception or as soon as pregnancy is

confirmed. Alternative antihypertensive agents suitable for use during pregnancy should be substituted'.[28] In practice, an individualised discussion should be held with each woman regarding her own renal condition and the risks and benefits of antihypertensive agent cessation at various time points. At the latest, RAS blockade should be ceased as soon as pregnancy is detected.

Lactation

Labetalol, oxprenolol, nifedipine and the ACE inhibitors enalapril and captopril are not contraindicated with breastfeeding.[108] Clonidine accumulates in neonatal serum, so is not routinely used during lactation.[91,99] Methyldopa may exacerbate postnatal depression, so should be used with caution postpartum.[109]

Lipid-lowering agents

Statins

Historically, statins have been considered teratogenic and contraindicated in pregnancy.

The most recent systematic review concluded that there is no strong evidence that statin use in the first trimester is teratogenic, after accounting for potential confounding factors such as diabetes.[110] This systematic review included a number of small case-control or cohort studies. The primary large study driving the findings was a cohort study from Medicaid data in the USA including 886 996 pregnancies with 1152 having first-trimester statin exposure.[111] This registry study reported that while the RR for congenital malformation use was 1.79 (95% CI 1.43–2.23), when adjusted for confounders, particularly diabetes, there was no increase in risk (RR 1.07, 95% CI 0.85–1.37).[111] Other recent large retrospective cohort studies have reported an increased pregnancy loss rate with statin exposure in the first trimester (hazard ratio 1.64, 95% CI 1.10–2.46)[112] and an increased rate of fetal ventricular septal defect (OR 3.3, 95% CI 1.8–6.0).[113]

If not ceased prior to conception, statins should be ceased when pregnancy is detected. In general, statin use in pregnancy should be avoided unless the potential benefits outweigh the risks, for example, in women with ischaemic heart disease.

Lactation Levels of rosuvastatin (~23 ng/mL) and pravastatin (1.4% of maternal weight-adjusted dose) are low in breastmilk.[91] These drugs are generally avoided during breastfeeding.

Fibrates

There are only case reports of the use of fibrates in pregnancy, which are in the setting of severe lipid disorders and pancreatitis.[114–116] Reproduction studies in rodents and rabbits show embryocidal and teratogenic effects.[64] Fibrates are not recommended for routine use in pregnancy. However, fibrates could be considered in the setting of severe hyperlipidaemia disorders and prevention of pancreatitis.

Lactation No information available.[91]

Alternative lipid-lowering agents

Bile acid sequestrants, such as cholestyramine (pregnancy category B2), are not systemically absorbed from the gastrointestinal tract, so their use is thought to be relatively acceptable in pregnancy and lactation.[117] However, their use may be limited by side effects including constipation and elevated triglycerides. Other non-statin lipid-lowering agents, including nicotinic acid and ezetimibe are associated with teratogenicity, so are not recommended for antenatal use in Australia and New Zealand. PCSK9 inhibitors have not been tested in pregnancy, so are contraindicated for antenatal use.

Preconception screening for diabetes complications and other autoimmune diseases

Adequate contraception should be prescribed until optimal glycaemia is achieved and diabetes complications assessments are complete. If a recent preconception complications assessment has not been undertaken, it should be performed as early as possible in pregnancy.

Retinal screening

Women with pre-existing diabetes should be referred for a retinal assessment preconception.[28,118]

Women with pre-existing diabetes should be informed of the risks of developing new-onset and/or progression of DR in pregnancy. DR is a leading cause of blindness in women of reproductive age.[119] The prevalence of DR in early pregnancy is 34–72% in women with type 1 diabetes[119–124] and 14–28% in women with type 2 diabetes.[125] New-onset DR in pregnancy occurs in 15% of women with pre-existing diabetes, with 0.5% of these women progressing to proliferative DR.[119] In women with baseline non-proliferative DR, 30% progress with 10% progressing to proliferative DR.[119] The mean known duration of diabetes in women with progressive DR in pregnancy is more than 10–15 years for type 1 diabetes and less than 10 years for type 2 diabetes.[119] Maculopathy can also progress during pregnancy.[126]

New-onset and/or progression of DR in pregnancy may be exacerbated by a rapid tightening of glycaemic levels,[123,126] as well as related to pregnancy-specific factors, such as an increase in angiogenic growth factors,[127] an increase in blood volume and fluid retention.[128] The potential benefits of optimal antenatal glycaemic levels are thought to outweigh the risks of new-onset and/or progression of DR. Other factors that increase the risk of DR progression in pregnancy include long duration of diabetes, raised glycaemic levels, baseline DR, smoking and hypertension.[120]

The increased DR risk persists for 6-12 months postpartum, although in many cases DR will regress. A history of spontaneous preterm birth[129] and pre-eclampsia[130,131] appear to be risk factors for the future development of DR. However, these obstetric outcomes are confounded by associated suboptimal

glycaemic levels. The long-term risk of DR in women with type 1 diabetes does not appear to differ between parous and nulliparous women.[132–134] Similarly, mode of birth does not appear to influence long-term DR progression in women with type 1 diabetes.[135]

Modifiable risk factors (glycaemia, hypertension) should be treated preconception.[119]

Referral

Women with moderate to severe non-proliferative DR, proliferative DR or diabetic macular oedema should be referred to an ophthalmologist for treatment prior to pregnancy.[28,118,119,122] Ideally, any required retinal laser photocoagulation should be completed prior to commencing rapid tightening of glycaemic levels.[119] However, if required, laser and intra-ocular steroids are safe.[125] Anti-vascular endothelial growth factor agents are relatively contraindicated and should only be used when sight is threatened and other treatment modalities have failed.[125]

Renal screening

Women with pre-existing diabetes should be screened for chronic kidney disease (CKD) preconception. Serum creatinine, eGFR and urine ACR should be assessed. According to Kidney Health Australia, CKD is defined as either eGFR < 60 mL/min/1.73m^2 for ≥3 months or evidence of kidney damage for ≥3 months, which includes any of the following: albuminuria; haematuria after exclusion of urological causes; structural abnormalities (eg on kidney imaging tests); or pathological abnormalities (eg renal biopsy).[136]

Outside pregnancy, eGFR is considered a more sensitive marker for CKD than serum creatinine. A persistently reduced eGFR <60 mL/min/1.73m^2, measured at least three times over a period of at least three months, is indicative of CKD in the absence of confounders, such as very low or very high protein diets and extremes of body size.[137,138]

Urine ACR has a greater sensitivity than urine PCR for detecting low levels of proteinuria, preferably measured on a first morning void to minimise the postural effect on albumin excretion. A positive urine ACR should be repeated on a first morning void sample to confirm clinically important, persistent albuminuria.[137,138] Two elevated urine ACRs over a period of at least three months, is indicative of CKD in the absence of confounders, such as intercurrent illness, recent exercise and acute fluid loads.

Albuminuria in women is defined as:

- microalbuminuria = urine ACR 3.5–35 mg/mmol
- macroalbuminuria = urine ACR > 35 mg/mmol

Albuminuria alone, with eGFR >60 mL/min/1.73m^2, is concerning and warrants preconception review with a specialist physician with experience in renal disease in pregnancy.[136]

Women with CKD, and their partners, should be informed of potential associated adverse pregnancy outcomes. These adverse outcomes include fetal growth restriction, pre-eclampsia, preterm birth, emergency caesarean section and perinatal mortality.[139–141] The risk of these adverse outcomes is highest for women with albuminuria and a reduced eGFR, who also face the risk of an irreversible decline in renal function during pregnancy. Pregnancy does not appear to permanently worsen renal function in women with CKD and a normal serum creatinine/ eGFR, as long as BP is well-controlled.[134,140–146]

Hypertension should be treated preconception. In non-pregnant women with diabetes and CKD (confirmed proteinuria, reduced eGFR or elevated serum creatinine), aim for a systolic BP target of 120–129 mmHg and a diastolic BP target <80 mmHg.[138,147,148]

Low-dose aspirin (100–150 mg daily) and calcium supplementation (total 1.5 g daily including dietary calcium) are indicated for women with CKD who are planning a pregnancy in order to reduce the risk of pre-eclampsia.[99]

Referral

Women with CKD should be offered referral to a specialist renal service, obstetric physician, or obstetric nephrologist and an APD for pre-pregnancy planning. They also require specialist obstetric and/or maternal-fetal medicine advice for preconception counselling. In particular, women with CKD and any of the following should be referred:[136]

- eGFR < 30 mL/min/1.73m^2 (Stage 4 or 5 CKD of any cause)
- persistent macroalbuminuria (urine ACR > 35 mg/mmol)
- a sustained decrease in eGFR of 25% or more, or a sustained decrease in eGFR of 15 mL/min/1.73m^2 within 12 months
- CKD with resistant hypertension despite three antihypertensive agents.

Coronary artery disease screening

Pregnancy is associated with an increase in lipids, blood volume, cardiac output and thrombosis risk. Pregnancy increases the risk of myocardial infarction three-fold,[149,150] with an associated mortality of 5–11%.[149,151] In a study of 50 pregnancies to 43 women with known CAD, 26% were complicated with ischaemic cardiac events (new or progressive angina, acute coronary syndrome/myocardial infarction, ventricular arrhythmia, cardiac arrest).[152] The Cardiac Disease in Pregnancy (CARPREG) II score is a predictive tool to estimate the risk of a primary cardiac event in pregnancy for women with known cardiac disease and could be performed by any member of the multidisciplinary team.[153] The predictive risk for a primary cardiac event ranges from 5% for 0-1 point CARPREG II score to 41% for >4 points. However, the CARPREG II score is not specific for women with CAD and it does not take into

account the severity of the cardiac lesion, previous treatment and other comorbidities. The CARPREG II risk prediction index is available at http://www.onlinejacc.org/content/71/21/2419.

Diabetes increases the risk of CAD, heart failure and stroke in young women. Although CAD in pregnancy is rare, it is a leading cause of maternal death in developed countries.[154–156] CAD is more likely in women with long-standing diabetes, hypertension, hyperlipidaemia, obesity, history of cigarette smoking, strong family history of CAD and increased maternal age (>30 years).[151]

Referral

Women should be screened for symptoms of CAD (exertional fatigue, exertional dyspnoea, nausea, dizziness, sweating, light-headedness, or chest pain) and evaluated preconception. In symptomatic women, or women who are at high risk, further evaluation with an exercise tolerance test, stress echocardiography and/or coronary artery imaging should be considered.[157]

Women with known CAD should be informed of potential associated adverse pregnancy outcomes, have their treatment optimised and offered referral to a cardiologist.

Women should be informed of the potential deleterious health effects associated with stopping potentially teratogenic medications such as statins, ACE inhibitors and angiotensin receptor blockers prior to conception. Stress tests, such as an exercise tolerance test or dobutamine echocardiography, should be considered to identify inducible ischaemia and determine whether pregnancy is likely to be tolerated. Transthoracic echocardiography should be arranged to determine left ventricular ejection fraction (LVEF). Women with an LVEF >40% and a good response to exercise testing will likely tolerate pregnancy, although complications can still occur.[152,153] Women with impaired left ventricular function have a high risk of cardiac events in pregnancy.[153]

Pregnancy may be considered in women with known CAD if there is no evidence of residual ischaemia and LVEF >40%.[158]

Autonomic neuropathy screening

Women with pre-existing diabetes should be screened for autonomic neuropathy and the potential associated adverse pregnancy outcomes should be discussed. Pregnancy does not appear to alter the course of autonomic neuropathy.[132] However, gastroparesis, impaired hypoglycaemia awareness and orthostatic hypotension can be problematic. Severe gastroparesis is considered a relative contraindication to pregnancy.[159]

The symptoms of gastroparesis include nausea and vomiting, early satiety and post-prandial pain or bloating. If symptoms are severe, women should be referred for radiological imaging to evaluate gastric emptying. Successful pregnancies have been reported in women with gastroparesis in whom symptoms were well-controlled preconception.[159] Pregnancy risks of gastroparesis include hyperemesis, difficulty controlling blood glucose levels, an increased risk of DKA and malnutrition. Prior to conception, glycaemic levels should be optimised, the diet should be modified (small frequent meals with a lower fat and fibre content) and pro-kinetic agents such as metoclopramide should be considered for symptom control.[160]

Orthostatic hypotension may worsen in pregnancy due to the additive effects of the fall in systemic vascular resistance and potential dehydration from the nausea and vomiting of pregnancy.

Diabetic foot disease

Women should be screened for diabetic foot disease, including peripheral neuropathy and peripheral vascular disease and, if necessary, women should be referred to a podiatrist or high-risk foot care service.

Screening for other autoimmune diseases

Women with type 1 diabetes should be screened for the presence of other autoimmune conditions, such as thyroid dysfunction (via TSH measurement and TPO autoantibody testing) and coeliac disease (via symptoms of coeliac disease and coeliac autoantibody testing as appropriate).[161]

TYPE 1 DIABETES AND TYPE 2 DIABETES: MANAGEMENT DURING PREGNANCY

General management

Women with type 1 diabetes or type 2 diabetes should be referred to a local, specialised multidisciplinary diabetes and obstetric team as early as possible in the pregnancy. However, this may not always be possible and ADIPS recognises the diverse nature and complexities of clinical practice in regional Australia and New Zealand. ADIPS supports a woman-centred approach.[11] Women should have the opportunity to make informed decisions regarding their care, in partnership with their healthcare professional and lead maternity care providers.

Alternative models of care can be considered, respecting the woman's choice and local logistics. However, it is vital that open communication and documented pathways be established in collaboration with the birthing facility, lead maternity care provider, and local and tertiary diabetes clinicians in order to optimise care.[11] Services such as Telehealth may be available so that local health professionals can be linked with specialist diabetes in pregnancy services. Women with a diabetes complication may be advised to travel to a major centre with a diabetes in pregnancy service for specialised care.

The psychosocial aspects of antenatal care for women with pre-existing diabetes are extremely important. Both diabetes distress and more severe psychological/ psychiatric problems impact greatly on the care of women with diabetes and specific

arrangements should be made for access to appropriate care for these problems. Care providers should have an understanding and supportive attitude.

Dietary advice

Women should be referred to an APD for medical nutrition therapy.[162] Dietary advice should be individualised and culturally appropriate. Dietary education should include healthy eating, the five food groups (fruit, vegetables, grains, meat/alternatives and dairy/alternatives; four in NZ (fruit and vegetable groups are combined)), macro- and micro-nutritional requirements of pregnancy (eg folic acid, iodine), carbohydrate foods and the influence of these foods on blood glucose levels, portion size, label reading, carbohydrate distribution throughout the day, glycaemic index and the importance of including adequate carbohydrate to avoid deleterious effects on the fetus. A food diary should be encouraged in preparation for review appointments.

For women with pre-existing diabetes, medical nutrition therapy typically includes a minimum of 175 g carbohydrate per day.[163,164] The carbohydrate load is generally split as 30–40 g per main meal and 20–25 g per mid-meal snack, with a preference for low glycaemic index foods.[165,166] For women who are underweight, additional serves of the five food groups may be required. For women who are overweight or obese, or gaining weight too quickly, limiting additional serves and avoiding energy-dense foods may limit excessive weight gain. Weight loss diets are not recommended during pregnancy.[11] Specific nutritional requirements need to be considered for women with co-existing conditions such as coeliac disease, cystic fibrosis, gastroparesis and post-bariatric surgery. Women participating in Ramadan fasting will require a practical approach and close consultation with an APD.[167]

Ideally, the minimum schedule of dietary appointments would include an initial appointment and at least two review appointments. Additional dietary reviews are recommended if co-existing conditions are present.

Physical activity

Pregnant women with diabetes are encouraged to remain active. Low- to moderate-intensity physical activity during pregnancy is associated with a range of health benefits and is not associated with adverse outcomes.[11] Physical activity after meals may improve post-prandial blood glucose levels.[168] Nonetheless, there is very little information to guide specific physical activity recommendations in women with pre-existing diabetes in pregnancy.

Prior to commencing an exercise program, an assessment of medical and obstetric risks should be undertaken to identify potential contraindications to exercise.[169] Ideally, women should undertake approximately 30 min of low- to moderate-intensity physical activity on most days of the week.[170] Women who are sedentary, overweight or obese may need to start with a shorter duration of exercise (15–20 min) before slowly building up to 30 min.

The 'talk test' can be used to guide the exercise intensity in pregnancy, that is, a pregnant woman should be able to maintain a conversation while exercising.[171]

Weight gain recommendations

Women should be advised about appropriate weight gain during pregnancy based on their pre-pregnancy BMI. Pre-pregnancy overweight or obesity increases the risk of pregnancy complications, including congenital anomalies, macrosomia, low birth weight, stillbirth, preterm birth, gestational hypertension, pre-eclampsia, thromboses, postpartum haemorrhage and major depressive disorders.[11] Excessive gestational weight gain is an independent risk factor for macrosomia.[172]

The 2009 US Institute of Medicine (IOM) recommendations for weight gain during pregnancy based on pre-pregnancy BMI are presented in Table 3.[173] For women with pre-existing diabetes and pre-pregnancy obesity (BMI ≥ 30 kg/m^2), Danish data suggest safety and improved outcomes with less gestational weight gain (0–5 kg).[174,175]

Women should be weighed at each antenatal visit and, if their weight change is inappropriate, it should be discussed in relation to their diet, level of physical activity and pregnancy comorbidities or complications.

Glycaemic monitoring during pregnancy

Self-monitoring of blood glucose

SMBG is recommended in pregnancy, and typically consists of 6–10 tests per day i.e. fasting, pre-meal, post-meals, prior to driving and, as required, overnight. SMBG levels should be reviewed by the healthcare provider every 1–2 weeks during pregnancy.

Blood glucose targets need to be individualised, particularly taking into account the frequency and severity of previous hypoglycaemia, as well as any impaired awareness of

TABLE 3 2009 Institute of Medicine (IOM) recommendations for weight gain during pregnancy [173]

Pre-pregnancy body mass index (kg/m^2)	Singleton pregnancy total weight gain range (kg)	Rates of weight gain in 2nd and 3rd trimesters (mean [range] in kg/week)[†]
<18.5	12.5–18.0	0.51 [0.44–0.58]
18.5–24.9	11.5–16.0	0.42 [0.35–0.50]
25.0–29.9	7.0–11.5	0.28 [0.23–0.33]
≥30	5.0–9.0	0.22 [0.17–0.27]

[†]Calculations assume 0.5–2 kg weight gain in the 1st trimester and presume a linear weight gain throughout the 2nd and 3rd trimesters, and apply to singleton pregnancies only. Refer to the IOM guideline for multiple births.

TABLE 4 2020 Australasian Diabetes in Pregnancy Society recommendations for self-monitoring of blood glucose targets for pre-existing diabetes

	Preconception†	Pregnancy†
Fasting and pre-meal (mmol/L)	<6.0	4.0–5.3
1-h post-meal (mmol/L)	<8.5	5.5–7.8
2-h post-meal (mmol/L)	<7.5	5.0–6.7

†If these targets can be safely achieved without causing significant hypoglycaemia.

TABLE 5 2020 Australasian Diabetes in Pregnancy Society recommendations for HbA1c targets for pre-existing diabetes

	Preconception and 1st trimester†	2nd and 3rd trimesters†
HbA1c	≤6.5% (48 mmol/mol)	≤6.0% (42 mmol/mol)

†If these targets can be safely achieved without causing significant hypoglycaemia.

hypoglycaemia. ADIPS recognise that at present, glycaemic targets for women with pre-existing diabetes vary between centres in Australia and New Zealand and around the world. There are no RCTs comparing different fasting, pre-meal and post-meal glucose targets. For pregnant women with pre-existing diabetes, ADIPS recommends a fasting and pre-meal SMBG target of 4.0–5.3 mmol/L and a post-meal SMBG target of 5.5–7.8 mmol/L (1-h post-meal) or 5.0–6.7 mmol/L (2-h post-meal), provided that these levels can be achieved without causing significant hypoglycaemia (Table 4). These targets are consistent with current recommendations by the American Diabetes Association[93] and Diabetes Canada.[176]

If these SMBG targets cannot be achieved without causing significant hypoglycaemia, ADIPS recommends the use of less stringent targets, based on individualised clinical assessment.

HbA1c targets in pregnancy

HbA1c is a useful adjunct for assessing glycaemia and should be performed at least once each trimester. In early pregnancy, the HbA1c target for women with pre-existing diabetes is ≤6.5% (48 mmol/mol; Table 5), which is the same as the preconception target. HbA1c is slightly lower in pregnancy compared with outside pregnancy due to increased red blood cell turnover. Therefore, as the pregnancy progresses, a lower HbA1c ≤6.0% (42 mmol/mol) can be targeted if this can be achieved without causing significant hypoglycaemia.

If the HbA1c targets cannot be achieved without causing significant hypoglycaemia, ADIPS recommends the use of less stringent targets, based on individualised clinical assessment.

Continuous glucose monitoring and flash glucose monitoring in pregnancy

For information regarding CGM and flash glucose monitoring in pregnancy, refer to the preconception section. For women with type 1 diabetes, the CGM targets during pregnancy include:

- Range: 3.5–7.8 mmol/L
- Time in range: >70% (i.e. >16.8 h per day)
- Time below range: <4% (1 h per day) at < 3.5 mmol/L and <1% (15 min per day) at <3.0 mmol/L
- Glycaemic variability (%CV): aim ≤36%.[61]

Glycaemic management during pregnancy

Insulin requirements

The pattern of change in insulin dose requirements during pregnancy in type 1 diabetes is well-documented. While there is very significant individual variation, typically, insulin requirements fall early in the first trimester[177] and then rise progressively from around 16 weeks gestation to around 36 weeks gestation,[178] before declining slightly towards term. Detailed studies in women with type 1 diabetes using CSII show a predominant increase in mealtime (bolus) and corrective dose requirements[179,180] in pregnancy, with lesser changes in basal insulin requirements. A recent Australian report noted a greater increase in insulin dose for women with type 2 diabetes, compared to those with type 1 diabetes,[181] with convergence of late pregnancy total daily insulin requirement at approximately 1 unit/kg/day for both type 1 and type 2 diabetes.

While small reductions (5-10%) in insulin dose requirements after 34–36 weeks gestation are common, marked decreases (>15%) in insulin requirements in later pregnancy raise concern regarding placental function. Evidence regarding the significance of these late pregnancy changes is conflicting. A recent Australian cohort study found a relationship between falling insulin requirements and adverse pregnancy outcomes (a composite of pre-eclampsia, small for gestational age ≤5th centile, stillbirth, premature birth <30 weeks gestation and placental abruption),[182,183] but others have reported no such association.[178,184–186] Given this disparity, women with a marked reduction (>15%) in insulin requirements in late pregnancy should have increased fetal and maternal surveillance and investigations for placental insufficiency. Falling insulin requirements alone should not prompt immediate delivery.

Despite the 'common patterns' documented above, the changes in insulin needs during pregnancy vary widely between individual women with diabetes. Careful clinical management and frequent insulin dose assessment and adjustment throughout pregnancy are of paramount importance.

Insulin therapy

Insulin therapy, essential in type 1 diabetes and frequently indicated in type 2 diabetes, is the mainstay of pharmacotherapy to achieve euglycaemia in pregnancy, with intensive treatment regimens (basal/bolus or CSII) generally favoured. For information regarding the safety of insulin analogues in pregnancy, refer to the preconception section. Women with high insulin requirements may benefit from more frequent changes in their CSII cannula sites and the use of concentrated insulin, such as U500 insulin.

CSII is frequently used in pregnancy for women with type 1 diabetes, but evidence for superiority over multiple daily injection therapy (MDI) is lacking. The most recent (2016) Cochrane review showed no clear differences.[187] However, data were limited and involved outdated pump technology. CSII has also been used successfully in women with type 2 diabetes requiring large doses of insulin.[188] The CONCEPTT study demonstrated that MDI users had a greater improvement in HbA1c and less gestational hypertension, neonatal hypoglycaemia and neonatal intensive care admissions than pump users, with the authors concluding that the implementation of pump therapy in pregnancy may be suboptimal in some women.[189]

Given the sparsity of high-level evidence, the decision regarding optimal insulin therapy in pregnancy needs to be made on an individual basis. Insulin regimens should be adapted to achieve near normoglycaemia while avoiding hypoglycaemia, to optimise maternal and fetal well-being.

Hypoglycaemia

Severe hypoglycaemia (such that the woman is unable to treat the hypoglycaemia herself and requires someone else to administer treatment) is more frequent during pregnancy, especially during 7–12 weeks gestation, and represents a major factor limiting intensification of insulin therapy.[177,190] Attempts to rapidly improve glycaemic levels, nausea and vomiting of pregnancy and hormonal changes may be contributing factors to first trimester hypoglycaemia.[177] Reported factors predisposing to severe hypoglycaemia include a prior history of severe hypoglycaemia, long duration of diabetes, lower baseline HbA1c and higher total daily insulin dose.[191] Focused patient and provider education is of proven benefit in reducing severe hypoglycaemia risk in pregnancy, hence access to preconception care is paramount.[192]

On a clinical level, patient education regarding the prevention, recognition and treatment of hypoglycaemia is a key component of early pregnancy care. Rapid and effective treatment of hypoglycaemia with glucose can prevent subsequent overeating and rebound hyperglycaemia. A simple treatment for mild hypoglycaemia is the 15-15 rule, that is, women should consume 15 g glucose (either glucose tablets, 6–7 regular jelly beans, half a cup of juice, or one tablespoon of sugar) then wait 15 min and retest their blood glucose level. Once the hypoglycaemia has resolved, the woman should eat some complex carbohydrate. However, if hypoglycaemia persists, the 15-15 step should be repeated. Alternatively, weight-adjusted treatment of hypoglycaemia may be more effective using 0.3 g glucose/kg body weight.[193] Partner/carer education regarding emergency treatment of severe hypoglycaemia, including the use of subcutaneous or intramuscular glucagon therapy (Adults: inject full dose (1mL, marked on syringe as 1/1)[194]) and a clear plan of action for contacting an ambulance or emergency service, are vital. Women with type 1 diabetes need to have in date glucagon readily available. Glucagon is a pregnancy category B drug, and is regarded as safe in pregnancy.

Driving

All pregnant women are advised to check their car insurance policy for regulatory requirements for driving in view of both the diabetes and the pregnancy.

National medical standards for licensing in Australia (Austroads) and in New Zealand (NZTA) provide guidelines for health professionals to assess the fitness of people with diabetes to drive (available at:

AUSTROADS:https://austroads.com.au/__data/assets/pdf_file/0022/104197/AP-G56-17_Assessing_fitness_to_drive_2016_amended_Aug2017.pdf

NZTA:https://www.nzta.govt.nz/assets/resources/medical-aspects/Medical-aspects-of-fitness-to-drive-A-guide-or-health-practitioners.pdf). However, driving requirements for pregnant women with pre-existing diabetes are not specifically discussed in either document, so individual circumstances need to be considered by the treating health professional.

For women with diabetes, the main concern with regards to licensing is the possibility of hypoglycaemia. A severe hypoglycaemia event reduces cognition both during and for up to ~ 45 min after the low blood glucose event. After any severe hypoglycaemia event, women should be advised not to drive until they have been cleared to drive by an appropriate medical practitioner. The minimum non-driving period after a severe hypoglycaemia event is generally 6 weeks.

In order to avoid a severe hypoglycaemia event, women should be advised to take the following steps[195]:

- Comply with medical review requirements
- Not drive if her blood glucose is ≤5.0 mmol/L or if she is feeling unwell
- Avoid delaying or missing a main meal
- Perform SMBG before driving and at least every 2 h during a journey (unless using CGM with alarms 'on') and ensure blood glucose is maintained >5.0 mmol/L
- Carry adequate glucose and longer-acting carbohydrate in the vehicle for self-treatment of hypoglycaemia

- If symptoms of hypoglycaemia occur while driving, stay calm, safely steer the vehicle to the side of the road, turn the engine off, remove the keys from the ignition, and treat hypoglycaemia
- Check the blood glucose 15 min after hypoglycaemia has been treated, and wait at least 30 min after the blood glucose is >5.0 mmol/L before recommencing driving.

Recurrent hypoglycaemia increases the risk of impaired awareness of hypoglycaemia, which in turn increases the risk of a severe hypoglycaemia event, escalating the risk of motor vehicle accidents and physical injury. Women with impaired awareness of hypoglycaemia should be under the care of an appropriate medical practitioner (endocrinologist or diabetes physician) who should be involved in assessing their fitness to drive. Women with persistent impaired awareness of hypoglycaemia are generally not fit to drive.

Diabetic ketoacidosis and ketone monitoring

Pregnancy is a ketogenic state. Women with type 1 diabetes, and to a lesser extent, those with type 2 diabetes, are at risk of DKA with intercurrent illness,[93] while fasting (including for religious reasons), with low carbohydrate diets or if insulin dosing is inadequate (intentional or inadvertent). DKA is an uncommon event, but needs to be considered at lower blood glucose levels in pregnant women compared to non-pregnant women,[93] at a mean blood glucose of 16.3 ± 4.6 mmol/L versus 27.5 ± 4.8 mmol/L, respectively, in one study.[196] In pregnancy, DKA can also occur at normal glucose levels i.e. euglycaemic DKA, especially if vomiting.

Women are advised to check their blood ketone levels (even if the blood glucose level is normal) if they are showing signs of DKA, including:

- Nausea, vomiting and/or abdominal pain
- Increased thirst or dry mouth
- Reduced urine output
- An unusual or fruity smelling breath
- Rapid breathing or breathlessness
- Rapid heartbeat
- Drowsiness, confusion or disorientation.

Women should also check their blood ketone levels if their blood glucose levels are persistently elevated eg ≥15 mmol/L, even if they feel well.

If a woman is unable to eat or drink and/or an elevated blood glucose level is not improving over 1–2 h, she needs to seek further medical advice. Ketone strips can be useful with this decision.

An abnormal ketone result (blood ketones ≥0.6 or urine ketones >1+) warrants action (unless pre-breakfast, in which case the woman should eat breakfast and recheck). If there are elevated ketones (irrespective of the glucose level), or the blood glucose levels are high and there are signs of ketoacidosis, the woman should be aware of the need to seek immediate treatment that may require going to hospital. An individual plan needs to be made with all women with pre-existing diabetes.

Blood ketone monitoring appears superior to urine ketone testing for the detection of early ketoacidosis, in terms of reduced hospitalisation, more rapid recovery and greater treatment satisfaction.[197] However, pregnancy-related data are absent and uptake of blood ketone monitoring into routine ambulatory care has been slow.

Blood ketone monitoring remains an important part of inpatient antenatal and postpartum care for women with type 1 diabetes and should be routinely included in diabetes monitoring protocols for acute clinical care of these women.

Sick day management

Sick day education provided preconception should be repeated in early pregnancy, and periodically thereafter, to reduce the risk of DKA. The importance of avoiding hyperglycaemia and DKA, particularly in the event of sick days, should not be underestimated. In one study, the risk of fetal demise at the time of, or following, a DKA event in pregnant women with type 1 diabetes was 15.6%.[198]

Maternal education includes development of a written sick day plan and sick day kit, provision of a ketone meter for testing ketones when unwell, discussion of the prevention (insulin supplementation) and detection of DKA and hypoglycaemia, as well as information on when to seek urgent medical advice. The woman's support person/s should be invited to join the education session. Practice points are summarised in Table 6.

Glycaemic management after corticosteroid administration

Blood glucose levels typically start to rise 4–6 h after a betamethasone injection, with the main impact on blood glucose levels occurring in the first 24 h after the injection.[199–201] There may be a diminishing effect on blood glucose levels for up to 6 days. The impact of oral steroids on blood glucose levels also needs consideration.

TABLE 6 Practice points for sick day management in pregnancy

- Provide written advice for nausea and vomiting of pregnancy and intercurrent illness
- Ensure access to capillary blood glucose and ketone meter, with test strips in date
- Advise that if unwell (dehydrated, vomiting, unable to eat), suspect ketosis/DKA and:
  - a Check capillary blood glucose levels 1-2 hourly
  - b Check blood ketones when blood glucose level ≥ 15mmol/L or if unwell
  - c Continue taking insulin (basal insulin with bolus correction doses as needed)
  - d Seek urgent medical advice and consider hospital admission

Clinical practice regarding management of hyperglycaemia following antenatal glucocorticoid therapy to enhance fetal lung maturation varies widely across Australasia. Some centres rely entirely on subcutaneous insulin to manage hyperglycaemia in this setting, while others use routine intravenous insulin infusions. Some centres add an insulin infusion on top of usual subcutaneous insulin doses. There is no evidence that one method is superior to another. However, having a protocol in place for glycaemic management after corticosteroid administration, including ketone testing, is important to reduce the risk of DKA. A UK group has claimed efficacy for their intravenous insulin therapy protocol,[202] while a Copenhagen group has similarly reported positive outcomes for their corrective subcutaneous insulin protocol.[203] Women, particularly those with type 1 diabetes, may require hospital admission for intensive glucose monitoring and glycaemic management.

Screening for diabetes complications and other autoimmune diseases during pregnancy

Retinal screening

Retinal screening recommendations are based on limited data and expert consensus.[28,118,119,122] Retinal screening should be performed in the first trimester, unless already performed within three months prior to conception.[28] Retinal screening should ideally consist of digital photo-screening through dilated (tropicamide) pupils with a minimum field size of two 45 degree fields, and include disc-centred and macular-centred views.[118] An early assessment enables the detection and prompt treatment of sight-threatening DR/maculopathy and provides a baseline from which to detect a progression of DR.

If there is no DR on the initial screen, consider repeating the retinal assessment at 28 weeks gestation according to local management practices.[28] NZ guidance states that 'women with no DR and no modifiable risk factors can continue with their normal two- or three- yearly screening'.[118,204]

Referral

If DR/maculopathy is present on the initial screen, or at any stage of pregnancy, women should be referred to an ophthalmologist for review, with follow-up arranged according to ophthalmological opinion.[28,118]

Postpartum, ophthalmological follow-up should be arranged for at least six months postpartum if there was any referrable DR or maculopathy in pregnancy.[28]

Renal screening

Renal assessment should be performed at the first antenatal visit. If there is no history of renal impairment, a serum creatinine and spot urine ACR or PCR should be performed. In the event of later development of hypertension and proteinuria, it is helpful to know whether proteinuria was present in early gestation. If there is known moderate proteinuria (urine ACR ≥ 70 mg/mmol), a urine PCR should be performed.

If no abnormality or microalbuminuria (urine ACR < 35 mg/mmol) is detected, urinalysis should be performed to check for proteinuria, and the BP measured, at each subsequent antenatal visit to screen for pre-eclampsia. If the urinalysis is positive for proteinuria (1+ or more), exclude a urinary tract infection and then quantify the proteinuria with a urine PCR.

If macroalbuminuria (urine ACR > 35 mg/mmol) is detected, arrange monthly urine PCR to track progression of proteinuria. A gradual increase (approximate doubling throughout pregnancy) is expected but a sudden increase in the absence of a urinary tract infection should prompt an assessment to exclude pre-eclampsia. Consider thromboprophylaxis with low molecular weight heparin in women with nephrotic range proteinuria (urine ACR >220 mg/mmol, urine PCR > 500 mg/mmol and serum albumin <20–25 g/L).[205,206] Most experts agree that nephrotic syndrome in pregnancy with one additional risk factor (previous venous thrombosis, family history of venous thrombosis, hospital admission, BMI ≥ 30kg/m^2, age ≥ 35 years, smoker, varicose veins, the first 6 weeks postpartum) warrants thromboprophylaxis.[207,208] Others would offer antenatal thromboprophylaxis in women with nephrotic syndrome regardless of additional risk factors, either throughout pregnancy[209] or from 28 weeks gestation onwards.[207]

If serum creatinine is elevated, monitor at least monthly throughout pregnancy. As eGFR underestimates GFR in pregnancy,[210,211] serum creatinine should be used to monitor antenatal renal function. In women with an elevated creatinine (taking into account the increased GFR and lower creatinine in healthy pregnant women), multidisciplinary decision making is required around timing of birth, with consideration for maternal and fetal health, obstetric issues, and the woman's desire to preserve renal function and avoid dialysis.

Referral

Consider referral to an obstetric physician or obstetric nephrologist if CKD (pre-pregnancy eGFR < 60mL/min/173m^2, or elevated serum creatinine in pregnancy, and/or proteinuria) is present. The combination of diabetes, hypertension and kidney disease in pregnancy, even if all three are mild, warrants a review and pregnancy management action plan.[136]

If CKD is present, maintaining optimal blood glucose levels and BP decrease the risk of deteriorating renal function.[210,211] There is insufficient evidence regarding BP targets for CKD in pregnancy. A RCT in pregnant women with non-proteinuric pre-existing or gestational hypertension demonstrated that a target diastolic BP of 85 mmHg reduced the frequency of severe maternal hypertension without increasing the risk of perinatal harm.[212] The 2019 NICE guideline for hypertension in pregnancy recommends a target BP of 135/85 mmHg for pregnant women with chronic hypertension, gestational hypertension or pre-eclampsia.[213] ADIPS recommends a target BP of <135/85 mmHg for pregnant women

with pre-existing diabetes and CKD. Placental perfusion needs to be considered in BP management, and a clinical decision needs to be made regarding the lowest acceptable BP for each individual woman and the feto-placental characteristics.

Coronary artery disease screening

BP should be checked at each antenatal visit. Women at high risk of CAD should have a baseline ECG and be monitored throughout pregnancy for symptoms of angina. Atypical symptoms of ischaemic heart disease such as dyspnoea, nausea and vomiting, fatigue, weakness, pre-syncope and syncope, atypical chest pain, arm or back pain, and atypical anxiety should prompt a careful clinical examination in women with pre-existing diabetes.[214] Chest pain should be urgently investigated with an ECG and cardiac biomarkers, with referral to a cardiologist as appropriate.

Autonomic neuropathy screening

A lying and standing assessment of BP and pulse should be performed at the initial antenatal visit and at any stage of the pregnancy if the woman describes symptoms of postural hypotension. Ensure adequate salt and fluid intake throughout pregnancy. Compression stockings may help alleviate symptoms. Gastroparesis can be problematic, and can require specialist dietitian review, enteral feeding, and medical therapy including prokinetics and anti-emetics.[215]

Screening for other autoimmune diseases

Early in pregnancy, women with type 1 diabetes should be screened for other autoimmune diseases. At the initial antenatal visit, women with type 1 diabetes should have TSH measured, unless they have had a normal TSH and negative TPO autoantibody screen within three months prior to conception and have no other risk factors for thyroid disease in pregnancy. TSH measurement should be repeated at six weeks, three months and six months postpartum to screen for postpartum thyroiditis.[206] Enquire about symptoms of coeliac disease and arrange antibody testing if not already documented in the previous two years.[216]

Prevention of pre-eclampsia

The spectrum of hypertensive disorders in pregnancy, particularly pre-eclampsia, poses a significant risk to the mother and her child. Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity, directly accounting for 6.3% of maternal mortality in Australia in 2012–2014.[156] Pre-eclampsia is a multisystem disorder characterised by hypertension (new-onset or worsening pre-existing) and involvement of one or more other organ systems and/or the fetus. Proteinuria is no longer considered essential to the diagnosis.[99,217] Pre-eclampsia is associated with intrauterine fetal growth restriction and iatrogenic premature birth of the fetus, creating significant fetal morbidity and mortality. For the mother, associated organ dysfunction (thrombocytopaenia, coagulation abnormalities, liver and kidney dysfunction, heart and lung dysfunction, intracerebral vascular events) accounts for the majority of morbidity and mortality. There is currently no effective treatment for pre-eclampsia aside from delivery of the fetus and removal of the placenta. Therefore, efforts to predict those at risk of pre-eclampsia, together with efforts to reduce the risk of developing pre-eclampsia with interventions such as aspirin therapy and calcium supplementation, may significantly impact maternal and fetal morbidity and mortality.

Type 1 and type 2 diabetes are both high-risk factors for the development of pre-eclampsia.[218] Type 1 diabetes is associated with a 15–20% incidence of pre-eclampsia whereas type 2 diabetes is associated with a 10–15% incidence.[219] The risk of pre-eclampsia is higher in the presence of established nephropathy and/or retinopathy (40-50%).[219]

Clinical models for predicting pre-eclampsia have been used to target an at-risk population and are becoming more widely used in clinical practice.[220] More elaborate algorithmic models have been developed to screen for pre-eclampsia between 11–13 weeks gestation, using factors such as maternal risk factors, mean arterial pressure, ultrasound assessment of the uterine artery pulsatility index, maternal serum pregnancy-associated plasma protein-A (PAPP-A), soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF).[221,222] The algorithm used in the Aspirin for Evidence-based Pre-eclampsia Prevention (ASPRE) trial is available at https://fetalmedicine.org/research/assess/preeclampsia.

A consideration for the implementation of personalised pre-eclampsia prediction using these methods is the cost and availability of ultrasound access. Using numbers from the ASPRE trial, the number needed to screen to prevent one case of pre-eclampsia is 330.[223] In the ASPRE trial, the rate of early-onset pre-eclampsia (before 34 weeks gestation) for women with pre-existing diabetes was 1.3% in the screen negative group. Given the costs of screening, the remaining substantial risk of early-onset pre-eclampsia in the screen negative group, and the low cost and low side effect profile of prevention with low-dose aspirin, it is pragmatic to offer intervention to all women with pre-existing diabetes without screening (Table 7).

TABLE 7 Australasian Diabetes in Pregnancy Society recommendations for pre-eclampsia prevention

- Type 1 diabetes and type 2 diabetes are both high-risk factors for the development of pre-eclampsia. Therefore, all women with pre-existing diabetes should receive pre-eclampsia prophylaxis.
- Aspirin 100–150 mg daily with the evening meal (unless contraindicated) from 12 weeks gestation. Aspirin can usually be ceased at 36 weeks gestation.
- Calcium supplementation (total 1.5 g daily including dietary calcium) from 12 weeks gestation.

Aspirin

Aspirin therapy (100–150 mg) has been demonstrated to reduce the incidence of early-onset pre-eclampsia in high-risk pregnancies when the onset of treatment was ≤16 weeks gestation[221,224] and may be more effective if given in the evening.[225] The 2014 Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guideline for the management of hypertensive disorders of pregnancy, endorsed by ADIPS, recommends low-dose aspirin (dose not specified) for women with moderate to high risk of pre-eclampsia.[99] Aspirin can usually be ceased at 36 weeks gestation, although the continuation of aspirin therapy to birth is thought to be safe.[99,226]

The 2014 guideline from the International Society for the Study of Hypertension in Pregnancy (ISSHP) states that 'Aspirin should be given at a dose between 75 and 150 mg per day, started preferably before 16 weeks, possibly taken at night, and continued until birth; about 70 women need to be treated to prevent one case of pre-eclampsia, particularly severe pre-eclampsia'.[227] The American College of Obstetrics and Gynecology (ACOG) and Society for Maternal-Fetal Medicine recommend initiating aspirin between 12 weeks and 28 weeks gestation, ideally before 16 weeks gestation.[228]

Medical precautions for the use of aspirin include von Willebrand disease, peptic ulceration, hypersensitivity to aspirin and present use of another drug with the potential to interact with aspirin.

Low-dose aspirin in pregnancy has not been shown to increase the risk of placental abruption, postpartum haemorrhage or adverse regional anaesthetic outcome, or increase the risk of fetal morbidities such as intraventricular haemorrhage, neonatal bleeding or antenatal closure of the ductus arteriosus. An increased risk of congenital anomalies with low-dose aspirin use in pregnancy has not been reported.[221,229,230]

Given that aspirin loses potency when exposed to air, women who use half of a 300 mg tablet each day should discard the remaining half tablet.[231]

Calcium supplementation

Calcium supplements in pregnancy have been demonstrated to significantly reduce the risk of pre-eclampsia, particularly in high-risk women and those with low dietary calcium intake.[232] Calcium supplements have also been shown to reduce the risk of preterm birth.[232] Calcium supplementation (total 1.5 g daily including dietary calcium) should be offered to women with moderate to high risk of pre-eclampsia, particularly those with low dietary calcium intake.[99,232]Calcium supplementation is usually managed with attention to dietary intake and supplementation with calcium carbonate 600 mg twice daily.

Obstetric monitoring

Screening for fetal aneuploidy

Women with pre-existing diabetes are not at an increased risk of fetal aneuploidy. They should be offered the same screening as all pregnant women. The markers for first trimester combined screening, nuchal translucency, PAPP-A and free β-human chorionic gonadotropin are affected by diabetes and the testing laboratory should be notified that the woman has diabetes to enable appropriate adjustment of the calculations. Increasingly, women are being screened by maternal cell-free fetal DNA (non-invasive prenatal screening, NIPS) as the primary screen for fetal aneuploidy from 10 weeks gestation. There is no reason to expect that this test performs differently in the presence of maternal diabetes. However, the fetal DNA fraction decreases (and may be suboptimal) with increasing maternal weight. The risk of 'no result' is ~20% when maternal weight is ≥95 kg and >50% with maternal weight ≥160 kg.[233] In addition, some of the second-trimester markers (eg alpha-fetoprotein (AFP), inhibin and estriol) can be altered in diabetes and adjustments need to be made if this test is used.

Ultrasound

Ultrasound should be performed for the usual obstetric indications. Accurate dating of pregnancy is vital for accurate timing of investigations (eg first trimester combined screening for aneuploidy) and birth.

A late first trimester scan is recommended to detect major fetal anomalies (eg anencephaly, spina bifida, major cardiac anomalies). This scan can also be part of aneuploidy screening if NIPS has not been done, and then must be undertaken between 11 and 13+6 weeks gestation.

A fetal anomaly scan that includes a four-chamber cardiac view and outflow tracts, consistent with the recommendations of the Australasian Society for Ultrasound in Medicine (ASUM) should be performed at around 20–22 weeks gestation in all women with pre-existing diabetes due to the increased risk of fetal anomalies, particularly neural tube defects and cardiac anomalies.[234,235] In obese women, the ability to detect fetal anomalies is higher around 22 weeks gestation, compared to earlier in the range.

In order to examine fetal growth, serial ultrasounds are recommended every 2–4 weeks from 28 weeks gestation, the precise frequency of which depends on the clinical context and local management practices. If there is suspected fetal growth restriction, particularly in the presence of maternal hypertension, past history of fetal growth restriction and/or diabetic nephropathy, more frequent or earlier initiation of scanning may be required.

Fetal surveillance in late pregnancy

While the risk of stillbirth decreases with effective glycaemic management, late pregnancy stillbirth remains more common in women with pre-existing diabetes than in the general population. Therefore, some form of fetal surveillance is recommended in late pregnancy. There is a paucity of high-quality published data to guide third trimester fetal surveillance. Advice, particularly regarding Doppler assessment of fetal vessels, has been extrapolated from surveillance of the growth-restricted fetus, so applicability in the setting of macrosomia secondary to diabetes is not clear.[236,237] Maternal assessment of fetal movements should take place from 28 weeks gestation and any decrease in fetal movements should be promptly reported to the health professional.[238] A reasonable regimen of investigation is to perform a weekly assessment of fetal well-being, commencing at 34 weeks gestation, using antenatal CTG and amniotic fluid assessment on ultrasound.[239,240] Women at higher risk of stillbirth due to ongoing significant hyperglycaemia, macrosomia, poor past obstetric history, fetal growth restriction, pre-eclampsia, falling insulin requirements or other obstetric complications may warrant more frequent or more detailed surveillance. Specialised maternal-fetal medicine advice should be sought if there are any concerns regarding fetal well-being.

TYPE 1 DIABETES AND TYPE 2 DIABETES: MANAGEMENT DURING BIRTH

Timing and mode of birth

The RR of stillbirth in women with pre-existing diabetes after 39 weeks gestation compared to other women is 7.2 (95% CI 1.31–39.63), with an absolute risk increase of nearly 1%.[241] Therefore, women with pre-existing diabetes should be advised to give birth by the end of 38 completed weeks gestation, depending on the presence of fetal macrosomia, glycaemic levels and any other complicating factors. In women without diabetes, induction of labour for a suspected large for gestational age fetus is associated with a reduced risk of shoulder dystocia and associated morbidity compared with expectant management, but limited data exist for women with diabetes.[242]

If the estimated fetal weight (EFW) at the time of birth is >4500 g in women with pre-existing diabetes, the risk of shoulder dystocia is >20%.[243] For this reason, elective caesarean section should be considered.[243] Counselling regarding the mode of birth should include the known variation in EFW compared to birth weight, which is as high as 15% in either direction. For women with pre-existing diabetes, it is estimated that 443 women with EFW >4500 g would need to have an elective caesarean section to avoid one permanent brachial plexus injury.[244]

The proportion of women who deliver by caesarean section is significantly greater for women with pre-existing diabetes than without. A large retrospective audit of women with pre-existing diabetes demonstrated a higher incidence of both elective caesarean section (29.4% type 1 diabetes, 30.5% type 2 diabetes, 9.6% without diabetes) and emergency caesarean section (38.3% type 1 diabetes, 29.1% type 2 diabetes, 14.6% without diabetes), and an increasing trend over time toward elective caesarean section in women with type 1 diabetes.[245]

Corticosteroid administration

It is appropriate to use betamethasone to accelerate fetal lung maturity where there is a risk of birth before 34 weeks gestation.

There is a lack of evidence for the use of betamethasone after 34 weeks gestation for women with pre-existing diabetes, as these women were excluded from the studies. RCTs or quasi-RCTs comparing prophylactic antenatal corticosteroid administration with placebo or with no treatment given before elective caesarean section at or after 37 weeks gestation resulted in a significant reduction in the risk of admission to the neonatal intensive care unit for respiratory morbidity (OR 0.15, 95% CI 0.03–0.64).[246] However, there was no significant reduction in respiratory distress syndrome, transient tachypnoea of the newborn, the need for mechanical ventilation or length of stay in the neonatal intensive care unit. The only RCT to include pregnant women with diabetes had small numbers of women with diabetes (n = 6) and, therefore, the safety of prophylactic corticosteroids in this subgroup could not be assessed.[247]

Data do not exist to support administration or non-administration of betamethasone after 37 weeks gestation for elective caesarean section. Given the lack of data, the decision for betamethasone after 37 weeks gestation should be made after discussion with clinicians involved in the care of the mother, taking into account unique features of the clinical situation, advice from local paediatricians or neonatologists, consideration of local guidelines, and discussion with the woman.

Glycaemic management after corticosteroid administration is discussed earlier in this guideline.

Neonatal considerations in preparation for birth

Neonates born to women with pre-existing diabetes have high rates of macrosomia and large for gestational age despite glycaemic management in pregnancy.[248] In addition, there is an increased risk of preterm birth, neonatal hypoglycaemia and respiratory distress. Women with pre-existing diabetes should, therefore, plan to give birth at a hospital with adequate access to neonatal support.[28] Women should be offered lactation consultant support from 32 weeks gestation to discuss breastfeeding in the setting of pre-existing diabetes.

Glycaemic management prior to induction of labour or elective caesarean section

Induction of labour or elective caesarean section necessitates a glycaemic management plan be developed by the multidisciplinary diabetes and obstetric team, in accordance with local management practices. For clinicians practising in areas without a specialist diabetes in pregnancy service, accessing specialist advice and support is encouraged.

Preparation for induction of labour

If induction of labour is scheduled, the night before induction, women with pre-existing diabetes who are taking insulin are typically advised to:

- take the usual dose of pre-dinner rapid-acting insulin
- take the usual dose of pre-bed intermediate-acting insulin (eg isophane)
- reduce the dose of pre-bed long-acting insulin (eg detemir, glargine) by 30–50%.

On the morning of induction, women with pre-existing diabetes are typically advised to:

- reduce the dose of pre-breakfast rapid-acting insulin
- reduce the dose of pre-breakfast intermediate/ long-acting insulin by 50%
- perform 1-2 hourly SMBG (target range of 4.0–7.0 mmol/L).

Insulin pump therapy

Women on insulin pump therapy should continue their usual basal rate prior to the induction of labour.

Variations in clinical practice occur, so local policies should be followed. For clinicians unfamiliar with managing women with pre-existing diabetes in the peripartum, specialist telephone advice should be sought.

Preparation for elective caesarean section

If possible, women with pre-existing diabetes should be scheduled for elective caesarean section early in the morning (ideally first on the list), in order to reduce the propensity toward maternal hypoglycaemia while fasting.

The night before the elective caesarean section, women with pre-existing diabetes who are taking insulin are typically advised to:

- take the usual dose of pre-dinner rapid-acting insulin
- take the usual dose of pre-bed intermediate-acting insulin (eg isophane)
- reduce the dose of pre-bed long-acting insulin (eg detemir, glargine) by 30–50%.

On the morning of the elective caesarean section, women with pre-existing diabetes are typically advised to:

- omit the pre-breakfast rapid-acting insulin
- reduce the dose of pre-breakfast intermediate/ long-acting insulin by 50%
- perform hourly SMBG from 6 am (target range of 4.0–7.0 mmol/L).

Insulin pump therapy

Women on insulin pump therapy should continue their usual basal rate during the night before the scheduled elective caesarean section, and then reduce their basal rate by 25–50% shortly prior to the elective caesarean section (e.g. 1–2 h prior to the elective caesarean section or at 6 am if first on the morning list). For women on insulin pump therapy, the infusion set should be changed in the morning (or early afternoon) of the day prior to the elective caesarean section with adequate time to ensure correct functionality. Most women on insulin pump therapy can continue to manage their diabetes via the insulin pump during the caesarean section.[249] Patients should be advised to ensure that the infusion set and CGM, if applicable, is sited well away from the surgical field, considering both a low transverse abdominal incision and the rare necessity for a midline incision. A teflon cannula (rather than metal) is required for safety during diathermy. Alternatively, an intravenous insulin and glucose infusion can be considered.

Variations in clinical practice occur so local policies should be followed.

Glycaemic management during birth

The general principles of labour management in high-risk pregnancies apply to women with pre-existing diabetes. These principles include adequate hydration (oral and/or intravenous), regular assessment for progression of labour and continuous fetal heart rate monitoring once active labour is established.

The goal of glycaemic management during birth is to optimise maternal and fetal outcomes. Maternal hyperglycaemia during labour increases the risk of neonatal hypoglycaemia, particularly in neonates born to women with type 1 diabetes. In one study of women with type 1 diabetes, maternal blood glucose levels >10.0 mmol/L during labour were associated with neonatal hypoglycaemia in all cases.[250]

The work of labour increases whole-body glucose utilisation, which increases the risk of maternal hypoglycaemia during labour and immediately after birth, affecting up to 56% of women with pre-existing diabetes.[251]

Few studies have examined the optimal method of managing maternal glycaemia during labour.[250,252,253] Therefore, local policies should be followed. Hourly SMBG is recommended during labour, with a target range of 4.0–7.0 mmol/L.[28,176] CGM can be safely used during labour, although it has not been found to offer

an advantage over SMBG.[254] CGM should not be worn in theatre, as it cannot be used with diathermy.

Intravenous insulin/glucose infusions may be used to achieve blood glucose levels within the target range and to avoid insulin deficiency, particularly in women with type 1 diabetes. Local protocols for insulin/glucose infusions should be followed. Typically, two simultaneous intravenous infusions are used: (A) insulin infusion (eg 50 units of regular (Actrapid) insulin in 50 mL normal saline; ensure line is primed and flushed with 20 mL insulin/saline solution to saturate the binding to plastic giving sets prior to connecting the line to the woman;[255] insulin infusion rate typically starts at 1.0 unit/h); and (B) 5% glucose infusion (typically at a fixed rate as prescribed by the endocrinologist/ physician). The infusion rates should be titrated according to the blood glucose level, checked hourly. If the blood glucose level is <4.0 mmol/L, glucose (oral or intravenous 5% glucose) is required to treat the hypoglycaemia and the insulin infusion may be temporarily ceased (refer to local protocol). If the blood glucose level is >7.0 mmol/L, the insulin infusion rate should be increased according to the local protocol.

Insulin pump therapy during birth

Insulin pump therapy can be safely used during labour or elective caesarean section in accordance with local policies, providing that women and their partners are competent in its use and function, and the health professional team is familiar with pumps during birth.[28,249,256] Blood glucose levels should be monitored hourly and basal rates adjusted accordingly. In the unlikely scenario that general anaesthesia is used for the delivery, insulin pump therapy can be continued as long as blood glucose monitoring occurs every 30 min from induction of general anaesthesia until after the baby is born and the woman is fully conscious.[28]

Alternatively, insulin pump therapy could be ceased and replaced with an intravenous insulin/glucose infusion, following local protocols, for the duration of labour and birth. One study demonstrated a benefit in achieving euglycaemia in women who were maintained on their insulin pump rather than changed to an intravenous insulin infusion.[256] However, neither approach is favoured over the other with respect to neonatal hypoglycaemia.

Given that insulin requirements fall during labour, it is advantageous to program basal rates, designed specifically for the onset of labour, into the pump. For example, when in early labour, a basal rate of around 50% of the usual antenatal basal rate could be applied, and once in active labour, the basal rate could be reduced to around 5–10% of the usual antenatal basal rate.[257] The early postpartum basal rate (typically half the pre-pregnancy rate) can also be programmed into the pump. An alternative approach is to use the temporary basal rate feature of the insulin pump. For women with a sensor-augmented insulin pump, the insulin-suspend feature is useful in averting predicted hypoglycaemia. Basal rates should be adjusted according to blood glucose levels. It is useful to provide women with a written plan documenting the recommended basal rates. Women should be advised to change the line and sensor the day before the planned birth to avoid issues with a failed infusion set on the day of birth.

Midwives who are caring for the woman in labour should be informed that an insulin pump is in place and reminded to remove the pump catheter should an emergency arise.

Ketone testing during labour

During labour, whole-body glucose stores are depleted and ketogenesis is stimulated. For women with pre-existing diabetes, particularly type 1 diabetes, ketogenesis can be exaggerated as a result of the insulin-deplete state. High levels of maternal ketone production can compromise fetal well-being.[258] In addition, ketonaemia in women with pre-existing diabetes can predispose to DKA, which is associated with poor neonatal outcomes, including fetal demise.[198]

Although specific studies examining the benefits of ketone testing during labour have not been performed, having a protocol in place for ketone testing during labour is important to reduce the risk of DKA. If the blood ketone level is >0.6 mmol/L, an intravenous insulin/glucose infusion should be commenced. Close attention to fetal heart monitoring is required.

Intrapartum care

Continuous electronic fetal monitoring should occur during labour to detect fetal compromise.[259] The risk of shoulder dystocia is increased in women with diabetes. This risk should be considered when planning instrumental delivery, or after slow progress in labour. Intrapartum care should include planning for the presence of a sufficient number of appropriately skilled senior staff to be present at the time of birth to manage shoulder dystocia if it occurs, and appropriate positioning of the woman in the second stage of labour to enable rapid management of shoulder dystocia.

TYPE 1 DIABETES AND TYPE 2 DIABETES: POSTPARTUM MANAGEMENT

Type 1 diabetes: postpartum glycaemic management

Immediately after the birth, insulin requirements fall rapidly[260] because the placental hormone secretions that increase insulin resistance in the latter part of pregnancy are immediately ameliorated once the placenta is delivered.[261]

Intrapartum insulin/glucose infusion

Immediately after the birth, the insulin/glucose infusion should be ceased. Hourly measurement of blood glucose levels should

continue. Subcutaneous insulin should be restarted at approximately half the pre-pregnancy dose once blood glucose levels reach around 8–10 mmol/L. Consider blood ketone testing if not eating for >6 h, blood glucose levels >10 mmol/L or any clinical concerns. Subcutaneous insulin should then be titrated according to blood glucose levels. Close monitoring and regular adjustment is required. In the first 24–48 h after birth, insulin requirements are usually dramatically less than during pregnancy.[260]

Insulin pump therapy

Immediately after the birth, the basal rate should be reduced to approximately half the pre-pregnancy rate. Hourly measurement of blood glucose levels should continue until the first meal has been consumed. Bolus insulin doses also need to be substantially reduced. Regular adjustment of insulin rates is required in response to blood glucose levels.

After the first meal, SMBG can decrease to fasting, pre-meal, two-hour post-meal and overnight, with a target range of 5.0–10.0 mmol/L in the early postpartum period. Additional blood glucose monitoring may be required to assess the impact of breastfeeding on glucose levels. Alternatively, CGM or flash glucose monitoring can be used.

Minimising maternal hypoglycaemia should be a primary treatment goal in the early postpartum period. It is vital for women and midwives to understand the effect of breastfeeding on energy expenditure, which predisposes to lower blood glucose levels. Women should expect a reduction in insulin requirement/doses in the early postpartum period. Plans to detect and manage nocturnal hypoglycaemia should be developed.

Women who are breastfeeding may need to have an additional protein/carbohydrate based snack at the commencement of each breastfeed.[262,263] Ongoing dietary prudence, in consultation with a dietitian, should be encouraged lifelong to prevent hyperglycaemia and minimise hypoglycaemia, which may also be important for the long-term metabolic health of the neonate.

Severe hyperglycaemia in the immediate postpartum should also be avoided, to reduce the risk of infection. Prior to leaving hospital, ensure women with diabetes have contact details of the local lactation consultant/service and appropriate diabetes health professional for ongoing advice to maintain breastfeeding and euglycaemia.

Type 2 diabetes: postpartum glycaemic management

For women with type 2 diabetes, the insulin/glucose infusion (if used) should be ceased immediately after the birth. Women should have frequent measurement of blood glucose levels. Long-acting insulin (eg glargine) prior to birth can increase the risk of hypoglycaemia in the fasted state post-birth, which is why a dose reduction is recommended before induction of labour or elective caesarean section.

For many women with type 2 diabetes, diet alone will achieve adequate glycaemia for a period after the birth, so insulin/ oral glucose-lowering agents may not be required. SMBG (fasting, two-hour post-meal and overnight) is advised, with a target range of 5.0–10.0 mmol/L in the early postpartum period, to assess whether additional glucose-lowering treatment is required.

If maternal hyperglycaemia is evident, treatment options include insulin, metformin or glibenclamide.[264] In practice, glibenclamide is generally not used postpartum in the Australian and New Zealand setting. Very little metformin[265] or glibenclamide[98] is excreted into human breastmilk. Other oral glucose-lowering agents should be avoided until breastfeeding has ceased.

Lifestyle advice, including healthy eating, regular physical activity, social connection, and supporting good psychological health should be provided to women with type 2 diabetes in the early postpartum period. A reminder for biannual pathology and review provides an opportunity to reaffirm preconception advice.

Breastfeeding

Just as for all mothers and babies, breastfeeding is advantageous in the setting of pre-existing diabetes. Breastfeeding establishment rates are lower in women with pre-existing diabetes compared to women without diabetes,[266–271] despite known neonatal and maternal benefits. Decreased obesity has been demonstrated in infants of women with type 1 diabetes who breastfed for longer than four months.[272] Reduced subsequent development of type 1 and type 2 diabetes has been demonstrated in predisposed infants who were breastfed.[273–276] Breastfeeding has also been associated with improved glycaemia in women with type 1 diabetes[263] and decreased maternal long-term cardiometabolic risks.[277]

Breastfeeding at discharge[278–280] and total breastfeeding duration[266–269,279] are reduced in women with pre-existing diabetes compared to women without diabetes. Factors that are independently negatively correlated with the establishment and duration of breastfeeding in women with pre-existing diabetes include a lower maternal education,[266,279,281] younger and older maternal age,[267,279,282] primiparity,[267,279] overweight or obese

TABLE 8 Checklist to promote breastfeeding[314]

a	Discuss the importance of breastfeeding with pregnant women and their families
b	Facilitate immediate and uninterrupted skin-to-skin contact
c	Support mothers to initiate breastfeeding as soon as possible after birth (ideally within 30–60 min of birth) or express breastmilk if baby unable to feed
d	Encourage exclusive breastfeeding
e	Encourage demand feeding or express breastmilk
f	Enable mothers and infants to remain together (rooming-in)
g	Support mothers to maintain breastfeeding and manage common difficulties
h	Counsel mothers on the use and risks of feeding bottles, teats and pacifiers
i	Offer lactation consultant support from 32 weeks gestation, in the early postpartum period and after discharge

BMI,[281,283-285] increased severity of insulin resistance,[282,285] preterm birth,[266] delay in first breastfeed (particularly if more than one hour after birth)[266] and decreased early breastfeeding in hospital.[279] Pre-existing diabetes has been associated with a delay in secretory activation (milk 'coming in' or 'lactogenesis II'),[286] which is correlated with decreased lactation establishment and duration.[287,288]

Information about the benefits of breastfeeding, and practical advice, should be provided to women during pregnancy (Table 8). There is currently insufficient information regarding interventions to increase breastfeeding in women with pre-existing diabetes. However, data from women without diabetes show a longer duration of breastfeeding in women who breastfeed within two hours of birth[289] and increased breastmilk volume at three weeks postpartum in mothers of premature infants who initially express at one vs five hours postpartum.[290] Women should ideally be offered the opportunity to breastfeed within 30–60 min of birth or to express breastmilk within this timeframe if the baby requires nursery admission or is unable to feed. Thereafter, women should be encouraged to demand feed or express breastmilk, with early lactation consultant support if required. Women who are admitted to intensive care should be assisted to express breastmilk regularly, commencing immediately following stabilisation. Intensive care departments should develop policies to facilitate early breastmilk expression, and should ensure consent and adequate staff skilling so that early expression is not delayed. Hand expression may be as effective as breast pump expression prior to secretory activation.[291] Simultaneous double pumping results in greater milk volume production than single-sided pumping.[292]

Antenatal expression of colostrum is widely practised. In women with pre-existing diabetes and no additional risk factors for preterm labour or fetal compromise, the antenatal expression of colostrum from 36 weeks gestation has been associated with increased early breastfeeding.[293] While it appears to be safe and does not appear to increase the risk of premature labour in women with pre-existing diabetes, it has not been shown to reduce morbidity, neonatal special care/intensive care unit admissions or long-term breastfeeding establishment, and only 43 women with pre-existing diabetes were included in this study.[293] Therefore, the antenatal expression of colostrum may be considered in consultation with the woman and treating clinician in women with no additional risk factors for preterm labour or fetal compromise.

Women benefit from midwifery continuity of care models. Ongoing support from a lactation consultant/service and midwifery team is required after discharge.

The Australian Breastfeeding Association is an important resource for all nursing mothers and provides a national 24/7 hotline via trained breastfeeding counsellors, with funding from the federal government.

Information and follow-up after birth

Arrangements for follow-up of women with pre-existing diabetes should be determined during pregnancy. Ongoing care with the woman's diabetes providers (general practitioner, endocrinologist, CDE, APD, diabetes centre) needs to be supported and facilitated. Women need clear advice regarding who to contact for advice and support in the early postpartum period and this needs to be established prior to discharge.

A review of all pre-pregnancy medication (aspirin, antihypertensive agents, statins) needs to occur and a plan for recommencement of these agents needs to be developed. Aspirin is safe to use during breastfeeding. ACE inhibitors such as captopril and enalapril have a long track record of use in breastfeeding and can be reinstituted in the early postpartum period.[107] Statins should be recommenced at the completion of breastfeeding.[294]

Lifestyle advice, including healthy eating, regular physical activity, stress management and sleep hygiene, should be provided. Weight management advice should be individualised, goal-driven and BMI-specific.

Contraception and preconception care

A clear plan for contraception needs to be established for women with pre-existing diabetes. Options for contraception should be discussed during pregnancy to allow for discussion such as tubal ligation at the time of a planned or emergency caesarean section. Other contraception plans need to be finalised prior to discharge. Pre-existing diabetes is not a contraindication to any method of contraception.[295]

Women with pre-existing diabetes need to be advised of the importance of preconception care when planning future pregnancies.[296]

MONOGENIC DIABETES AND PREGNANCY

Monogenic diabetes is caused by single gene mutations. The subtypes of monogenic diabetes that have particular relevance in pregnancy include glucokinase maturity-onset diabetes of the young (GCK-MODY) and sulfonylurea-treated monogenic diabetes. These disorders have an autosomal dominant inheritance so theoretically, each fetus has a 50% chance of inheriting the mutation from their parent. Management of monogenic diabetes during pregnancy requires specialist endocrinologist input.

If a woman with gestational diabetes is suspected of having monogenic diabetes, the standard treatment approach for gestational diabetes should be continued until a genetic diagnosis is confirmed.

GCK-MODY

GCK plays an important role in regulating insulin secretion. Women with GCK-MODY have mild, stable fasting hyperglycaemia, typically in the range of 5.5–8.0 mmol/L. Treatment of the mild hyperglycaemia is not usually necessary outside pregnancy and diabetes-related complications are rare. In pregnancy, the management of GCK-MODY differs from the management of other types of diabetes.

Fetal inheritance of the *GCK* mutation determines fetal size. If the fetus inherits the maternal *GCK* mutation, the fetus will have a similarly high glucose set-point as their mother, and will typically have a normal birth weight, so treatment of maternal hyperglycaemia is not required.[297,298] If the fetus does not inherit the maternal *GCK* mutation, the fetus will be exposed to maternal hyperglycaemia which increases the risk of macrosomia, caesarean section and neonatal hypoglycaemia, so treatment of maternal hyperglycaemia is recommended.[297,299]

The difficulty in managing pregnancies for women with GCK-MODY is that the fetal genotype is not usually known during pregnancy, so serial fetal ultrasounds are recommended every two weeks from 26 weeks gestation to assess fetal growth and determine whether to treat maternal hyperglycaemia.[300] If the fetal abdominal circumference is increasing disproportionately above the 75th centile, it is assumed that the fetus does not have the *GCK* mutation,[300] and SMBG and intensive insulin treatment is commenced. It may be difficult to lower maternal blood glucose levels without causing symptoms of hypoglycaemia. For women with ultrasound evidence of accelerating fetal growth, birth at 38 weeks gestation should be considered.[300]

If a pregnant woman with GCK-MODY has chorionic villus sampling or amniocentesis for another reason, the fetal DNA should be tested for the *GCK* mutation.[301] However, these invasive procedures are not indicated for fetal *GCK* genotyping alone because the risk of miscarriage associated with these procedures outweighs the benefit of knowing the fetal genotype.[302]

Postpartum, any insulin treatment should be immediately ceased. A yearly HbA1c is recommended. OGTTs are not recommended. Preconception counselling for any future pregnancies is advisable. Preconception high-dose folic acid can be considered.[303]

Sulfonylurea-treated monogenic diabetes

Sulfonylurea-treated monogenic diabetes includes hepatic nuclear factor 1 alpha – MODY (HNF1A-MODY), hepatic nuclear factor 4 alpha – MODY (HNF4A-MODY) and KCNJ11/ABCC8 permanent neonatal diabetes.

HNF1A-MODY is characterised by normal glucose tolerance *in utero* and at birth, and progressive increase in blood glucose levels over time due to progressive beta cell dysfunction, such that diabetes rarely develops before adolescence.[304] Fetal inheritance of the *HNF1A* mutation does not appear to affect fetal birth weight.[305]

HNF4A-MODY is characterised by increased insulin secretion *in utero* which progresses to reduced insulin secretion and diabetes in adolescence or early adulthood.[304] Fetal inheritance of the *HNF4A* mutation causes up to 800 g weight gain *in utero*, which increases the risk of macrosomia, birth-related injuries, caesarean section and neonatal hypoglycaemia.[306] The neonatal hypoglycaemia can be profound and may persist for months to years. Early birth and extended monitoring for neonatal hypoglycaemia are recommended.[305]

Permanent neonatal diabetes is most commonly caused by activating mutations in the *KCNJ11* or *ABCC8* genes that encode the beta cell K_{ATP} channel, which reduces the ability of adenosine triphosphate to close the K_{ATP} channel, thereby preventing insulin release.[307] Fetal inheritance of either of these gene mutations causes reduced fetal insulin secretion, which reduces fetal growth by ~900 g.[305]

First-line treatment for both HNF1A-MODY and HNF4A-MODY outside pregnancy is a low-dose sulfonylurea. First-line treatment for KCNJ11/ABCC8 permanent neonatal diabetes is a high-dose sulfonylurea, which can close most mutated K_{ATP} channels. While the sulfonylurea, glibenclamide, has been used widely in pregnancy, particularly overseas, it crosses the placenta and stimulates fetal insulin secretion. Current guidelines recommend that women transfer from glibenclamide to insulin either at preconception or during the second trimester.[305] For all types of sulfonylurea-treated monogenic diabetes, serial fetal ultrasounds are recommended every two weeks from 28 weeks gestation, to guide management.[305]

CYSTIC FIBROSIS-RELATED DIABETES AND PREGNANCY

Pregnancies among women with cystic fibrosis are becoming increasingly common. They are complicated by issues of managing the necessary weight gain and nutritional quality, cystic fibrosis-related diabetes (CFRD), lung function and respiratory infections requiring hospital admission. Registry data of pregnancy comparing those complicated by cystic fibrosis with the general population report increased rate of maternal death (adjusted OR (aOR) 76, 95% CI 31.6–183) and pre-existing diabetes (aOR 14, 95% CI 11.8–16.7),[308] as well as preterm delivery (aOR 2.3, 95% CI 1.2–4.4), caesarean section (aOR 2.2, 95% CI 1.1–4.1), low infant birth weight and congenital malformation (aOR 2.6, 95% CI 1.4–5.0).[309] The impact specifically of CFRD is challenging to draw out with current data.

CFRD has unique challenges in diagnosis and management. Hyperglycaemia is linked with poor overall long-term outcomes

and a primary intention of glucose management is prevention of weight loss and reduction in lung function.[310] Current guidelines for CFRD suggest management with insulin should occur.[311]

There is little evidence as to the influence of CFRD on pregnancy outcomes. One recent cohort study of 249 women with 314 infants with 11.6% having CFRD reported women with diabetes had higher rates of assisted conception and caesarean section, with similar rates of preterm birth and similar infant birth weight.[312]

Women with cystic fibrosis who are planning a pregnancy or have had pregnancy confirmed should be screened for CFRD at the earliest opportunity using an OGTT. If nausea and vomiting of pregnancy preclude an OGTT, consider five days of SMBG. Women who do not have CFRD should be screened for gestational diabetes.

Women with cystic fibrosis should be managed during pregnancy in a multidisciplinary team setting with appropriate support and resources to guide a high-risk pregnancy.

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DISCLAIMER

This guideline is intended as a guide and provided for information purposes only. The information has been prepared using a multidisciplinary approach with reference to the best information and evidence available at the time of preparation. No assurance is given that the information is entirely complete, current, or accurate in every respect.

The guideline is not a substitute for clinical judgement, knowledge and expertise, or medical advice. Variation from the guideline, taking into account individual circumstances may be appropriate.

This guideline does not address all elements of standard practice and accepts that individual clinicians are responsible for:

- providing care within the context of locally available resources, expertise, and scope of practice
- supporting consumer rights and informed decision making in partnership with healthcare practitioners including the right to decline intervention or ongoing management
- advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
- ensuring informed consent is obtained prior to delivering care
- meeting all legislative requirements and professional standards
- applying standard precautions, and additional precautions as necessary, when delivering care
- documenting all care in accordance with mandatory and local requirements.

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