Managing diabetes during pregnancy

Guide for family physicians

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ABSTRACT

OBJECTIVE To provide a guide family physicians can use to interpret current evidence on treating women with pregestational and gestational diabetes mellitus (GDM) and to develop a model for managing these patients.

QUALITY OF EVIDENCE A MEDLINE search from January 1980 to December 2002 found randomized controlled trials (RCTs) and descriptive studies that had conflicting results regarding screening recommendations. Studies of intensive insulin therapy were predominantly large RCTs (level I evidence). Glycemic targets and guidelines for monitoring pregnant women are based primarily on consensus statements from large national societies.

MAIN MESSAGE Most pregnant women should be screened for GDM. Good glycemic control during pregnancy reduces congenital anomalies and stillbirths. Women failing to meet glycemic targets should be referred to multidisciplinary teams and considered for insulin therapy. Intensive insulin therapy reduces the risk of macrosomia and might reduce cesarean section rates and other serious outcomes.

CONCLUSION Despite controversy, family physicians can follow a plan for managing diabetic patients during pregnancy that is supported by the best available evidence.

RÉSUMÉ

OBJECTIF Fournir au médecin de famille un guide lui permettant d'interpréter les données actuelles sur le traitement des femmes souffrant de diabète prégestationnel ou gestationnel (DG) et développer un modèle de traitement pour ces patientes.

QUALITÉ DES PREUVES Les essais randomisés (ER) et les études descriptives repérés dans MEDLINE entre janvier 1980 et décembre 2002 contenaient des recommandations contradictoires à propos du dépistage. Les études sur l'insulinothérapie intensive étaient surtout des ER (preuves de niveau I). Les glycémies cibles recommandées et les directives concernant la surveillance des femmes enceintes sont basées principalement sur les déclarations consensuelles de grandes sociétés nationales.

PRINCIPAL MESSAGE La plupart des femmes enceintes devraient subir un test de dépistage du DG. Un bon contrôle de la glycémie durant la grossesse diminue le risque d'anomalies congénitales et de mortinatalité. Quand les glycémies cibles ne sont pas atteintes, les femmes devraient être dirigées vers des équipes multidisciplinaires et une insulinothérapie devrait être envisagée. L'insulinothérapie intensive diminue le risque de macrosomie et pourrait aussi réduire le taux de césariennes et d'autres issues graves.

CONCLUSION En dépit de controverses, le médecin de famille peut traiter les patientes enceintes diabétiques à l'aide d'un plan reposant sur les meilleures données disponibles.

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The percentage of family physicians in Canada who deliver babies has declined to a low of 17.6%; however, 53.9% continue to provide prenatal care to their patients.[1] Despite extensive research on gestational diabetes mellitus (GDM), there is still a lack of consensus regarding the benefit of treatment and even about the importance of GDM as a meaningful diagnosis.

The challenge for family physicians is to determine which investigations and treatments are required for their patients, given current understanding of GDM. Although patients with diabetes during pregnancy are frequently managed in multidisciplinary clinics, such services are not universally available. As a result, many family physicians need to know how to provide comprehensive care for these women, including insulin therapy and intrapartum care.

Quality of evidence

MEDLINE was searched from January 1980 to December 2002 using the MeSH headings diabetes, gestational; pregnancy; dystocia; fetal macrosomia; cesarean section; and prenatal care. Articles were selected based on clinical relevance, level of evidence, and date of publication. In the area of screening for GDM, the literature includes several randomized controlled trials (RCTs) (level I evidence) and descriptive studies (level II evidence) but these studies have conflicting results. Thus, the conclusions in this paper are predominantly based on consensus statements and expert opinion (level III evidence).

Studies used to evaluate outcomes (glycemic control, macrosomia) of intensive insulin therapy are predominantly large RCTs (level I evidence). Other aspects of management, such as glycemic targets, monitoring, and investigations, are based primarily on consensus statements from large organizations, such as the Society of Obstetricians and Gynaecologists of Canada (SOGC), the American College of Obstetricians and Gynecologists (ACOG), the American Diabetes Association (ADA), and the Canadian Diabetes Association (CDA). These organizations have produced guidelines that are evidence based and applicable to family physicians. Opinions differ depending on whether the information is interpreted from an obstetric or endocrinologic perspective and on country of origin.

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Definitions

The term GDM is used if diabetes is diagnosed for the first time during pregnancy. When women with previously diagnosed type 1 or 2 diabetes become pregnant, the term pregestational diabetes mellitus is used. A retrospective analysis of pregnant women in Alberta from 1991 to 1997 revealed a 2.5% prevalence of GDM.[2] Actual regional prevalence depends on racial mix and the screening and confirmatory diagnostic thresholds used.

Etiology and pathogenesis

The etiology of glucose intolerance during pregnancy is largely unknown. Pregnancy is associated with a 50% to 70% reduction in insulin sensitivity.[3] Postprandial insulin secretion increases during normal pregnancies; however, it increases less and has a delayed peak in GDM. Some researchers postulate that there are post–receptor-binding changes in GDM.[2] The prevalence of GDM is higher among people of aboriginal, Hispanic, Asian, and African descent than among white people.[4,5]

Fetal complications

Fetal complications can be divided into those caused by hyperglycemia early in pregnancy (before 12 weeks) and those associated with hyperglycemia at any gestation age. Complications of hyperglycemia include congenital anomalies, miscarriage, and stillbirth. Level I evidence shows that the rate of congenital malformations doubles or triples among diabetic women over the rate in the general population and that the rate is inversely proportional to first-trimester glycemic control.[6-8] Early hyperglycemia is mainly associated with pre-existing diabetes, but it can also occur with GDM.

Hyperglycemia at any stage of gestation can cause macrosomia, shoulder dystocia, fetal birth trauma, and fetal metabolic abnormalities, such as hyperbilirubinemia, hypocalcemia, hypoglycemia, and polycythemia. Infants of women with GDM are at increased risk of cesarean delivery. Studies have shown that children of women with GDM might be at increased risk of adolescent obesity and glucose intolerance.[9,10]

Macrosomia is defined as a fetal weight >4500 g. It should be noted that more than 90% of macrosomic infants are born to nondiabetic women. Factors such as parents' body size and gestational age at delivery have been implicated.[11] Macrosomic infants born to

women with GDM have increased abdominal girth and a higher chance of shoulder dystocia for the same fetal weight.[12]

Shoulder dystocia has a prevalence of 1.5%; evidence suggests that both macrosomia and GDM increase the risk of shoulder dystocia.[12] In subsequent pregnancies, the recurrence rate can be as high as 16.7%.[13] Shoulder dystocia can lead to birth trauma including fractured clavicle and brachial plexus injury.[14]

Maternal complications

Gestational diabetes mellitus has a recurrence rate of up to 35% in subsequent pregnancies.[15] Patients also have at least a 50% increased risk of having type 2 diabetes in the future.[16] Trauma to the perineum, pregnancy-induced hypertension, operative delivery, and an increased likelihood of cesarean section are additional complications.

Screening tests for GDM

The traditional screening test is the 50-g oral glucose challenge at 24 to 28 weeks' gestation. Risk assessment for GDM, however, should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, history of GDM, glucosuria, high-risk ethnic background, or a family history of diabetes) should undergo screening as soon as feasible in the pregnancy.[17,18] If patients do not have GDM at that initial screening, they should be retested between 24 and 28 weeks' gestation. **Table 1** lists tests and diagnostic thresholds. A serum glucose concentration of ≥10.3 mmol/L 1 hour after a 50-g oral glucose load is diagnostic of GDM; a concentration of ≥7.8 mmol/L requires a confirmatory oral glucose tolerance test (OGTT).[19]

A recent Swiss study has suggested adopting a simpler screen using fasting plasma glucose testing. The authors found that using a diagnostic threshold of >4.8 mmol/L produced similar sensitivity and specificity to the 50-g oral glucose challenge.[20] This approach needs further evaluation.

There is controversy over whether screening for GDM should be universal or selective. Both the ADA and the CDA advocate selective screening of women who do not meet all the following five low-risk criteria: younger than 25 years; body mass index <27; not of aboriginal, Hispanic, Asian, or African descent; no family history of diabetes; and no previous child weighing >4 kg[21] at birth (level III evidence). The SOGC's 2002 clinical practice guideline recommends that, until further evidence is available, universal, selective, and no screening are all acceptable.[18]

An analysis of 6032 women in Australia showed that selective screening would miss only 0.6% of women with GDM and would avoid screening 17% of the women.[21] In contrast, a 1999 study found that, if screens were reduced by only 10%, they missed 3% of women with GDM.[22] In 2000, an Irish prospective RCT of universal screening compared with risk-factor–based screening found a prevalence of GDM of 2.7% in the universally screened group, significantly higher than the 1.45% detected in the risk-factor–screened group ($P < .03$). Universal screening also facilitated earlier diagnosis than selective screening (mean gestation 30 ± 2.6 weeks versus 33 ± 3.7 weeks, $P < .05$). A higher rate of spontaneous vaginal delivery at term and lower rates of macrosomia, cesarean section, prematurity, preeclampsia, and admission to neonatal intensive care units were observed in the universally screened, early diagnosed group.[23]

Confirmatory testing for GDM

The traditional confirmatory test as described by O'Sullivan and adopted by the National Diabetes Data Group has been the 3-hour, 100-g OGTT.[24] In 1982, Carpenter and Coustan[25] modified the diagnostic thresholds. Their modification was adopted by the ADA, and lower diagnostic thresholds were recommended.[25] Finally, in 1998, a new 75-g, 2-hour OGTT, which would take less time, produce less nausea, and cost less,[26] was recommended for use in the 1998 CDA guidelines and was adopted by the ACOG in 2000[27] (level III evidence). Two abnormal values indicate GDM; one abnormal value suggests impaired glucose tolerance during pregnancy (**Table 1**).

Management of established GDM

An overview of management is given in **Table 2**.[18] Women can be referred to diabetes education centres, if they are available, for counseling on nutrition and instruction on how to monitor their blood glucose levels. Restricting the diet should be tried for 1 to 2 weeks with a goal of achieving a fasting plasma glucose level of <5.3 mmol/L, a 1-hour postprandial level of <7.8 mmol/L, and a 2-hour postprandial level of <6.7 mmol/L.[19,28] Regular moderate exercise, such as postprandial walks, can sometimes improve glycemic control without use of insulin.[29] Self-monitoring of blood glucose levels (fasting and 1 or 2 hours after meals) is recommended.

Traditionally, oral antihyperglycemic agents have been contraindicated throughout pregnancy. A recent

Table 1. Summary of screening and confirmatory tests for GDM

EARLY 50-G CHALLENGE
For high-risk women (obesity, personal or family history of diabetes, glucosuria, high-risk ethnic background)
24- to 28-WEEK 50-G ORAL GLUCOSE CHALLENGE
The 2002 SOGC guidelines consider universal, selective, or no screening acceptable until further evidence is available.
Selective screening: Screen all women unless they meet all the following five low-risk criteria. • Patient is younger than 25 years • Body mass index is <27 • Patient is not of aboriginal, Hispanic, Asian, or African descent • Patient has no family history of diabetes • Patient has had no previous infant >4 kg at birth
No fasting is required. Patient receives a 50-g glucose load orally and returns in 1 hour: a 1-hour plasma glucose level of ≥7.8 mmol/L is abnormal and requires a confirmatory test; 1-hour level of ≥10.3 mmol/L is diagnostic of GDM.
CONFIRMATORY 75-G, 2-HOUR ORAL GLUCOSE TOLERANCE TEST
Fasting is required. Patient receives a 75-g glucose load, and levels are tested immediately and at 1 and 2 hours after a meal. Two of three abnormal results (fasting plasma glucose level of >5.3 mmol/L; 1-hour postprandial level of >10.6 mmol/L; 2-hour postprandial level of >8.9 mmol/L) confirm GDM; one of three confirms impaired glucose tolerance during pregnancy.

GDM—gestational diabetes mellitus, SOGC—Society of Obstetricians and Gynaecologists of Canada.

Table 2. Summary of management of confirmed gestational diabetes mellitus

Refer for nutrition support and initiation of blood-glucose self-monitoring.
Attempt a trial of diet therapy for 1 to 2 weeks.
Aim for a fasting glucose level of <5.3 mmol/L, a 1-hour postprandial level of <7.8 mmol/L, and a 2-hour postprandial level of <6.7 mmol/L.
Consider referral or initiate insulin therapy if these target levels are not achieved.
• A typical starting dose of insulin is 4 U of short-acting (regular) or rapid-acting (lispro) insulin before meals and 4 U of intermediate-acting (NPH) insulin at bedtime. • Total daily doses are approximately 0.6 U/kg before 6 weeks' gestation, 0.7 U/kg from 6 to 18 weeks, 0.8 U/kg from 18 to 26 weeks, 0.9 U/kg from 26 to 30 weeks, and 1.0 U/kg from 36 to 40 weeks.
Intrapartum care • Check glucose level every 1 to 2 hours. • Give an intravenous insulin infusion and dextrose infusions if glucose level is >6.5 mmol/L.
Early induction of labour at 38 to 40 weeks and prophylactic cesarean section for macrosomia are controversial.
Postpartum care • Do a 75-g, 2-hour oral glucose tolerance test 6 weeks to 6 months after birth. • Do an annual fasting glucose test to screen for type 2 diabetes (abnormal level is >7.0 mmol/L[18]). • Recommend lifestyle modification.

study comparing glyburide with insulin in women diagnosed with GDM, however, showed similar reductions in macrosomia and no adverse effects.[30] Risk of teratogenicity is unknown because all women commenced therapy after 11 weeks' gestation. Use of glyburide to manage GDM requires further evaluation before it can be recommended.

Initiation of insulin therapy and referral to a GDM clinic is recommended if glucose readings fail to meet target levels. Family physicians practising in rural and remote areas might not have access to specialty services and will need to be proficient in managing insulin therapy during pregnancy. Results of patient self-monitoring should guide dosage and timing of the insulin regimen.

Level I evidence indicates that four-injection insulin regimens with short- (regular) or rapid-acting (lispro) insulin before meals and intermediate-acting (NPH) insulin at bedtime result in better glycemic control and perinatal outcomes.[31] Although lispro insulin is not formally approved for use during pregnancy, it has been used safely and does not appear to cross the placenta. A small case-control study (level II evidence) comparing regular insulin with lispro insulin showed a higher incidence of unusual pregnancy course in the lispro group, but the result was not statistically significant.[32] Further research is needed in this area.

A typical starting dose is 4 U of short- or rapid-acting insulin before meals and 4 U of NPH at bedtime. Patients should be taught how to adjust doses based on results of blood-glucose monitoring. Physicians can estimate typical insulin requirements based on mother's weight and stage of gestation along with estimated total daily requirements as shown in **Table 2**.[18]

The 2001 ACOG guidelines advise against use of routine ultrasound screening to detect macrosomia because clinical evaluation is considered equally effective. Ultrasound can be used to estimate fetal weight and amniotic fluid volume if a patient is clinically large for dates. Biophysical assessments should be done for the usual obstetric indications.

Active induction of labour at 38 to 40 weeks is controversial. The single RCT of women with GDM or pre-existing diabetes taking insulin showed a reduction in fetal macrosomia but not cesarean section rates.[33] Further study is needed to determine which diabetic women would benefit from early delivery. In labour, glucose should be checked every 1 to 2 hours, and intravenous insulin and dextrose infusions started if plasma glucose exceeds 6.5 mmol/L.[34] Current ACOG recommendations suggest that prophylactic cesarean section be considered for all women whose fetuses are estimated to weigh >5000 g and for all women with GDM whose fetuses are thought to weigh >4500 g, although this recommendation is not universally accepted.[12]

Improving outcomes

Langer et al[35] compared 1316 patients receiving conventional therapy with 1145 patients receiving intensive therapy for GDM and found that intensive therapy reduced the incidence of macrosomia, shoulder dystocia, cesarean section, and stillbirth, and shortened infants' length of stay in neonatal intensive care.[35] The Toronto Tri-Hospital Gestational Diabetes Project assessed maternal and fetal outcomes in 3836 women, 145 of whom had GDM, and showed a clear relationship between glycemic control and macrosomia.[36] Even when intensive therapy is initiated late in pregnancy, there is evidence that it can reduce the weight of already large fetuses.[37,38] Overaggressive treatment, however, can result in fetal weight loss and small for gestational age infants.[38]

There are conflicting results on whether intensive treatment lowers cesarean section rates. The study by Langer et al demonstrated a reduction in cesarean-section rates (rates were 15% in the intensive care arm and 21.5% in the conventional arm), whereas the Toronto tri-hospital study showed no reduction in the rate (33%) despite a significant reduction in macrosomia. It appeared that "labeling" patients with GDM increased the risk of cesarean section in this latter study.[35]

Diagnosing GDM could lead to better postpartum maternal outcomes, better preventive care in the future, and prevention of type 2 diabetes. Women with a history of GDM should use effective birth control methods to ensure they have the opportunity to enter any subsequent pregnancies with optimal glycemic control. The 2002 SOGC and 1998 CDA guidelines recommend a 75-g, 2-hour OGTT 6 weeks to 6 months after birth.[18,19] Those with negative results should have annual fasting blood-glucose screening for type 2 diabetes.

Pregestational diabetes

Family physicians should begin to counsel women with diabetes as early as adolescence regarding the need to plan pregnancy (**Table 3**). Women with pre-existing type 1 or type 2 diabetes should be seen before they conceive to optimize glycemic control. The incidence of type 2 diabetes is rising in Canada and affecting more women in their reproductive years, so family physicians must be vigilant in screening high-risk women before pregnancy.

Table 3. Management of pre-existing diabetes during pregnancy

Be aware of the added risk of congenital anomalies, stillbirth, and miscarriage
Screen high-risk women for diabetes before pregnancy
Offer preconception counseling
Convert from oral antihyperglycemic medication to insulin therapy
Goals of insulin therapy and intrapartum care are similar to those for women with gestational diabetes mellitus (**Table 2**[18])
Early induction of labour at 38 to 40 weeks is controversial

Potential contraindications to pregnancy for diabetic women include coronary artery disease, untreated proliferative retinopathy, serious renal insufficiency or proteinuria, and severe gastroenteropathy.

In addition to the risks of women with GDM, women with pregestational diabetes are at increased risk of pregnancy-induced hypertension and pyelonephritis. Complications caused by first-trimester hyperglycemia, such as congenital anomalies, miscarriage, and stillbirth, are more prevalent among these women. Diabetic retinal disease can progress during pregnancy; increased ophthalmologic surveillance is required during pregnancy and the first year postpartum. Renal disease can worsen in pregnancy; however, renal function tends to revert to prepregnancy levels after delivery.[7]

Use of insulin for women with pre-existing diabetes follows goals and methods similar to those outlined for women with GDM. Early induction of labour and delivery for women with pregestational diabetes has been shown to lessen risk of stillbirth but is still controversial.[39]

Outcomes of patients with pre-existing diabetes

Improved glycemic control during the first trimester has been shown to lower rates of fetal malformations.[6]

The Diabetes Control and Complications Trial demonstrated that intensive therapy before pregnancy to normalize glycemic control reduced the incidence of congenital anomalies compared with conventional therapy.[40] The beneficial effect of good glycemic control on reducing macrosomia is similar to that seen in women with GDM.

Conclusion

For women with GDM, level I evidence shows that improved glycemic control can reduce secondary outcome measures, such as macrosomia, although its effect on primary end points, such as serious maternal and fetal complications and cesarean section rates, requires further study. Current guidelines advise physicians to selectively screen all pregnant women who do not meet all five low-risk criteria (level III evidence).

Women with pre-existing diabetes should be diagnosed and counseled before pregnancy and converted from treatment with oral agents to insulin therapy. Level I evidence shows that congenital anomalies can be reduced with effective first-trimester glycemic control.

Women with GDM should commence nutritional therapy and monitor their own blood glucose. Those not meeting target goals should be started on insulin or referred to a multidisciplinary team if one is available. All women with GDM should be screened and counseled about the risk of progressing to type 2 diabetes in the future.

Competing interests

None declared

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Editor's key points

- Pregnant women can have both pre-existing diabetes (types 1 and 2) and, more commonly, gestational diabetes mellitus (GDM). Incidence is about 2% to 3% in the general population, but higher among aboriginal, Hispanic, Asian, and African people.
- Fetal complications include increased risk of congenital abnormalities, miscarriages, and stillbirths, as well as macrosomia, birth trauma, metabolic abnormalities, and cesarean section.
- Maternal complications include a 35% chance of recurrent GDM, a 50% chance of developing type 2 diabetes later in life, and the effects of macrosomia: birth trauma, operative delivery, and cesarean section.
- Despite controversy, universal screening for GDM appears to lead to reduced rates of macrosomia and, according to some studies, cesarean section.
- Managing diabetes during pregnancy includes excellent glucose control with short- and medium-acting insulins, care with exercise and diet, and careful monitoring during labour. Referral to a diabetes education centre facilitates this intensive and complex intervention. Induction at 38 to 40 weeks is controversial.

Points de repère du rédacteur

- Les femmes enceintes peuvent avoir un diabète préexistant (de type 1 ou 2) ou, plus souvent, un diabète de grossesse (DG). L'incidence est d'environ 2 à 3% dans la population générale, mais elle est plus élevée chez les autochtones, les hispaniques, les asiatiques et les africains.
- Les complications pour le fœtus incluent un risque accru de malformations congénitales, d'avortement, mais aussi de macrosomie, de traumatisme à l'accouchement, d'anomalie métabolique et de césarienne.
- Les complications maternelles incluent une possibilité de 35% de récidive du DG, de 50% de développer ultérieurement un diabète de type 2 et les effets de la macrosomie fœtale: traumatisme à l'accouchement, délivrance chirurgicale et césarienne.
- Quoique controversé, le dépistage systématique du DG semble favoriser un taux plus faible de macrosomie et, d'après certaines études, de césariennes.
- Le traitement du diabète durant la grossesse comprend un excellent contrôle de la glycémie à l'aide d'insulines à courte et à moyenne action, une attention à l'exercice et au régime, et une surveillance attentive durant le travail. L'orientation vers un centre d'information sur le diabète facilite cette prise en charge intensive et complexe. Le déclenchement du travail à 38-40 semaines est controversé.

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