Pre-existing Diabetes and Pregnancy

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

**PRECONCEPTION CARE FOR WOMEN WITH DIABETES**

Care by an interdisciplinary diabetes healthcare (DHC) team prior to conception and during pregnancy has been shown to minimize maternal and fetal risks in women with diabetes mellitus (1-5). An early working relationship should be established between the woman and the DHC team (composed of diabetes nurse educators, registered dietitians, obstetricians and endocrinologists/internists) to optimize care and assess whether self-care practices and social supports will be adequate during pregnancy (2-4,6). When such care results in optimal glycemic control, the risks of spontaneous abortion, congenital malformations, pre-eclampsia and progression of retinopathy are reduced (1-11). The incidence of congenital anomalies (the most significant fetal complication) decreases as preconception glycemic control improves (5,8-10,12). Women with type 1 or type 2 diabetes should strive to optimize glycemic control (see “Targets for Glycemic Control,” p. S18, and Table 1) (7,8,13).

While an increasing number of women with type 2 diabetes are being managed in pregnancy clinics, they are often referred postconception, still using oral antihyperglycemic agents and with poor metabolic control (14). Whenever possible, women with type 2 diabetes who are planning pregnancy should be referred to the DHC team. Oral antihyperglycemic agents should be discontinued, and an insulin regimen appropriate for pregnancy should be established.

Women with poorly controlled diabetes have a 2- to 3-fold increased risk of offspring with all congenital anomalies, including a 1% risk for neural tube defects (15). A folic acid supplement of 1 to 4 mg/d day from preconception until 13 weeks’ gestation may reduce this risk (15,16).

**Assessment of complications**

In women with pre-existing diabetes, the risk of progression of any existing complications should be evaluated and discussed, preferably prior to pregnancy, or as early in pregnancy as possible (17-23).

<table>
<thead>
<tr>
<th>Glycemic targets</th>
<th>Preconception and during pregnancy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>A1C (%)</td>
<td>≤7.0 (≤6.0, if possible)</td>
</tr>
<tr>
<td><strong>Once pregnant</strong></td>
<td></td>
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<tr>
<td>FPG (mmol/L)</td>
<td>3.8–5.2</td>
</tr>
<tr>
<td>1-hour postprandial (mmol/L)</td>
<td>5.5–7.7</td>
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<tr>
<td>2-hour postprandial (mmol/L)</td>
<td>5.0–6.6</td>
</tr>
<tr>
<td>Pre-bedtime snack (mmol/L)</td>
<td>4.0–5.9</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>≤6.0 (normal)</td>
</tr>
</tbody>
</table>

*In women with type 1 diabetes, attempts to achieve these glycemic targets all the time may be associated with an unacceptable increase in severe hypoglycemic episodes. Glycemic targets may need to be individualized.

A1C = glycosylated hemoglobin
FPG = fasting plasma glucose
PG = plasma glucose
to minimize this risk. Women with a creatinine clearance of ≤90 mL/minute are at increased risk of long-term worsening of nephropathy; such women should be followed concurrently with a nephrologist whenever possible (21,31). The risk of hypertension is increased in any woman with preconception microalbuminuria or proteinuria (32,33). Significant preconception proteinuria (>300 mg/day) will usually increase during pregnancy despite good BP and glycemic control, but will return to baseline by 6 months postpartum (22). If hypertension is uncontrolled during pregnancy, proteinuria will increase significantly and can be associated with worsening of renal function (21,34,35). Whether from worsening underlying hypertension or superimposed pre-eclampsia, if BP remains uncontrolled, early delivery may need to be considered (21,34).

Angiotensin converting enzyme (ACE) inhibitors have been associated with major problems with fetal development, and angiotensin II receptor antagonists (ARBs), due to similar mechanisms of action, may have similar effects. Women using ACE inhibitors and/or ARBs should be changed to alternative antihypertensive medications known to be safe in pregnancy (e.g. methyl dopa, calcium channel blockers, thiazide diuretics, beta blockers, hydralazine), preferably prior to conception, but at least as soon as pregnancy is diagnosed (36-38).

Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarction in pregnancy is associated with poor maternal and fetal outcomes (20,39). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy.

**MANAGEMENT OF DIABETES DURING PREGNANCY**

**Glycemic control**

Meticulous glycemic control is required for optimal maternal and fetal outcomes. Glycemic targets recommended during pregnancy are outlined in Table 1 (1,40-42). Hyperglycemia has adverse effects on the fetus throughout pregnancy. Hyperglycemia at conception and during the first trimester increases the risk of fetal malformations; later in pregnancy, it increases the risk of macrosomia and metabolic complications at birth (43).

During pregnancy, there is a blunting of normal counter-regulatory hormone responses to hypoglycemia (44,45). This, and the risk of recurrent hypoglycemic episodes as a result of striving to reach glyemic targets, may lead to hypoglycemia unawareness. Women with type 1 diabetes may therefore be at high risk of severe hypoglycemia, especially during the first trimester before relative insulin resistance from placental hormones develops, and care should be taken to counsel them about these risks. There do not appear to be significant adverse neonatal effects of hypoglycemia on the fetus (46). However, in the presence of hypoglycemia unawareness, there may be an increased risk of macrosomia related to erratic glycemic control, as well as an increased risk of maternal seizures (47-49).

**Monitoring**

Self-monitoring of blood glucose (SMBG) is essential during pregnancy (2,50). Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycemic targets (8,13,51). Due to the increased risk of nocturnal hypoglycemia during pregnancy, testing during the night is often necessary (47). Since starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate (50,52).

**Lifestyle interventions**

During pregnancy, women with diabetes should be evaluated and followed by a registered dietitian to ensure that nutritional therapy promotes euglycemia, appropriate weight gain and adequate nutritional intake (53-56). Meal planning should emphasize carbohydrate restriction, especially at breakfast, and distribution over 3 meals and at least 3 snacks (1 of which should be a bedtime snack) (53,55,56). Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis, and are likely inadequate in key nutrients required during pregnancy, such as protein and calcium (52,55-57). Pre-pregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (55).

Physical activity should be encouraged unless obstetrical contraindications exist or glycemic control is worsened by the activity (2,57).

**Pharmacologic interventions**

**Insulin**

Insulin therapy must be individualized and regularly adapted to the changing needs of the pregnancy (2,3,42,58-60). Intensive insulin therapy (multiple daily injections [2,3,42] or continuous subcutaneous insulin infusion [CSII] [2,61]) is recommended to achieve glycemic targets. Women using CSII therapy should be educated about an increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure, since DKA is a potentially fatal complication for the fetus (62).

Insulin analogues (insulin lispro [Humalog®] and insulin aspart [NovoRapid®]) may help achieve postprandial glycemnic targets without causing severe hypoglycemia (63,64). Insulin lispro does not appear to cross the placenta and can be used safely in pregnancy (65,66). Placental transfer of insulin aspart has not yet been assessed, although insulin aspart has been shown to control postprandial plasma glucose levels in pregnancy (67). The extended long-acting insulin analogue glargine (Lantus®) stimulates insulin-like growth factor-1 (IGF-1) receptors significantly more than do other insulins, potentially altering growth, and should not be used in pregnancy until concerns about its safety have been addressed (68,69).
RECOMMENDATIONS

1. Women with pre-existing diabetes should plan their pregnancy, preferably in consultation with an interdisciplinary pregnancy team, to optimize maternal and neonatal outcomes [Grade C, Level 3 (3,5,8)].

2. Women with type 1 diabetes who are planning a pregnancy should strive to attain a preconception glycosylated hemoglobin (A1C) ≤7.0% to decrease the risk of spontaneous abortion, congenital malformations [Grade C, Level 3 (5,10)], pre-eclampsia [Grade C, Level 3 (35)], and the progression of retinopathy [Grade A, Level 1A (11)].

3. Women with type 2 diabetes who are planning pregnancy should be encouraged to attain a preconception A1C ≤7.0% to reduce the risk of congenital anomalies [Grade D, Consensus].

4. Women with type 2 diabetes who are planning pregnancy should discontinue oral antihyperglycemic agents prior to conception and attain glycemic targets using insulin, if needed [Grade D, Consensus].

5. Prior to conception, women with pre-existing diabetes should receive nutrition counselling from a registered dietitian who is part of the DHC team [Grade C, Level 3 (3)] with reassessment as needed during pregnancy and postpartum [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be based on prepravid body mass index [Grade D, Consensus].

6. If planning pregnancy, women using ACE inhibitors or ARBs should change to other antihypertensives that are safe in pregnancy for BP control [Grade D, Consensus].

7. Women with type 1 and type 2 diabetes who are planning a pregnancy should have ophthalmologic assessments prior to conception, during the first trimester, as needed during pregnancy and within the first year postpartum [Grade A, Level 1 for type 1 diabetes (11,25); Grade D, Consensus for type 2 diabetes].

8. Prior to conception, women with diabetes should be screened for nephropathy [Grade A, Level 1 (29)]. If microalbuminuria or overt nephropathy is found, glycemic and BP control should be optimized to minimize maternal and fetal complications and progression of nephropathy [Grade D, Consensus].

9. During pregnancy, women with type 1 or type 2 diabetes should aim to achieve glycemic targets while avoiding significant hypoglycemia [Grade D, Consensus].

10. To attain glycemic targets during pregnancy, women with type 1 diabetes should receive intensive insulin therapy using multiple daily injections or CSII [Grade A, Level 1A (1,59,61)]. Insulin regimens for women with type 2 diabetes should be individualized and adjusted to achieve glycemic targets, with consideration given to intensive insulin regimens, as needed [Grade A, Level 1A (59)].

11. Pregnant women with type 1 or type 2 diabetes should use both preprandial and postprandial SMBG, often ≥4 times per day, in order to make insulin adjustments to attain glycemic targets [Grade C, Level 3 (2)].

12. Ketosis should be avoided during pregnancy [Grade C, Level 3 (52)].

Oral antihyperglycemic agents

Use of glyburide or metformin during pregnancy does not appear to be associated with an increase in congenital anomalies independent of glycemic control. However, the evidence is inadequate to warrant recommendation of their use in pregnancy (70-73).

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S18
Nephropathy, p. S66
Type 1 Diabetes in Children and Adolescents, p. S84

REFERENCES


