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# DIABETES CANADA



### 2018 Clinical Practice Guidelines

## Diabetes and Pregnancy

### Diabetes Canada Clinical Practice Guidelines Expert Committee

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#### KEY MESSAGES

##### Pre-Existing Diabetes

###### Preconception and During Pregnancy

- All women with pre-existing type 1 or type 2 diabetes should receive preconception care to optimize glycemic control, assess for complications, review medications and begin folic acid supplementation.
- Effective contraception should be provided until the woman is ready for pregnancy.
- Care by an interprofessional diabetes health-care team composed of a diabetes nurse educator, dietitian, obstetrician and endocrinologist/internist with expertise in diabetes, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 and type 2 diabetes.
- Women should aim for a glycosylated hemoglobin (A1C) of  $\leq 7.0\%$  (ideally  $\leq 6.5\%$  if possible) when planning pregnancy, or  $\leq 6.5\%$  (ideally  $\leq 6.1\%$  if possible) during pregnancy.
- Women should consider the use of the continuous glucose monitor during pregnancy to improve glycemic control and neonatal outcomes.

###### Postpartum

- All women should be given information regarding the benefits of breastfeeding, effective birth control and the importance of planning another pregnancy.

##### Gestational Diabetes Mellitus

###### During Pregnancy

- Untreated gestational diabetes leads to increased maternal and perinatal morbidity. Treatment reduces these adverse pregnancy outcomes.
- In women at high risk of undiagnosed type 2 diabetes, early screening (<20 weeks) with an A1C should be done to identify women with potentially overt diabetes to guide fetal surveillance and early maternal treatment, including self-monitoring of blood glucose, interventions that promote healthy behaviours and healthy weight gain.
- The diagnostic criteria for gestational diabetes (GDM) remain controversial; however, these guidelines identify a “preferred” and an “alternate” screening approach. The preferred approach is an initial 50 g glucose challenge test, followed, if abnormal, with a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting  $\geq 5.3$  mmol/L, 1 hour  $\geq 10.6$  mmol/L, 2 hours  $\geq 9.0$  mmol/L). The alternate approach is a 1-step approach of a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting  $\geq 5.1$  mmol/L, 1 hour  $\geq 10.0$  mmol/L, 2 hours  $\geq 8.5$  mmol/L).
- First-line therapy consists of diet and physical activity. If glycemic targets are not met, insulin or metformin can then be used.

###### Postpartum

- Women with gestational diabetes should be encouraged to breastfeed immediately after birth and for a minimum of 4 months to prevent neonatal hypoglycemia, childhood obesity, and diabetes for both the mother and child.

- Women should be screened for diabetes between 6 weeks and 6 months postpartum, with a 75 g oral glucose tolerance test and be given ongoing education regarding strategies to reduce the risk of developing type 2 diabetes.

#### KEY MESSAGES FOR WOMEN WITH DIABETES WHO ARE PREGNANT OR PLANNING A PREGNANCY

##### Pre-Existing Diabetes

- The key to a healthy pregnancy for a woman with diabetes is keeping blood glucose levels in the target range—both before she is pregnant and during her pregnancy.
- Poorly controlled diabetes in a pregnant woman with type 1 or type 2 diabetes increases her risk of miscarriage, having a baby born with a malformation and having a stillborn.
- Women with type 1 or type 2 diabetes should discuss pregnancy plans with their diabetes health-care team to:
  - Review blood glucose targets
  - Assess general health and status of any diabetes-related complications
  - Aim for optimal weight and, if overweight, start weight loss before pregnancy with healthy eating
  - Review medications
  - Start folic acid supplementation (1.0 mg daily)
  - Ensure appropriate vaccinations have occurred.

##### Gestational Diabetes

- Between 3% to 20% of pregnant women develop gestational diabetes, depending on their risk factors
- Risk Factors include:
  - Being:
    - 35 years of age or older
    - from a high-risk group (African, Arab, Asian, Hispanic, Indigenous, or South Asian)
  - Using:
    - Corticosteroid medication
  - Having:
    - Obesity (a body mass index greater than or equal to 30 kg/m<sup>2</sup>)
    - Prediabetes
    - Gestational diabetes in a previous pregnancy
    - Given birth to a baby that weighed more than 4 kg
    - A parent, brother or sister with type 2 diabetes
    - Polycystic ovary syndrome or acanthosis nigricans (darkened patches of skin).
- All pregnant women without known pre-existing diabetes should be screened for gestational diabetes between 24 to 28 weeks of pregnancy
- If you were diagnosed with gestational diabetes during your pregnancy, it is important to:
  - Breastfeed immediately after birth and for a minimum of 4 months in order to prevent hypoglycemia in your newborn, obesity in childhood, and diabetes for both you and your child

Conflict of interest statements can be found on page S274.

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- Reduce your weight, targeting a normal body mass index in order to reduce your risk of gestational diabetes in the next pregnancy and developing type 2 diabetes
- Be screened for type 2 diabetes after your pregnancy:
  - within 6 weeks to 6 months of giving birth
  - before planning another pregnancy
  - every 3 years (or more often depending on your risk factors).

## Introduction

This chapter discusses pregnancy in both pre-existing diabetes (type 1 and type 2 diabetes diagnosed prior to pregnancy), overt diabetes diagnosed early in pregnancy and gestational diabetes (GDM or glucose intolerance first recognized in pregnancy). Some management principles are common to all types of diabetes.

## Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy

The term “pre-existing diabetes in pregnancy” refers to diabetes diagnosed before pregnancy. The prevalence of pre-existing diabetes has increased in the past decade (1) primarily as a result of the increase in type 2 diabetes (2). Studies of women with pre-existing diabetes show higher rates of complications compared to the general population, including perinatal mortality, congenital malformations, hypertension, preterm delivery, large-for-gestational-age (LGA) infants, caesarean delivery and other neonatal morbidities (1,3–5).

### Preconception care

Preconception care improves maternal and fetal outcomes in women with pre-existing diabetes. This involves educating women about the importance of optimal glycemic control prior to pregnancy, discontinuing potentially harmful medications and achieving a health body weight. Hyperglycemia is teratogenic and if glycemic control is poor in the first few weeks of conception, the risk of congenital anomalies is increased. Women with diabetes should be helped to achieve optimal glycemic control preconception as this is associated with a reduction of congenital anomalies by 70% (6–9). However, even women who achieve a glycated hemoglobin (A1C)  $\leq 7.0\%$  preconception have an increased risk of complications compared to the general population. This may be caused, in part, by maternal obesity, especially in women with type 2 diabetes (10–13).

Preconception care should also include advice regarding folic acid supplementation. In 1 case-control study in the United States, women with diabetes who did not take folic acid containing vitamins were at a 3-fold higher rate of congenital anomalies compared to women with diabetes who did (14). There are no intervention trials to support folic acid doses greater than 1 mg for women with diabetes. Obesity, which is more common in women with type 2 diabetes, is associated with lower serum folate levels for the same intake, lower intake of folate rich foods and increased risk of neural tube defects independent of glycemic control (15–17). A higher dose of folic acid may be considered in women with obesity, although there is no clinical evidence that this higher dose reduces congenital anomalies. Measurement of red blood cell (RBC) folate may also be useful to guide adjustment of folic acid dosage in women with obesity or women who have had bariatric surgery.

A multifaceted preconception program that included patient information specialized clinics, electronic health records, online

resources and local guidelines, increased folic acid use by 26%, improved glycemic control and decreased the risk of congenital malformations from 5% to 1.8% (9). Although receiving care at an interprofessional preconception clinic has been shown to be associated with improved pregnancy outcomes, approximately 50% of women do not receive such care (18,19). The following factors are associated with women with pre-existing diabetes being less likely to receive preconception care: overweight; younger age; smoking history; lower socioeconomic status; lower health literacy and/or poor relationship with their health-care provider (7,20–22). Additionally, some studies have shown that women with type 2 diabetes are less likely to receive preconception care compared to women with type 1 diabetes (19,23).

### Assessment and management of complications

**Retinopathy.** Women with type 1 (24,25) and type 2 diabetes (26) should ideally have ophthalmological assessments before conception, during the first trimester, as needed during pregnancy, and within the first year postpartum (27,28). The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and progression may occur for up to 1 year postpartum (25,27). Additional risk factors for retinopathy progression include: chronic and pregnancy-induced hypertension, preeclampsia, more severe pre-existing diabetic retinopathy (24,29–31), and a greater decrease in A1C between the first and third trimester of pregnancy (32). Closer retinal surveillance is recommended for women with more severe pre-existing retinopathy, those with poor glycemic control or women with greater reductions in A1C during pregnancy (27,33). Laser photocoagulation for severe nonproliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy (34); if not performed prior to pregnancy, it is still considered safe to receive during pregnancy.

There is insufficient evidence to confirm safety or harm from the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections for diabetic macular edema or proliferative diabetic retinopathy during pregnancy (35). Potential side effects include hypertension, proteinuria, defective embryogenesis and fetal loss (36,37). It is not known if these medications cross the placenta or if they are secreted in breastmilk. Gestational timing of exposure needs to be considered in situations where potential benefit to the woman justifies the potential fetal risk. Until more safety information is available, we support the recommendations of others: a) to ensure a negative pregnancy test and contraception use during intravitreal anti-VEGF therapy, and b) to consider delaying conception for 3 months after the last intravitreal injection (38,39). Intravitreal anti-VEGF therapy in pregnancy should be avoided especially in the first trimester. Second and third trimester use should occur only if absolutely necessary after discussion of the potential risks and benefits. Diabetic macular edema may often regress after pregnancy without specific therapy. Data are lacking to guide treatment recommendations for diabetic macular edema during pregnancy.

One retrospective study of 193 women with type 1 diabetes, 63 with an active second-stage delivery (3 with proliferative diabetic retinopathy) found no impact of expulsive efforts in the active second stage of labour on retinopathy progression in women with stable retinopathy (40). Data from the Diabetes Control and Complications Trial (DCCT) has suggested that pregnancy does not affect the long-term outcome of mild-to-moderate retinopathy (27). More recently, preeclampsia and pregnancy-induced hypertension in women with type 1 diabetes has been shown to be associated with an increased risk of severe diabetic retinopathy later in life (41).

**Hypertension.** Women may have pre-existing hypertension or develop hypertension/preeclampsia during pregnancy. Women with type 1 and type 2 diabetes have a 40% to 45% incidence of hypertension complicating pregnancy (31). A systematic review of risk factors for preeclampsia demonstrated a 3.7 risk (relative risk [RR] 3.1 to 4.3) for the development of preeclampsia in women with pre-existing diabetes (42). Type 1 diabetes is more often associated with preeclampsia whereas type 2 diabetes is more often associated with chronic hypertension. In the general population, the risk of preeclampsia is highest in nulliparous women and lower in multiparous women. However, in women with type 1 diabetes, the risk of preeclampsia is similar in nulliparous and multiparous women (43). Other risk factors for hypertension, such as poor glycemic control in early pregnancy, are potentially modifiable. Some studies (44,45), but not all (46), have found that increased urinary protein excretion in early pregnancy is associated with an increased risk of hypertension.

Any type and degree of hypertension is associated with adverse outcomes. A large randomized controlled trial in pregnant women with nonproteinuric pre-existing or gestational hypertension (that included women with GDM) showed that targeting a diastolic blood pressure (BP) of 85 mmHg vs. 100 mmHg reduced neonatal respiratory complications, rates of severe maternal hypertension (i.e. >160/110 mmHg) and did not increase the incidence of small for gestational age (SGA) (47). Finally, a number of antihypertensive medications are safe and effective in pregnancy, including calcium channel blockers, labetalol and methyldopa.

Although there are no intervention trials for ASA prophylaxis for the prevention of preeclampsia specific to women with pre-existing diabetes, ASA prophylaxis started between 12 to 16 weeks of gestation is likely to be beneficial, given the evidence of benefit in other high-risk populations, (48).

Based on a meta-analysis and systematic review, calcium supplementation (of at least 1,000 mg/day) in high-risk populations, especially in those with low dietary calcium intake, may reduce preeclampsia rates by up to 40%, although evidence is limited (49).

**Chronic kidney disease.** Prior to conception, women should be screened for chronic kidney disease (CKD). Albuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (50–55). An estimated glomerular filtration rate (eGFR) should be used prior to pregnancy to determine risk of adverse outcomes. In 1 small study, women with poorer mean preconception creatinine clearance (CrCl) of 61 mL/min/1.73 m<sup>2</sup> (range 37 to 73) showed a 36% lower creatinine clearance (CrCl) 3 months postpartum, whereas in women with a mean preconception CrCl of 80 mL/min/1.73 m<sup>2</sup> (range 70 to 93), no deterioration in renal function was observed (56). However, inadequate BP control in pregnancy may account for this observed difference in this study.

During pregnancy, serum creatinine (not eGFR) should be used, as eGFR will underestimate GFR in pregnancy (57,58). Proteinuria increases during pregnancy, but, in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as BP and blood glucose (BG) are well controlled (50–53,56,59,60). One small series found that women with serum creatinine >124 µmol/L at pregnancy onset had a greater than 40% chance of accelerated progression of diabetic nephropathy as a result of pregnancy (61). First trimester BP elevations and protein excretion are associated with delivery before 37 weeks, usually due to preeclampsia (62). Small cohort studies have suggested that antihypertensive therapy for BP >135/85 mmHg in women with diabetes and albuminuria during pregnancy may reduce the risk of preeclampsia and preterm delivery without adversely impacting other pregnancy outcomes (60,63,64).

There is conflicting information on whether first-trimester exposure to angiotensin-converting enzyme (ACE) inhibitors and

angiotensin receptor blockers (ARBs) is associated with an increased risk of congenital malformations (65,66). A meta-analysis, limited by small study size (n=786), demonstrated a significant risk ratio (relative risk [RR] 1.78, 95% confidence interval [CI] 1.07–2.94) of increased anomalies in infants exposed to first-trimester ACE inhibitors and ARBs compared to the general population (67). However, when the group exposed to ACE inhibitor/ARB was compared to a group of women who were exposed to other antihypertensives used in pregnancies, they were both associated with malformations with no statistically significant difference. Fetal exposure in the second and third trimesters is clearly associated with a fetal renin angiotensin aldosterone system (RAAS) blockade syndrome, which includes renal failure, oligohydramnios, hypotension, intrauterine growth restriction and death (68). The decision to discontinue an ACE inhibitor or ARB prior to pregnancy should be discussed with the woman and may depend on the indication for use and availability of an effective alternative medication. However, once a woman is pregnant, ACE inhibitors and ARBs should be discontinued.

**Painful peripheral neuropathy management.** As with all medications used in pregnancy, benefits need to be weighed against risk. In the relatively small number of reported pregnancies in which women were exposed to first trimester gabapentin monotherapy (n=294), no increased risk of congenital malformations was found (69,70). However, neonatal gabapentin withdrawal has been described with maternal oral gabapentin 600 mg 3 times daily throughout pregnancy (69).

**Cardiovascular disease.** Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarct (MI) in pregnancy is associated with poor maternal and fetal outcomes (71,72). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy. As well, statins and/or fibrates should be discontinued prior to pregnancy as they are not recommended for use during pregnancy.

## Management

Care by an interprofessional diabetes health-care (DHC) team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists/internists with expertise in diabetes, both preconception and during pregnancy, has been shown to minimize maternal and fetal risks in women with diabetes (73–76) (see Organization of Care chapter, p. S27). An early working relationship should be established between the woman and the DHC team to optimize care, facilitate the planning of pregnancy, ensure adequate self-care practices and to discuss the need for social support during pregnancy.

### Targets of glycemic control

Elevated BG levels have adverse effects on the fetus throughout pregnancy. At conception and during the first trimester, hyperglycemia increases the risk of fetal malformations and intrauterine fetal demise (77). Later in pregnancy, it increases the risk of macrosomia, fetal and infant death (77) as well as metabolic and obstetrical complications at birth (78,79). As a result, meticulous glycemic control throughout pregnancy is required for optimal maternal and fetal outcomes.

An important first step in achieving optimal glycemic control is to set target BG levels (74,79). However, optimal targets for fasting, preprandial and postprandial BG levels in women with pre-existing diabetes have not been examined in randomized controlled trials; and a variety of BG targets are used in clinical practice.

Older studies confirm that the lower the mean BG, the better the outcome, with some suggesting a target mean BG <6.7 mmol/L and, others, a mean <6.9 mmol/L. A fasting BG (FBG) target <5.9 mmol/L is still associated with a 29% macrosomia rate (74,80,81). Recent retrospective data demonstrated that a mean A1C  $\geq$ 6.0% in pregnant women with type 2 diabetes was associated with increased risk of neonatal complications (preterm birth, neonatal intensive care unit [NICU] admission, neonatal hypoglycemia and jaundice) compared to women with an A1C <6.0% (82). In women with type 1 diabetes and good glycemic control during pregnancy with an A1C of 4.5% to 7.0%, there is still a linear relationship between third trimester A1C and risk of macrosomia (83).

In the absence of comparative studies of specific BG targets for women with pre-existing diabetes, use of the mean BG plus 2 standard deviation (SD) of pregnant women without diabetes appears to be appropriate. This translates into BG targets of fasting and preprandial <5.3 mmol/L; 1 hour postprandial <7.5 mmol/L and 2 hours postprandial <6.7 mmol/L (84). Studies in gestational (GDM) indicate a 1 hour postprandial target <7.8 mmol/L is associated with good pregnancy outcomes (85–89); thus, harmonizing the 1 hour target <7.8 mmol/L is reasonable.

An A1C <6.5% should be strived for in all women with pre-existing diabetes during pregnancy; however, given the slightly increased risk of stillbirth in women with an A1C >6.1% (77), ideally a target A1C  $\leq$ 6.1% should be sought by the third trimester of pregnancy, if it can be achieved safely.

#### Definition of hypoglycemia in pregnancy

Hypoglycemia is traditionally defined as a BG <4.0 mmol/L; however, as demonstrated by a group who compared continuous glucose monitoring (CGM) with glucose levels from nonpregnant and pregnant women, BG levels are lower during pregnancy by a factor of 20% (90). By consensus, the American Diabetes Association and Endocrine Society Working Group defined hypoglycemia during pregnancy as a level <3.3 mmol/L (91). However, since the hypoglycemia level is often individualized to each person with diabetes, with consideration of symptoms, therapy, medical condition and associated risk; the official lower limit of BG level during pregnancy is difficult to clearly establish. Overall, it is understood that pregnant women have lower BG values that can be judged as normal even if below the traditional level of 4.0 mmol/L. However, women receiving insulin therapy should maintain BG values >3.7 mmol/L to avoid repeated hypoglycemia.

Hypoglycemia is generally considered to be without risk for the fetus, as demonstrated in women with pre-existing diabetes (79,92–94), as long as it is not sustained and maternal loss of consciousness, convulsion, and fall or trauma is avoided during the episode (91). However, repeated hypoglycemia and associated loss of glycemic control have been associated with macrosomia (95).

The limiting factor when targeting euglycemia in women with pre-existing diabetes is the increased risk of hypoglycemia during pregnancy, particularly in the first trimester (96–100), for both type 1 and type 2 diabetes (79). Up to 71% of pregnant women with pre-existing diabetes may experience severe hypoglycemia, with the major predictors being a history of severe hypoglycemia in the 1-year period preceding pregnancy, diabetes duration >10 years and hypoglycemic unawareness (96–100). The latter may relate, in part, to the loss of counterregulatory hormones reported in women with pre-existing diabetes during pregnancy, particularly growth hormone and epinephrine (95,101–103). This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control preconception and by the use of analogue insulins (100,104,105) (see Hypoglycemia chapter, p. S104). Health-care providers should

ensure that pregnant women with diabetes: a) have a glucagon kit; b) are advised regarding effective interventions if a severe hypoglycemic event occurs; and c) are encouraged to inform close relatives and co-workers of this increased risk, especially in the first and early second trimester.

#### Monitoring

Frequent self-monitoring of blood glucose (SMBG) in pregnant women with type 1 diabetes is essential during pregnancy in order to achieve the glycemic control associated with better outcomes (80). Preprandial testing (to guide mealtime insulin dose adjustment) and postprandial testing (to meet postprandial targets) are associated with less macrosomia in observational studies and reduced preeclampsia (81,106,107). Due to the increased risk of nocturnal hypoglycemia with any intensive insulin therapy, SMBG during the night is often necessary in pregnant women with diabetes receiving insulin (108). SMBG 4 to 7 times per day is also recommended for pregnant women with type 2 diabetes (i.e. fasting, preprandial and 1 or 2 hours postprandially) to achieve good glycemic control.

CGM may help identify periods of hyper- or hypoglycemia (109,110) and can confirm glycemic variability, especially in women with type 1 diabetes (111). Evidence for the use of CGM to improve glycemic control, and maternal and fetal outcomes is conflicting. One study using blinded, intermittent CGM with review of results with a clinician showed that CGM improved A1C and rates of macrosomia compared to standard care (109). However, a study of intermittent real-time CGM did not demonstrate benefit (112). Finally, a study examining CGM use to prevent episodes of severe hypoglycemia early in pregnancy in women with a history of episodes in the year prior to pregnancy did not demonstrate benefit. The Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy (CONCEPTT) trial randomized 325 women (215 pregnant and 110 planning pregnancy) to capillary blood glucose (CBG) monitoring with CGM or without. Pregnant CGM users spent more time in target (68% vs. 61%,  $p=0.0034$ ) and less time hyperglycemic (27% vs. 32%,  $p=0.0279$ ) than did pregnant control participants, with comparable severe hypoglycemic episodes and time spent hypoglycemic. Neonatal health outcomes were significantly improved, with lower incidence of LGA (OR 0.51, 95% CI 0.28–0.90,  $p=0.021$ ), fewer NICU admissions lasting more than 24 h (OR 0.48, 95% CI 0.26–0.86,  $p=0.0157$ ), and fewer incidences of neonatal hypoglycemia (OR 0.45; 95% CI 0.22–0.89,  $p=0.025$ ). No benefit was observed for women planning a pregnancy (113). Whether closed-loop systems will be beneficial for use in pregnancy remains to be seen (114). One study of pregnant women with type 1 diabetes showed overnight closed-loop therapy resulted in better glycemic control than sensor-augmented pump therapy (115).

Women with pre-existing diabetes during pregnancy should have A1C levels measured during pregnancy to assist in management. A1C levels can also be helpful predictors of adverse pregnancy outcomes (116,117). The optimal frequency of A1C measurement is not known; however, testing more than the usual every 3 months may be appropriate (see Monitoring Glycemic Control chapter, p. S47).

#### Weight gain

Institute of Medicine (IOM) guidelines for weight gain in pregnancy were first established in 1990 based on neonatal outcomes. Results of a systematic review of studies examining the 1990 IOM recommendations for maternal weight gain in women without diabetes, showed that those who followed guidelines were more likely to have good infant birthweight and fetal growth, and decreased the amount of weight loss required postpartum (118). The IOM

revised their recommendations in 2009 due to increasing rates of obesity and to take into consideration maternal obesity; however, IOM recommendations do not take into account pre-existing medical conditions (119).

Cohort studies of various body mass index (BMI) classes of women with pre-existing diabetes showed that excessive gestational weight gain (GWG) is characterized by higher birth weight infants independent of pre-pregnancy BMI and glycemic control (120,121). The researchers suggest that aiming for the lower weight gain range based on BMI category may be useful in the management of women with pre-existing diabetes. Furthermore, prepregnancy overweight and obesity are risk factors for adverse maternal and neonatal outcomes. Findings of cohort studies with pregnant women with type 2 diabetes who had overweight or obesity showed that weight gain greater than the IOM recommendations was associated with increased macrosomia (122–124), LGA (124), adverse neonatal outcomes (123) and higher rates of caesarean deliveries (122,123). The number of women with excessive GWG in these studies ranged from 40% (122) to 70% (124). Studies investigating weight gain below the IOM guidelines in women with obesity and type 2 diabetes have produced conflicting results ranging from: no evidence of worsened perinatal outcomes (122); increased risk of SGA (123); and lower birth weight, LGA and less perinatal morbidity with no increased risk of SGA (125).

Prepregnancy BMI, glycemic control and GWG can have independent and additive effects on fetal growth. Therefore, diabetes education and management for this group of women in preconception and regularly throughout pregnancy should be inclusive of both optimal glycemic control, healthy preconception weight and weight gain through pregnancy. Until additional data on specific weight gain recommendations for women with pre-existing diabetes becomes available, these women should be advised to gain weight as per the IOM guidelines based on their prepregnancy BMI category to lower the risk of LGA, macrosomia and caesarean deliveries.

#### *Pharmacological therapy*

**Insulin.** Insulin therapy must be individualized and regularly adapted to the changing needs of pregnancy (126–129). Intensive insulin therapy with basal-bolus therapy or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy is recommended to achieve glycemic targets prior to pregnancy and during pregnancy. Women using CSII should be educated about the possible increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure. However, recent studies using pumps have not demonstrated an increase in DKA compared to multiple daily injections (MDI) (130).

Rapid-acting bolus analogues (e.g. aspart, lispro) appear safe for use in pregnancy, with some studies showing improvement in postprandial glycemia and reduced maternal hypoglycemia compared to regular insulin (131–133). Although there are no studies that have examined placental transfer of aspart, lispro has been examined and does not cross the placenta except at very high doses (>50 units), similar to human insulin (134). A meta-analysis of observational studies (1561 women with pre-existing diabetes and GDM) found that lispro compared to regular insulin was associated with decreased rates of severe maternal hypoglycemia and neonatal jaundice, but increased rates of LGA infants (135). A randomized trial of 322 women with type 1 diabetes randomized to insulin aspart vs. human regular insulin, showed a trend toward reduced episodes of major hypoglycemia, with improved postprandial BG levels but similar overall glycemic control (104). In a smaller, underpowered study, perinatal outcomes were similar using insulin aspart and human insulin (136). A meta-analysis of randomized trials of 1,143 women with gestational or pre-existing diabetes assessing

the use of insulin aspart or premixed biphasic insulin aspart 30 compared to human regular insulin or premixed biphasic insulin aspart during pregnancy found similar rates of caesarean section and macrosomia (135). Finally, a case series of 303 women exposed to glulisine during pregnancy showed no noted pattern of few birth defects (137). There are no data to date on faster-acting insulin aspart.

Long-acting insulin analogues, glargine and detemir, appear safe with similar maternal and fetal outcomes compared to neutral protamine hagedorn (NPH) insulin. Both glargine and detemir (138) do not cross the placenta at therapeutic doses, although glargine does cross at very high doses (139). Notably, 2 randomized trials of detemir use compared with NPH in women with type 1 diabetes showed a lowering of FBG, but similar A1C, maternal hypoglycemia, and other maternal and fetal outcomes (140); another trial found less hypoglycemia with detemir compared with NPH (141). The research evidence for glargine are more limited (cohort and case control studies); however, in a meta-analysis of cohort studies comparing glargine to NPH, maternal and fetal outcomes were similar (142) and no adverse maternal or fetal effects have been described to date. Finally, there are no benefit or harms data on the use of glargine insulin U-300, lispro insulin U-200, degludec insulin U-100 and U-200, or glargine biosimilar in pregnancy.

**CSII therapy during pregnancy.** While the use of CSII may be preferred by some women with type 1 diabetes, older randomized studies have not demonstrated superiority over basal-bolus regimen (132,143–146). A meta-analysis of observational studies comparing the use of CSII (with insulin analogs) to MDI found no differences in maternal or fetal outcomes (147). However, recent studies not included in the meta-analysis suggest improved glycemic control with CSII (148–150), while other studies found no difference (151). Overall, studies show no difference in maternal or fetal outcomes with CSII, but also no increase in harms, such as maternal hypoglycemia, DKA or weight gain. More randomized trials are needed with current CSII technology to better assess the utility of CSII during pregnancy.

**Noninsulin antihyperglycemic agents and pregnant women with type 2 diabetes.** A meta-analysis of first-trimester use of either glyburide or metformin, and a meta-analysis of metformin alone in women with polycystic ovary syndrome (PCOS) showed no increased incidence of congenital anomalies (152,153). Women with type 2 diabetes who conceive on metformin or glyburide can continue these agents until insulin is initiated. Three smaller randomized trials have examined the use of metformin in pregnant women with type 2 diabetes. The first study was a small, open-label trial in Egypt (n=90) requiring high doses of insulin with poor glycemic control randomized to receive either metformin added to insulin or usual care (154); unfortunately, the authors did not specify whether the women had GDM or type 2 diabetes. The second trial completed in the United States (n=28) involved women with type 2 diabetes randomized to metformin or insulin and showed similar glycemic control in both groups (155). Finally, the third trial completed in Pakistan (n=206) involved women with untreated type 2 diabetes randomized to receive either metformin with insulin (as necessary), or insulin alone (156). In this study, 85% of patients in the metformin group required add-on insulin, but this group experienced less maternal weight gain, less pregnancy-induced hypertension; the infants had an increased rate of small for date, less hypoglycemia and less NICU admissions >24 hours. However, given the small sample sizes in the study and other methodological challenges, the findings from these studies offer limited generalizability.

Currently, a large, double-blind randomized trial is underway to determine whether adding metformin to insulin will benefit

**Table 1**  
Management of pregnant women with diabetes on insulin receiving betamethasone

Following the first dose of betamethasone	
Day 1	Increase the night insulin dose by 25%
Days 2 and 3	Increase all insulin doses by 40%
Day 4	Increase all insulin doses by 20%
Day 5	Increase all insulin doses by 10% to 20%
Days 6 and 7	Gradually taper insulin doses to pre-betamethasone doses

mothers with type 2 diabetes and their infants (Metformin in Women with Type 2 Diabetes in Pregnancy [MiTy] and Metformin in Women with Type 2 Diabetes in Pregnancy Kids [MiTy Kids] trials). In conclusion, some studies indicate a possible benefit to adding metformin to insulin in women with type 2 diabetes; however, due to limitations in the research, there is insufficient evidence to recommend the addition of metformin to insulin in pregnant women with type 2 diabetes.

*Pregnant women with diabetes receiving steroids.* In women suspected of preterm delivery, 2 doses of betamethasone is often given to aid in the maturation of the fetal lungs. The algorithm in Table 1 has been shown to prevent severe hyperglycemia, DKA and severe hypoglycemia in women with type 1 diabetes (157).

#### Perinatal mortality

Despite health care advances, including NICU, accurate ultrasound dating, SMBG and antenatal steroids for fetal lung maturity, perinatal mortality rates in women with pre-existing diabetes remain increased 1- to 10-fold compared to women without diabetes, and is influenced by glycemic control (1,77). In women with pre-existing diabetes, the risk of stillbirth is higher at all gestations after 32 weeks (158). Perinatal mortality is increased in pregnancies of women with pre-existing diabetes, particularly in those with poor glycemic control (159). In addition, a recent study found that peri-conception A1C >6.6% (adjusted odds ratio [aOR] 1.02), prepregnancy retinopathy (aOR 2.05), lack of prepregnancy folic acid consumption (aOR 2.52) and third-trimester A1C >6.1% (aOR 1.06) were all associated with an increased odds of fetal and infant death (77).

#### Significance of decreasing insulin requirements

Insulin requirements increase in pregnancy due largely to the “anti-insulin” effects of placental hormones. It has been hypothesized that a marked or rapid decrease in insulin requirements could be a harbinger of placental insufficiency. The relationship between falling insulin requirements and pregnancy outcomes has been explored in 4 retrospective studies (160–163). The 4 studies (n=481 pregnancies) comprised women with type 1 diabetes (n=366), women with type 2 diabetes (n=84), women diagnosed with overt diabetes in pregnancy (n=12) and women with insulin-requiring GDM (n=19). These studies reported decreased insulin requirements (at least 15%) occurred during the third trimester in 8% to 25% of these pregnancies. Only 2 stillbirths occurred: both in the same study of women with pre-existing diabetes (1 in a pregnancy with a >15% decrease in insulin requirements, the other in a pregnancy without a 15% decrease in insulin requirements) (160). This same study found that pregnancies with greater decreases in insulin requirements (>15%) were associated with more SGA neonates and more pre-eclampsia when compared to those that did not have at least a 15% decrease in insulin requirements, suggesting that dropping insulin requirements may be an indicator of placental insufficiency. Those with the ≥15% drop in insulin requirements compared to those without, were delivered slightly earlier

at a mean of 37.7 vs. 38.3 gestational weeks. Therefore, not surprisingly, those with the greater decrease in insulin requirements compared to those without, were admitted more frequently to the NICU (23.5% vs. 1.9%, p<0.001). Although care was taken not to include the period within 5 days of antenatal steroid administration when calculating the percent fall in insulin dosing in this study, the substantially higher antenatal steroid use in the pregnancies with falling insulin requirements (31.5% vs. 5.8%, p<0.001) in those without this same fall in insulin requirement suggests that antenatal steroid use may have impacted their retrospective determination of group assignment and, ultimately, their results. However, caution is required in the interpretation of these retrospective studies since decreasing insulin requirements may impact decisions regarding timing of delivery which may, in turn, impact pregnancy outcomes.

In contrast, results from other studies found no association with decreasing insulin requirements and birthweight, and neonatal weight distribution (i.e. SGA to LGA) (161). However, 1 study observed a trend for greater LGA neonates in women with decreasing insulin requirements (162). Caution is required when interpreting the findings as researchers used differing calculation methods to indicate fall in insulin requirements or perhaps due to heterogeneity in the population of women with type 2 diabetes included in the studies. The use of advanced sonographic and fetal doppler assessment in the surveillance of the fetus at risk, as in other high-risk pregnancies, may allow further stratification of risk in this population, but the optimal indicator of feto-placental compromise, particularly in women with diabetes, remains unclear.

In summary, the impact of decreasing insulin requirements is still not certain. While fetal monitoring in this situation can provide reassurance of current fetal well-being, it should not be viewed as a substitute for a well thought out plan for timing of delivery that takes into consideration other risks for perinatal mortality, such as gestational age, maternal glycemic control (both periconception and in later pregnancy), prepregnancy retinopathy (77), maternal age, obesity and smoking history.

#### Obstetrical considerations in women with pre-existing diabetes and GDM

The goal of fetal surveillance and planned delivery in women with pre-existing diabetes in pregnancy is the reduction of preventable stillbirth. However, not all stillbirths can be avoided due to the fact that many stillbirths in pre-existing diabetes occur prior to 36 weeks of gestation and that in a large number of cases no obvious cause is noted (164). Despite this, it is reasonable to apply surveillance strategies to pre-existing diabetes pregnancies that are similar to those in other pregnancies at high risk of fetal complications, such as intrauterine growth restriction (IUGR), chronic hypertension, and systemic lupus erythematosus (165). Although there is no single strategy for antenatal surveillance for pre-existing diabetes pregnancies, the initiation of some form of fetal surveillance in all women with pregnancies complicated by pre-existing diabetes while applying more intensive protocols for fetal surveillance in pregnancies with additional risk factors is required. These risk factors include: evidence of poor glycemic control, prepregnancy retinopathy (77), LGA, polyhydramnios or the presence of other comorbidities or high-risk conditions (hypertension, obesity, late maternal age, IUGR, previous stillbirth). As a general rule, intensified fetal surveillance should begin at a period in gestation when intervention (i.e. delivery) is possible and acceptable to both the parents and the neonatal care providers.

For GDM, fetal surveillance and timing of delivery are more complex as there is less evidence for increased perinatal mortality in this group. This is likely due to the fact that the risk for perinatal mortality is probably limited to the subgroup of women with poor glycemic control, inclusion of women with pre-existing diabetes

in GDM cohorts, obesity and other comorbidities and the rarity of these events. However, a large retrospective cohort (166) showed an increased risk of stillbirth in women with GDM between 36 to 39 weeks of gestation (unadjusted OR 1.1–2.00). Based on the large dataset, a relative risk was calculated of expectant management compared with induction of labour, while taking into consideration both the risk of stillbirth (expectant management) and infant death (expectant management and induction of labour) and showed a significant increased risk of stillbirth with expectant management at both 39 and 40 weeks of gestation when compared with induction of labour. As the absolute risk difference was small, the number needed to deliver to prevent 1 excess perinatal death was estimated as 1,518 at 39 weeks' gestation and 1,311 at 40 weeks' gestation. However, this study is limited by unadjusted confounders, including adequacy and method of glycemic control as well as obesity, thus limiting the generalizability of the study.

There are additional potential benefits of induction of labour in diabetic pregnancies, including reduction of excess fetal growth, shoulder dystocia and caesarean section rate. One randomized controlled trial compared induction of labour with expectant management of labour at term (167). In this trial of insulin requiring GDM and pre-existing diabetes in pregnancies, expectant management after 38 weeks of gestation was associated with increased birthweight and macrosomia, but no change in caesarean section rate. A recent retrospective cohort study from Ontario supports these findings, showing a significant reduction in caesarean section rate at both 38 and 39 weeks of gestation in women with GDM who underwent induction of labour when compared with those that underwent expectant management (168). Conversely, induction of labour at 38 but not 39 weeks was associated with an increase in NICU admission. Importantly, these results remained significant after adjusting for important confounders, including parity, insulin treatment and BMI. Two recently published randomized controlled trials shed additional light on this clinical question. One study randomized women with a suspected macrosomic fetus (>95%) to either induction of labour (IOL) at 37 to 39 weeks or expectant management up until 41 weeks. Although the trial population included diet-controlled GDM (10%), the results showed that IOL resulted in an increased rate of spontaneous vaginal delivery (RR 1.14, 95% CI 1.01–1.29), a decrease in the rate of shoulder dystocia (RR 0.32 95% CI 0.12–0.85) and an increase in the rate of neonatal hyperbilirubinemia (169). A second randomized controlled trial randomized women with both diet-controlled and medically treated GDM to IOL at 38 to 38+6 weeks or expectant management until 41 weeks' gestation. The study found no difference in caesarean section rates between groups, but an increase in hyperbilirubinemia was noted in the IOL group. However, the study was underpowered and discontinued due to recruitment difficulties; thus any extrapolations from the study cannot be made (170).

In summary, there is a paucity of quality evidence to guide clinical decisions regarding optimal fetal surveillance and timing of delivery in diabetic pregnancies. Clinical identification of increased risk of stillbirth should be the target of prenatal care and lead to an individualized approach to defining the appropriate regimen of fetal surveillance and timing of delivery. In pre-existing diabetes, poorly controlled GDM or pre-existing diabetes in pregnancy associated with comorbidities, initiation of weekly assessment of fetal well-being at 34 to 36 weeks gestation is recommended. Earlier onset and/or more frequent fetal health surveillance is recommended in those at highest risk. Acceptable methods of assessment of fetal well-being near term can include the nonstress test, amniotic fluid index, biophysical profile or a combination of these. When making decisions regarding timing of delivery before 40 weeks' gestation, the benefits with regards to prevention of stillbirth and a possible decrease in the caesarean rate need to be weighed against the likely increase in neonatal complications.

### *Glycemic control in labour and delivery*

Planning insulin management during labour and delivery is an important part of care and must be adaptable given the unpredictable combination of work of labour, dietary restrictions and need for an operative delivery. The goal is to avoid maternal hypoglycemia while preventing significant hyperglycemia which, in turn, may increase the risk of neonatal hypoglycemia (171). Options for peripartum BG control include watchful waiting until BG rises above a specified threshold (e.g. 7.0 mmol/L for type 2 diabetes or GDM), presumptive initiation of intravenous insulin infusions or continuing with CSII therapy. In a retrospective study of 161 consecutive women with type 1 diabetes, women who chose to continue on CSII during labour had better glycemic control than women using CSII during pregnancy but who chose to convert to intravenous insulin infusion during labour. There was no increase in maternal hypoglycemia, suggesting that the continuation of CSII during labour and delivery appears safe and efficacious (172). Similarly, another retrospective study found that women using CSII had excellent glycemic control without hypoglycemia (173). Observational studies comparing the use of CGM to SMBG during labour and delivery identified improved glycemic control with CGM (173,174); however, neonatal hypoglycemia was comparable between groups (172,174). Each centre should establish protocols which include BG targets, monitoring frequency, insulin regimen and intravenous glucose, based on nursing, medical and anaesthesia expertise available, and patient choice (171,172).

### *Postpartum care*

Postpartum care in women with pre-existing diabetes should include counselling on the following issues: 1) rapid decrease in insulin needs and risk of hypoglycemia in the immediate postpartum period; 2) risk of postpartum thyroid dysfunction in the first months; 3) benefits of breastfeeding; 4) contraceptive measures and; 5) psychosocial assessment and support during this transition period.

*Diabetes management and insulin sensitivity immediately postpartum.* In women with type 1 and type 2 diabetes, insulin requirements decrease rapidly immediately after the delivery of the placenta (175–177). This rapid increase in insulin sensitivity is related to the drop in circulating placental hormones (hPL, HGH) and, as a result, intravenous insulin infusion or CSII basal insulin should be immediately decreased by at least 50% after delivery to avoid hypoglycemia (175,178).

In the first days postpartum, insulin requirements are generally reduced by an average of 30% to 50% of the prepregnant insulin dosage in women with type 1 diabetes (175–177). In a recent study of 44 women with type 1 diabetes (73% on pumps, 27% on MDI), postpartum total daily insulin was 34% lower than preconception total needs (0.64 to 0.39 units/kg/day postpartum) independent of insulin administration mode or infant feeding. However, a nonsignificant trend toward lower requirements in exclusively breastfeeding mothers compared to partial or full formula feeding was also noted (176). A gradual return to pre-pregnant insulin doses has been noted after 6 to 8 weeks postpartum in some studies (179,180); however, another study found persistently reduced insulin needs up to 4 months postpartum (181). In some studies, reduced insulin needs have been especially noted in women with type 1 diabetes who were breastfeeding (180,181), although this has not been universally observed (176). Nevertheless, most clinicians advise women with type 1 diabetes who are breastfeeding of the potential increased risk of hypoglycemia, especially during night breastfeeding. Thus, for women with pre-existing diabetes in pregnancy, a post-delivery plan for reduced prepregnant insulin dosages, pump settings or

noninsulin antihyperglycemic agents should be discussed with the woman and recorded before delivery.

Evidence suggests that despite good glycemic control during pregnancy, continuous weight loss, as well as substantial diabetes education and follow up during pregnancy and in the first months postpartum, glycemic control is managed less effectively by mothers with diabetes in the first year postpartum, and A1C levels gradually increase and return to the pre-pregnancy level (182,183). Postpartum A1C levels are positively associated with pre-pregnancy BMI and postpartum weight retention in type 1 diabetes (182). In addition, most women are unable to return to prepregnancy weight (183). Improved postpartum care and specific interventions for women with pre-existing diabetes should be developed to help women achieve their target weight postpartum (182,183), to improve glycemic control in the first year postpartum (183) and to increase breastfeeding rates (184).

*Risk of postpartum thyroid dysfunction.* Women with type 1 diabetes are at high risk for autoimmune thyroid disease and, consequently, postpartum thyroid dysfunction. The estimated incidence is as high as 44% among women of childbearing age, and 25% in the first months postpartum (185), representing a 3-fold increase compared to a population without diabetes (185,186). Screening for thyroid hormonal abnormalities during pregnancy and at approximately 3 months postpartum in women with type 1 diabetes is recommended.

#### *Breastfeeding*

*Lower rate and difficulties around delayed lactation in women with diabetes.* A Canadian group demonstrated that women with pre-existing diabetes were less likely to initiate breastfeeding compared with noninsulin-treated mothers with diabetes, GDM women and mothers without diabetes (184). Concordant with other studies (187,188), women with all types of diabetes in pregnancy (GDM, pre-existing, insulin-treated or noninsulin-treated) in this study had also lower rates of exclusive breastfeeding in hospital and on discharge. However, women with pre-existing diabetes were disproportionately affected and had lower rates of breastfeeding (184,189). Lower education and maternal age less than 25 years of age were risk factors associated for lower rates of breastfeeding and exclusive breastfeeding postpartum (184).

Women with pre-existing diabetes tend to have delayed milk production. There is a greater delay in lactation onset in mothers with type 1 diabetes who had poor glycemic control (190). Women with type 1 diabetes also discontinue breastfeeding at a higher rate during the first week postpartum (191–193). Overall, women with any form of diabetes during pregnancy have more nursing difficulties with lower milk supply than women without diabetes (194). However, once established, lactation persists and duration is similar in mothers with and without diabetes (190,195).

There are several pathophysiologic and behavioural explanations for lower breastfeeding rates in women with diabetes. Poor glycemic control, insulin resistance, obesity and impaired bonding between mother and child caused by obstetrical complications (such as NICU admission, prematurity, caesarean section) are the major factors associated with delayed lactation (196). It has been demonstrated that ideal glucose and insulin levels are necessary for lactation (197). Good glycemic control enhances maternal serum and milk prolactin concentrations and decreases the delay in the establishment of lactation that has been observed in mothers with type 1 diabetes (190,198). Maternal obesity has also been correlated with delayed onset of lactogenesis II (>72 hours) postpartum, partly related to the fact that it can alter spontaneous release of prolactin. Moreover, infants of mothers with diabetes showed poorer and immature sucking patterns contributing to the difficulties to

breastfeed for those mothers in the first days postpartum (199). Protective factors associated with both higher rates of intention to breastfeed and exclusive breastfeeding included attending antenatal classes and having antenatal care delivered by a health-care provider other than an obstetrician. Indeed, women who received antenatal care from a family physician or other health-care providers were respectively 2 and 3 times more likely to exclusively breastfeed (184). Patient education with prenatal information and postnatal counselling on breastfeeding have been shown to lead to similar breastfeeding rates in women with type 1 diabetes as the population without diabetes (181).

*Use of noninsulin antihyperglycemic agents during breastfeeding.* Few studies have examined breastfeeding and the use of noninsulin antihyperglycemic agents. Three case series found metformin in the milk and plasma of breastfeeding women who were taking metformin 500 mg 2 or 3 times daily, but infant exposure was well below the 10% “level of concern” (0.182% to 0.65%) (200–202). A study looking at weight, height and motor-social development up to 6 months of age in children of mothers taking metformin while breastfeeding showed normal development and no difference from formula-fed infants (203). One case series that studied women taking glyburide or glipizide while breastfeeding found neither drug in the breastmilk, and the maximum theoretical infant dose was well below 10% (<1.5%), with no hypoglycemia found in the 3 infants tested (204). Although metformin and glyburide can be considered for use during breastfeeding, further long-term studies are needed to better clarify the safety of these drugs. Finally, there are no human studies to date looking at thiazolidinedione (TZD), glucagon-like polypeptide-1 (GLP-1) receptor agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor or sodium-glucose cotransporter-2 (SGLT2) inhibitor use while breastfeeding and, therefore, they should not be taken during breastfeeding.

*Use of insulin and newer insulin analogues during breastfeeding.* There is no contraindication for women with diabetes treated with insulin to breastfeed (175). Exogenous insulins are excreted into breastmilk, including newer insulin analogues (i.e. aspart, detemir, glargine, glulisine, lispro). Insulin is a normal component of breastmilk (205,206) and similar levels were found in the milk of women with type 1 diabetes, type 2 diabetes and women without diabetes, suggesting an active transport of endogenous and exogenous insulin into breastmilk (207). Insulin normally found in breastmilk of mothers with or without diabetes is thought to be required for intestinal maturation of the infant and could act as a positive modulator of the immune response to insulin as suggested by certain groups (208–210).

*Benefits of breastfeeding.* Breastfeeding immediately postpartum can be part of an early feeding strategy to reduce the risk of neonatal hypoglycemia in women with diabetes (211). Breastfeeding for more than 4 months has also been shown to be protective against the development of diabetes (OR 0.29, 95% CI 0.13–0.63) at 21 years of age in a cohort of 3,595 young adults (212). It was previously thought that early introduction of cow’s milk protein could be involved in the development of beta cell autoimmunity in infants at risk for type 1 diabetes. However, a randomized trial comparing the use of a hydrolyzed formula with smaller foreign proteins, compared with a conventional formula containing cow’s milk protein, did not reduce the incidence of diabetes-associated autoantibodies 7 years after exposure in offspring with genetic susceptibility to type 1 diabetes and a family member with type 1 diabetes. These data do not support a short-term benefit from the use of hydrolyzed formula but a longer effect on disease prevalence is under study (213) (see Reducing the Risk of Developing Diabetes chapter, p. S20). Finally, along with other known benefits of breastfeeding for mother and



child, although not specific to women with pre-existing diabetes, there is evidence that breastfeeding is a significant protective factor against obesity in children (214–216).

In summary, women with pre-existing diabetes should be encouraged to breastfeed immediately after delivery and for at least 4 months postpartum, as it may contribute to the reduction of neonatal hypoglycemia, offspring obesity and prevent the development of diabetes. Furthermore, exclusive breastfeeding up to 6 months and continuation of breastfeeding up to 2 years with appropriate complementary feeding has shown further benefits and is currently recommended for all women by the Canadian Paediatric Society (217,218). Health-care providers should pay particular attention to promoting breastfeeding in women with diabetes (184,189), especially in the context of maternal obesity, since this high-risk population has the lowest rates of breastfeeding despite demonstrated benefits for mother and child. Attention should be paid, however, to potential increased risk of hypoglycemia, especially during night feeding, in breastfeeding women with type 1 diabetes.

#### *Postpartum contraception*

Effective contraception is an important consideration until proper preparation occurs for a subsequent pregnancy in women with pre-existing diabetes. Regarding the choice of a contraceptive method, the same motivations and restrictions apply to women with type 1 and type 2 diabetes as with other women. Evaluation includes discussing women's preferences for a contraceptive method that will ensure compliance. Absolute and relative contraindications to estrogen (breastfeeding, high BP, and microvascular and CV diabetes-related complications) or to an intrauterine device (IUD) (219) also apply. The progesterone-only contraceptive and IUD are safe with breastfeeding (220).

## **GDM**

#### *Prevention and risk factors*

The incidence of GDM is increasing worldwide. The global prevalence of hyperglycemia during pregnancy has been estimated at 16.9% (21.4 million live births in 2013) using the World Health Organization criteria (221). A higher proportion of women entering pregnancy at an older age and/or with obesity contribute to this increase in prevalence, along with changes in screening strategies and diagnostic criteria. There is a need for an effective and acceptable intervention that will prevent the development of GDM. Such an approach has the potential to improve maternal and child health, with significant savings to the health-care system.

Understanding the pathophysiology of GDM and its risk factors is important for the development of preventive strategies. The GDM population includes a heterogeneous group of women with different metabolic profiles when exposed to pregnancy hormones. Various presentations include:

- Hyperglycemia that likely preceded the pregnancy (e.g. impaired glucose tolerance (IGT), elevated first trimester fasting glucose, overt diabetes in pregnancy, monogenic diabetes)
- Reduced and/or falling insulin secretory capacity (e.g. developing type 1 diabetes)
- Significant insulin resistance from early pregnancy (e.g. polycystic ovary syndrome, women with overweight or obesity, some specific ethnic groups)
- A combination of factors (e.g. family history of diabetes, previous GDM, genetic predisposition for GDM/type 2 diabetes (222,223)).

As insulin sensitivity decreases substantially with pregnancy (224), not all cases of GDM can be prevented. Studies need to focus on identifying the potential groups of women who can benefit from preventive interventions and adapt such strategies to their condition (e.g. preconception vs. during pregnancy, women with obesity or leanness). Considering the heterogeneity of GDM, it seems obvious that tailored recommendations will emerge for each identified group of at-risk women.

More than 30 randomized controlled trials on GDM prevention have been reported. The interventions tested to date include different diets sometimes combined with diverse physical activity plans, vitamin D supplements, myo-inositol, probiotics and metformin. However, only 3 interventions have demonstrated a significant risk reduction for GDM to date. Effective measures included healthy eating, myo-inositol supplementation and probiotic treatment. Among evaluated interventions, diet-based interventions appear to show the most potential for preventing GDM, especially when directed toward women with overweight or obesity as demonstrated in 3 meta-analyses (225–227). The first meta-analysis (225) of 14 randomized controlled trials (n=2,422 pregnant women) compared interventions with standard care in women with risk factors for GDM represented essentially in all studies by maternal overweight and obesity. Interventions evaluated and compared to standard care included diet, physical activity alone, lifestyle changes (diet and physical activity) and metformin. Dietary interventions were associated with a statistically significant lower incidence of GDM (OR 0.33; 95% CI 0.14–0.76) and gestational hypertension (OR 0.28; 95% CI 0.09–0.86) compared to standard care. There was no statistically significant difference in the incidence of GDM or in the secondary outcomes with physical activity alone, lifestyle changes (diet and physical activity) or metformin use compared to standard care. In the 3 randomized controlled trials focusing on diet, a total of 455 women were included, with comparable mean maternal age and mean BMI (36.1 vs. 36.4 kg/m<sup>2</sup>) in controls. GDM prevalence decreased from 18% to 7% in the diet groups. Healthy eating intervention consisted of a consultation with a trained dietitian, weighing at each antenatal visit and review of food records, but the duration and number of sessions differed among studies. In the second meta-analysis (226), there was a trend toward a reduced risk of GDM in diet-based intervention groups, but a significant reduction in GDM was noted again in subgroup analysis of pregnant women with obesity or overweight (RR 0.40, 95% CI 0.18–0.86). Finally, the composition of protein content of daily meals may be important as a large prospective cohort study demonstrated that an increased prepregnancy intake of animal protein, in particular red meat, was significantly and positively associated with GDM risk, while vegetable protein intake, specifically nuts, was significantly and inversely associated with GDM risk (228).

Mixed-approach interventions, including diet, physical activity and lifestyle modifications, do not appear to prevent GDM in some studies (225,226,229) but seem effective in a recent meta-analysis when introduced before 15 weeks of gestation (227); methodological problems with this study involving the inclusion of studies of diet alone and physical activity alone make this conclusion less reliable and in need of confirmation by further analyses. It can be argued that the complexity of healthy behaviour interventions, the variability of adherence and delay before introduction, as well as the heterogeneity of the maternal metabolic profile and diagnostic criteria in GDM are the main factors that may explain the discrepancies seen and inconclusive evidence for healthy behaviour interventions. Finally, results of meta-analyses on interventions based solely on physical activity programs to prevent GDM are not impressive (small protective effect [230] vs. nonsignificant impact [225]) and studies seem often underpowered with suspected low protocol adherence.

Studies looking at metformin use for GDM reduction in women with obesity (231) and with PCOS (232) have not shown benefit. Moreover, studies are currently insufficient to support clear clinical recommendations regarding vitamin D supplementation in pregnancy to prevent GDM. Only 3 of 8 observational studies (233) and 1 meta-analysis (234) demonstrate a significant inverse relationship between risk of GDM and maternal vitamin D status. Also, incidence of GDM and other obstetrical outcomes were not influenced by vitamin D supplementation (235). Overall, there is currently limited evidence to support lifestyle, physical activity interventions, metformin or vitamin D supplements for GDM prevention.

Probiotics combined with diet and myo-inositol have shown benefit for GDM prevention (226), but these nutritional supplements were assessed in only 1 trial each. One randomized controlled trial demonstrated a 60% GDM reduction with the use of antenatal probiotics, with no impact on GWG (236,237). Moreover, probiotics did not show an impact on glycemic control in GDM women, but attenuated the normal pregnancy-related rise in low-density lipoprotein cholesterol (LDL-C) levels in the third trimester (238). Similar results were obtained with myo-inositol supplements with a 58% risk reduction of developing GDM in pregnant women with overweight or obesity (239,240). However, those studies have been conducted by only 1 research group, with small sample sizes and these results have not been replicated. Before any further recommendations are made for probiotics or myo-inositol supplements for GDM prevention, large randomized trials are needed.

Finally, a recent meta-analysis demonstrated that excessive GWG, occurring in the first and second trimester, increased the risk of GDM by a factor of 1.4, with similar effect in women with normal weight, overweight or obesity (241). Also, BMI increase observed in the inter-pregnancy period in women with normal BMI or with a BMI >27 kg/m<sup>2</sup> is associated with higher risk of GDM in their second pregnancy (242). On the other hand, a decrease in inter-pregnancy BMI in women with overweight or obesity significantly decreases their risk of developing GDM in their second pregnancy, reinforcing the importance of a healthy diet and lifestyle during the preconception period for women with overweight or obesity (242). Along these lines, bariatric surgery is becoming increasingly common for the treatment of obesity, and studies looking at pregnancy outcomes following bariatric surgery have found both benefits (decreased GDM, hypertensive disorders, LGA infants) but also some adverse outcomes (SGA infants, preterm deliveries and NICU admissions) (243). As suggested by most experts and the British Obesity and Metabolic Surgery Society (244,245), women should delay pregnancy at least 12 to 18 months after bariatric surgery to limit adverse pregnancy outcomes and allow weight stabilization and replenishing of all vitamins and microelement deficiencies before conception. A study on children born before and after maternal surgical weight loss demonstrated reduced obesity rate and improved cardiometabolic profiles during childhood and adolescence in offspring born after maternal bariatric surgery, positioning bariatric surgery as 1 of the potential options to limit intergenerational transmission of obesity (246).

In summary, evidence is limited but current literature suggests that the only effective GDM preventive measure in early pregnancy that can be considered in high-risk women, especially prepregnant women with obesity, is a healthy diet and close follow up of weight gain to prevent excessive GWG. Nutritional supplements, such as probiotics and myo-inositol, have shown some encouraging results, but these need to be replicated in larger randomized trials. More studies using the same set of diagnostic criteria are needed and focus should be put on specific populations (prepregnant women with obesity, prior GDM and/or PCOS, as well as women with excessive GWG) to be able to develop effective

preventive interventions tailored for those high-risk populations to reduce GDM prevalence.

### Screening and diagnosis of GDM

**Early screening.** Screening for diabetes in the first trimester should be considered for diagnosing overt diabetes (diabetes present before pregnancy) in women who are at risk (see Screening for Diabetes chapter, p. S16), including those with a history of previous GDM. The ability to predict abnormal results on glucose screening tests at 24 to 28 weeks and risk of continued dysglycemia postpartum are other, but less compelling, reasons cited to screen in the first trimester.

The test of choice for early screening should be based primarily on the ability to predict poor obstetrical outcomes, which may be modifiable by lifestyle or pharmacological intervention. There are 2 strategies for testing glucose levels in early pregnancy—using the nonpregnancy-recommended screening tests (FPG or A1C) or using the typical 24- to 28-week gestational diabetes screening (50 g glucose challenge test [GCT] and/or 75 g oral glucose tolerance test [OGTT]) criteria (see below). To apply nonpregnant FPG or A1C criteria in early pregnancy does not take into account that both decrease early in pregnancy and may lead to underdiagnosis in women with pre-existing diabetes. On the other hand, there has been no rigorous validation that criteria accepted for the diagnosis of GDM in the second or third trimester are appropriate for use in the first trimester.

First trimester FPG levels are associated with macrosomia and increased caesarean section rates, as well as an increased risk of second-trimester diagnosis of GDM. The results of a retrospective cohort study (n=6,129) suggest that this association between first trimester fasting glucose and later diagnosis of GDM, macrosomia and caesarean section risk is a graded relationship with no clear cut point (247). In another large cohort study (n=17,186 pregnancies), 39% of women with a first trimester FPG over the GDM diagnostic criteria (5.1 mmol/L), will no longer have an elevated FPG if rescreened at 24 to 28 weeks (248). This suggests that first trimester FPG is not reliable for predicting second-trimester GDM.

First-trimester A1C has been used to predict risk of poor obstetrical outcomes, later development of GDM and persistence of postpartum dysglycemia. In 1 study of 16,122 women screened at a median of 47 days gestation, there were higher rates of major congenital anomalies (RR 2.67, 95% CI 1.28–5.53), preeclampsia (RR 2.42, 95% CI 1.28–5.53), shoulder dystocia (RR 2.47, 95% CI 1.05–5.85) and perinatal death (RR 3.96, 95% CI 1.54–10.16) with an A1C of 5.9% to 6.4% in the first trimester (249). However, only 23% of women in that study returned for a first-trimester OGTT, highlighting the low uptake of the OGTT in the first trimester. A retrospective cohort study of 2,812 women compared first trimester A1C to 24-week OGTT and found that an A1C of 5.7% to 6.4% had a 13% sensitivity and 94% specificity for predicting GDM based on a second-trimester 75 g OGTT (250). Another recent study in a multiethnic population of 1,156 women who underwent first trimester A1C and 24- to 28-week 2-stage glucose tolerance test, 48 out of 1,180 had an A1C of 5.9% to 6.4%, which was associated with a 3-fold higher rate of preeclampsia (OR 3.539, 95% CI 1.086–11.532) and macrosomia (OR 3.1, 95% CI 1.127–8.603). However, an elevated first trimester A1C shows a low sensitivity (14.5%) but high specificity (97.5%) for predicting second-trimester GDM (251). In a small cohort study of 160 women, the best cut-off for first trimester A1C to differentiate a diagnosis of postpartum type 2 diabetes was  $\geq 5.9\%$  (252). Thus, a first trimester A1C  $\geq 5.9\%$  appears to confer risk of adverse obstetrical outcome, later diagnosis of GDM and postpartum diabetes. Combining a first trimester FPG of 5.1 to 7.0 mmol/L or A1C 5.7% to 6.4%, is more predictive of need for medical management than when GDM is diagnosed later in pregnancy (253).

Although consideration can be given to treatment of women with A1C 5.9% to 6.4% in the first trimester given the evidence of adverse pregnancy outcomes, whether intervention earlier in pregnancy makes a difference remains unknown. In 1 small cohort study, early intervention appeared to lower the risk of preeclampsia (249). A larger cohort trial using a 75 g OGTT for screening high-risk women earlier in pregnancy continued to show higher rates of hypertensive disorders, preterm delivery, caesarean section rates, macrosomia, and neonatal intensive care despite intervention (254). Although widely used before 24 weeks of gestation for assessment of risk in women at high risk of developing GDM, the 75 g OGTT has no validated thresholds for diagnosis of GDM at this gestational age and there is no evidence yet to support a benefit for earlier management in those that screen positive by whatever threshold is used. If an OGTT is performed before 24 weeks of gestation and is negative by the thresholds used to diagnose GDM after 24 weeks, this test needs to be repeated between 24 to 28 weeks.

Finally, all women with diabetes diagnosed during pregnancy, whether diagnosed in the first trimester or later in pregnancy, should be retested postpartum. In 1 study, in women 6 to 8 weeks postpartum who had an A1C  $\geq 6.5\%$  or FPG  $\geq 7.0$  at 24 to 28 weeks during pregnancy, 21% had continued diabetes, 37% had impaired fasting glucose (IFG) or IGT and 41% had normal glucose levels (248,250,255).

### Screening and diagnosis

As previously outlined in the *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* (CPG), Diabetes Canada continues to support universal screening and diagnosis of GDM based on large randomized control trials and meta-analyses demonstrating that treatment of women with GDM reduces fetal overgrowth, shoulder dystocia and preeclampsia (85,256–259). Justification for supporting universal screening for GDM is outlined in detail in the 2013 CPG (260). Assuming universal screening, the method of screening can be either a sequential 2-step or a 1-step process. Methods for sequential screening include the use of glycosuria, A1C, FPG, random plasma glucose (RPG) and a glucose load. Aside from the glucose load, all the other methods mentioned have not been adopted due to their poorer performance as screening tests in most populations (261–267). The most common glucose test used in sequential screening is the 50 g GCT performed between 24 to 28 weeks of gestation, and it is the screening test recommended by Diabetes Canada in the 2013 and 2018 guidelines. The performance of the GCT as a screening test depends on the cut-off values used, the criteria for diagnosis of GDM and the prevalence of GDM in the screened population. As previously discussed in the 2013 CPG, despite its limitations, the 50 g GCT is practical, accepted by pregnant women and caregivers and retains a >98% negative predictive value for GDM in most populations (268). Results from a Canadian prospective study show that sequential screening is associated with lower direct and indirect costs while maintaining equivalent diagnostic power when compared with 1-step testing. Recent observational data demonstrated the feasibility and good uptake of the 2-step approach (269).

An additional question is whether there is a GCT threshold above which GDM can be reliably diagnosed without continuing to the diagnostic OGTT. It is recognized that using a cut-off of  $\geq 11.1$  mmol/L after a 50 g GCT will result in a small number of women receiving an erroneous diagnosis of GDM (270). However, these women are at increased risk of adverse perinatal outcomes and might benefit from the same management as those diagnosed with GDM (271), especially since those with a glucose screen  $>11.1$  mmol/L were found to have a 3.7-fold increased rate of insulin treatment compared to women diagnosed as GDM by National Diabetes Data Group (NDDG) or Carpenter and Coustan criteria (272). We thus have decided to

maintain the recommendation from the 2013 CPG to diagnose GDM if the glucose level 1 hour after the 50 g GCT is  $\geq 11.1$  mmol/L.

### What is the optimal method of diagnosis?

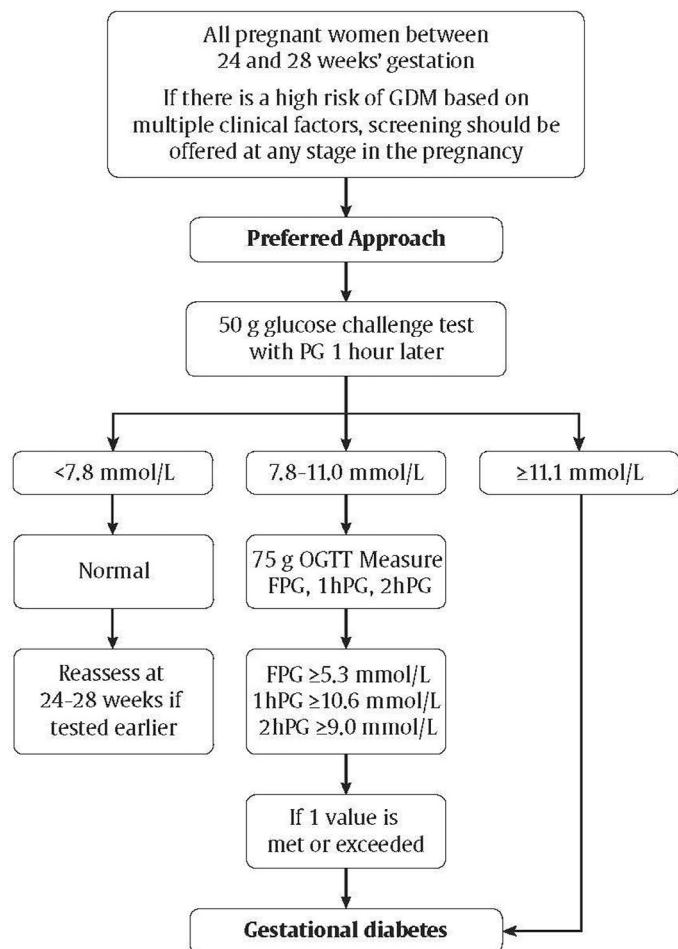
Since there is no clear glucose threshold above which pregnancy outcomes responsive to glycemic management occur (268,273,274), controversy persists as to the best diagnostic thresholds to define GDM. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel decided to create new diagnostic thresholds for GDM based on data from the Hyperglycemia and Adverse pregnancy Outcome (HAPO) study. IADPSG thresholds are the maternal glucose values from HAPO associated with a 1.75-fold increase of LGA, elevated C-peptide, high neonatal body fat or a combination of these factors, compared with the mean maternal BG values of women studied in HAPO. These arbitrary thresholds, when applied to the HAPO cohort, led to a GDM incidence of 17.8%. The National Institute of Health (NIH) 2013 Consensus Conference summary statement stated that “at present, the panel believes that there is not sufficient evidence to adopt a 1-step approach, such as that proposed by the IADPSG” (275). However, since this publication, national organizations have published guidelines that are divergent in their approach to screening and diagnosis of GDM (276–280), thus perpetuating the international lack of consensus on the criteria for diagnosis of GDM.

Given the lack of agreement that persists in the international community, the 2013 Canadian Diabetes Association Expert Committee acknowledged the controversy and opted to continue to recommend the “preferred” sequential 2-step approach (Figure 1) while recognizing the option of the 1-step IADPSG approach as an “alternative” strategy (Figure 2) (260). The “preferred” approach for sequential screening consists of a 50 g GCT followed by a 75 g OGTT using the glucose thresholds that result in an (also arbitrary) OR of 2.0 for the increased risk of LGA and cord C-peptide (fasting  $\geq 5.3$  mmol/L, 1 hour  $\geq 10.6$  mmol/L, 2 hours  $\geq 9.0$  mmol/L) (273) (Table 2). However, it was recognized that the IADPSG 1-step strategy has the potential to identify a subset of women who would not otherwise be identified as having GDM and could potentially benefit with regards to certain perinatal outcomes. Therefore, a diagnostic strategy consistent with the IADPSG approach of a 1-step 75 g OGTT using the glucose thresholds that result in an OR of 1.75 for the risk of LGA and cord C-peptide was added as an “alternative” method (Figure 2). As outlined in the 2013 CPG, those who believe that all cases of hyperglycemia in pregnancy need to be diagnosed and treated (i.e. increased sensitivity over specificity) will support the use of the 1-step method of GDM diagnosis.

Some data to support Diabetes Canada’s “preferred” strategy can be found in an analysis of 1,892 women with mild untreated glucose intolerance (281). In this study, perinatal outcomes for women with 75 g OGTT results that were positive by HAPO 1.75 OR thresholds (Diabetes Canada alternative) were compared to women with 75 g OGTT results that were positive by HAPO 2.0 OR thresholds (Diabetes Canada preferred). LGA rate and birth weight progressively increased with more dysglycemia and were increased in both groups. However, in this study, only women who were positive by HAPO 2.0 OR thresholds had an increased incidence of preeclampsia, preterm delivery, primary caesarean delivery, shoulder dystocia, ponderal index, transient tachypnea and neonatal hypoglycemia after adjustment for confounders (281).

### Impact of adoption of IADPSG criteria

Since the publication of the IADPSG consensus thresholds, there have been numerous retrospective studies that have examined the impact of adoption of these criteria. It is difficult to apply the results



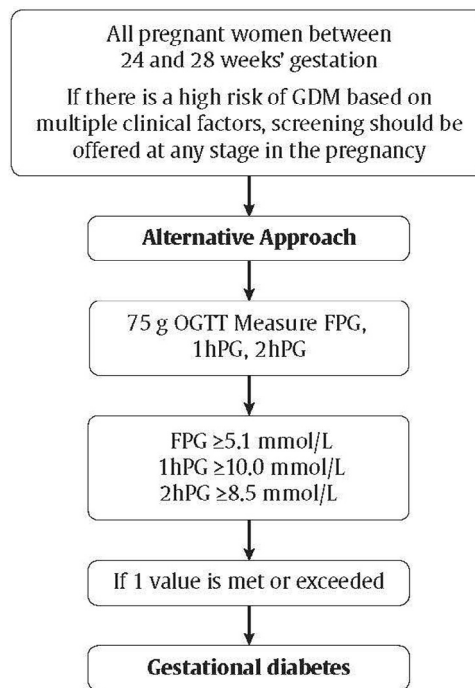
**Figure 1.** Preferred approach for the screening and diagnosis of gestational diabetes.

1hPG, 1-hour plasma glucose; 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

of these studies to clinical practice due to their retrospective nature and the wide variation in the comparison groups used. In all of these studies, adoption of IADPSG criteria has led to an increase in the number of cases diagnosed while the impact on perinatal outcomes is inconsistent (282–287). Studies comparing pregnancy outcomes before and after changing from a variety of different GDM diagnostic criteria to the IADPSG criteria show differing results. LGA (285) was lower in 1 study and caesarean delivery was lower in several studies (282,285) after adoption of the IADPSG criteria. However, others did not find reductions in LGA (282,283,286,287), and 1 study found an increase in primary caesarean section rate (286).

Given this lack of evidence, it is possible that the decision regarding the recommended screening method will be determined by the economic implications on health-care resources. Decision analysis modelling studies done in other countries (285,288–290) have yielded a variety of results and many are of questionable applicability in the Canadian setting because of differing cost and screening and diagnostic strategies.

A small observational study from Ireland suggested that maternal BMI may be an important consideration in choice of which diagnostic thresholds to use (291). When this group used the IADPSG diagnostic thresholds for all women, they observed a beneficial effect of GDM treatment in women with obesity, but not in women with BMI <25 kg/m<sup>2</sup>. Furthermore, secondary analysis of the Landon et al



**Figure 2.** Alternative approach for the screening and diagnosis of gestational diabetes.

1hPG, 1-hour plasma glucose; 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

**Table 2**

Differences between selecting an OR of 1.75 vs. 2.0 for the primary outcome in the HAPO cohort (273,479)

	OR 1.75	OR 2.0
<b>Threshold glucose levels (mmol/L)</b>		
Fasting	5.1	5.3
1 hour	10.0	10.6
2 hour	8.5	9.0
% of HAPO cohort that met ≥1 glucose threshold	16.1%	8.8%

HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; OR, odds ratio.

trial, that used a 2-step screening approach, found that GDM therapy had a beneficial effect on fetal growth only in women with class 1 and 2 obesity and not in women with normal weight or with more severe obesity (292).

In summary, until more high-quality information comparing the 2013 CPG “preferred” and “alternative” approaches for GDM screening and diagnosis becomes available, the committee agreed it was best to maintain the same diagnostic criteria as those introduced by the 2013 CPG. Further higher-quality evidence would be helpful in establishing if maternal BMI and other clinical risk factors should guide which diagnostic thresholds are used. Most cost analysis evaluations support a sequential screening approach to GDM. The 2018 Diabetes Canada Expert Committee recognizes the drawbacks of having different diagnostic strategies and different thresholds for the same 75 g OGTT but at this time there is insufficient evidence to support 1 strategy over the other (293). Therefore, adequately powered prospective studies to compare these 2 approaches are needed.

#### Monogenic diabetes in pregnancy

Since pregnancy may be the first time in their lives that women undergo glucose screening, monogenic diabetes may be picked up for the first time in pregnancy. Monogenic diabetes first diagnosed

in pregnancy should be suspected in the women with GDM who lack risk factors for GDM and type 1 diabetes and have no autoantibodies (see Definition, Classification, and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10). A detailed family history can be very helpful in determining the likely type of monogenic diabetes. This is important because the type of monogenic diabetes influences fetal risks and management considerations. The most common forms of monogenic diabetes in Canada are maturity onset diabetes of the young (MODY) 2 (heterozygotes for glucokinase [GCK] mutations) or MODY 3 (hepatocyte nuclear factor [HNF] 1 alpha mutation) (294). A history of family members with longstanding isolated elevated FBG with mild A1C elevations that do not progress to “frank” diabetes over a long duration is suggestive of MODY 2. During pregnancy, the usual phenotype for MODY 2 of isolated elevated FBG is not always seen, even though this phenotype may be present outside of pregnancy in the same woman (295). Fetal carriers of GCK mutations (50% of fetuses of an affected parent) do not usually have macrosomia. Fetuses without the GCK mutation of mothers with GCK mutation are at increased risk of macrosomia. The best way to manage women with GCK mutation during pregnancy has yet to be established, but regular fetal growth assessment can aid in the establishment of appropriate glucose targets during pregnancy for women with documented or strongly suspected GCK mutations.

A family history where approximately 50% of family members over 3 generations have diabetes, especially if they are thin and known to be very responsive to insulin secretagogues is highly suggestive of MODY 3 (HNF1 alpha) mutation. MODY 1 (HNF4 alpha mutation) has a similar phenotype to MODY 3 but is much less common. These forms of monogenetic diabetes have greater increased risk of macrosomia and neonatal hypoglycemia that may be prolonged especially in neonates that have MODY 1 (HNF4 alpha mutation). Although women with these later forms of monogenic diabetes are usually exquisitely sensitive to sulfonylureas, they should be transitioned to insulin as they prepare for pregnancy or switched to insulin during pregnancy, if this has not occurred preconception, for the same reasons as avoiding glyburide use in women with GDM.

#### *Management: Healthy behaviour interventions*

**Weight gain.** The 2009 IOM guidelines for weight gain during pregnancy were developed for a healthy population and little is known regarding optimal weight gain in women with GDM. Retrospective cohort studies of GDM pregnancies show that only 31.7% (296) to 42% (297) had GWG within IOM guidelines. Those gaining more than the IOM recommendations had an increased risk of preeclampsia (297), caesarean deliveries (296,297), macrosomia (296,297), LGA (296–298) and GDM requiring pharmacological agents (297). Modification of IOM criteria, including more restrictive targets of weight gain, did not improve perinatal outcomes of interest (296). A large population-based study including women with GDM, concluded that while pre-pregnancy BMI, GDM and excessive GWG are all associated with LGA, preventing excessive GWG has the greatest potential of reducing LGA risk (299). These researchers suggest that, in contrast to obesity and GDM prevention, preventing excessive GWG may be a more viable option as women are closely followed in pregnancy.

A large number of women with overweight or obesity and with GDM gain excessive weight in pregnancy (296,298) and a large proportion exceed their IOM total target by the time of GDM diagnosis (296). A systematic review found that pregnant women with overweight or obesity who gain below the IOM recommendation, but have an appropriately growing fetus, do not have an increased risk of having a SGA infant (118), leading some to recommend that encouraging increased weight gain to conform with IOM

guidelines will not improve maternal or fetal outcomes (300). However, other researchers urge caution as they have found that, in women with overweight or obesity and GDM, a weight loss or gain of  $\leq 5$  kg was associated with SGA and decreases in neonatal fat mass and lean body mass, including length and head circumference (301). The findings of a retrospective cohort study including women with overweight or obesity and with GDM show that after adjusting for confounding variables, modest weight loss after GDM diagnosis may not adversely impact fetal growth among those in obesity class II/III and those exceeding the IOM guidelines for total GWG at the time of GDM diagnosis (302).

A Cochrane review (49 trials of 11,444 women) was performed to evaluate the effectiveness of diet or exercise or both in preventing excessive gestational weight gain and associated adverse pregnancy outcomes (303). Study interventions involved mainly diet only, exercise only and combined diet and exercise interventions compared with standard care. Results show that diet or exercise or both reduced GWG on average by 20%. Low glycemic load (GL) diets, supervised or unsupervised exercise only or diet and exercise in combination all led to similar reductions in the number of women gaining excessive weight in pregnancy. There was no clear difference between intervention and control groups with regards to pre-eclampsia, caesarean section, preterm birth and macrosomia. In subgroup analysis by risk, high-risk women (having overweight or obesity, or with or at risk of GDM) who received combined diet and physical activity intervention experienced a 15% reduction in macrosomia.

Further studies are needed to develop weight gain guidelines for GDM patients and to determine whether weight gain less than the IOM guidelines or weight loss in pregnancy is safe. Until this data are available, women with GDM should be encouraged to gain weight as per the IOM guidelines for the BMI category to reduce adverse maternal and neonatal outcomes and postpartum weight retention.

**Nutrition therapy.** Nutrition therapy is a cornerstone for managing GDM. All women at risk for or diagnosed with GDM should be assessed, counselled and followed up by a registered dietitian when possible (304–306). Nutrition therapy should be designed to promote adequate nutritional intake without ketosis, achievement of glycemic goals, appropriate fetal growth and maternal weight gain (307–310). Recommendations for nutrition best practice (304) and a review of the role of nutrition therapy in GDM management (311) is available.

A great variety of diets are used for managing GDM. While carbohydrate moderation is usually recommended as first-line strategy to achieve euglycemia (312), evidence available to support the use of a low-glycemic-index (GI) diet is increasing. A randomized controlled trial of 70 healthy pregnant women, randomized to low glycemic index (GI) vs. a conventional high-fibre diet from 12 to 16 weeks' gestation, showed a lower prevalence of LGA without an increase in SGA in the low-GI group (313). This led to the hypothesis that a low-GI diet may be beneficial in women with GDM. An earlier systematic review of 9 randomized controlled trials, in which 11 different diet types were assessed within 6 different diet comparisons, did not support the recommendation of 1 diet type over another as no significant differences were noted in macrosomia, LGA or caesarean section rates (314). However, a more recent systematic review and meta-analysis does support the use of low GI diets (315). In this review and meta-analysis of 9 randomized controlled trials (n=884 women with GDM), 3 meta-analyses were performed according to type of dietary intervention used—low-GI, total energy restriction and low-carbohydrate diet. Only the low-GI diet was associated with less frequent insulin use and lower newborn weight without an increase in numbers of SGA and macrosomia (315). Results of a meta-analysis of 5 randomized controlled trials (316) and a systematic review (317) in GDM patients showed that

low-GI diets reduce the risk of macrosomia and LGA, respectively. Low-GI diets are associated with lower postprandial blood glucoses in recent randomized controlled trials (318,319).

In summary, current evidence although limited, suggests that women with GDM may benefit from following a low-GI meal pattern (320). Thus, advice on meal planning for women with GDM should emphasize a healthy diet during pregnancy, with a minimum of 175 g/day of carbohydrate (321) distributed over 3 moderate-sized meals and 2 or more snacks (1 of which should be at bedtime), (304,311) as well as replacing high-GI foods with low-GI ones.

**Physical activity.** In combination with nutritional intervention, physical activity appears to be more effective for GDM management than GDM prevention. A recent review reported that 5 of 7 studies (71%, 5 randomized controlled trials, 1 case-control, 1 self-enrolment) demonstrated a positive impact of physical activity interventions on GDM management by reducing insulin use and/or by improving glycemic control in women with GDM (322). Adherence to the physical activity program was good overall except among the 2 studies that were unsuccessful at improving glycemic control; 1 reported low compliance with physical activity recommendations, and the other proposed an exercise program with a higher level of intensity (>70% of maximal heart rate). No studies had an effect on infant birth weight or macrosomia rate and only 1 was successful in reducing GWG. It can be argued that these studies were not powered enough to demonstrate any impact on birthweight or on adverse pregnancy outcomes. Indeed, relevant limitations for these studies include the following: samples were small (mean of 43 participants per study), participants had different metabolic profiles and risks factors, and different diagnostic criteria for GDM were used.

The best type of intervention that should be recommended is unclear since all the successful programs used different exercise modalities in terms of intensity, type, duration and frequency. More recently, an initiative in India, the Wings Project, demonstrated that an intervention based on increasing total footsteps with pedometers was able to improve glycemic control in 151 women with GDM and reduce adverse neonatal outcomes in the more active tertiles when compared to their GDM counterparts in the upper tertiles of sedentary behaviour (323). Since no exercise-related injuries were experienced during pregnancy in all those studies, physical activity intervention seems safe to recommend.

All together, current knowledge suggests that physical activity interventions in women with GDM should be encouraged unless obstetrical contraindications exist as physical activity may be an important component of GDM management. However, identification of a specific program of physical activity that should be prescribed to GDM women is currently not possible. Further studies are needed involving larger populations to enable the prescription of an evidence-based physical activity intervention.

**Glycemic control.** In a systematic review of reports of BG levels in non-GDM pregnancies, normal BG levels during later pregnancy (mean and 1 SD above mean) were: fasting  $3.9 \pm 0.4$  mmol/L, 1 hour postprandial  $6.1 \pm 0.7$  mmol/L and 2 hours postprandial  $5.5 \pm 0.6$  mmol/L with a mean BG of  $4.9 \pm 0.6$  mmol/L (84). The peak postprandial BG occurred at  $69 \pm 24$  minutes (84). However, it should be noted that the mean FBG derived from the total of 255 subjects in this report was 0.6 mmol/L lower than that reported in the HAPO study (273). The HAPO study was the largest prospective study of glycemia in pregnancy and reported a mean FBG of  $4.5 \pm 0.4$  mmol/L, derived from 23,316 pregnant women (273). BG levels in pregnant women with obesity without diabetes were slightly higher than their lean counterparts in a study in which CGM was performed in early and late pregnancy after placing pregnant women with obesity or normal weight on a controlled diet (324).

Importantly, it has been demonstrated that the diagnostic OGTT values were not the best predictors of outcomes whereas CBG levels during treatment were strongly correlated to adverse pregnancy outcomes (325). For women with GDM, good outcomes have been reported using targets of FBG  $<5.3$  mmol/L, 1 hour postprandial BG  $<7.8$  mmol/L and 2 hours postprandial  $<6.7$  mmol/L (86–89) and are close to the targets of the 2 randomized controlled trials showing benefit for the treatment of GDM (85,256). Even if BG can normally and physiologically decrease during pregnancy below the traditional level of 4.0 mmol/L, women receiving insulin should maintain BG  $>3.7$  mmol/L to avoid repeated hypoglycemia—see *Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Definition of hypoglycemia during pregnancy*, for further details. On the other hand, recent studies have questioned the upper limit of the FBG target. A systematic review of 34 studies (9,433 women) suggests that a FBG  $\leq 5.0$  mmol/L was associated with a protective effect on the development of macrosomia (OR=0.53, 95% CI 0.31–0.90,  $p=0.02$ ), LGA (OR=0.68, 95% CI 0.53–0.88,  $p=0.01$ ), neonatal hypoglycemia (OR 0.65, 95% CI 0.49–0.85,  $p=0.01$ ), hyperbilirubinemia (OR 0.63, 95% CI 0.43–0.90,  $p=0.01$ ) and preeclampsia (OR 0.47, 95% CI 0.31–0.72,  $p=0.01$ ) when it was evaluated for the third trimester (326). Risks of maternal hypoglycemia or fetal low birth weight were not evaluated in this review and adjustment for maternal BMI and different diagnostic criteria for GDM was not performed. However, this meta-analysis supports the work of Rowan et al demonstrating that the lowest risk of complications was seen when fasting CBG was  $<4.9$  mmol/L (mean SD  $4.6 \pm 0.3$  mmol/L) (325). Even if the frequency of SGA infants was lower across the tertile of mean maternal fasting glycemia in this study, SGA rate in women with the lowest mean FBG was not increased and was, in fact, comparable with the rate of the background population. SGA rate was inversely correlated with maternal weight gain before assessment, suggesting that SGA could be partly prevented by adequate follow up of GWG in those women.

Overall, data suggests that a reduced FBG target of  $\leq 5.0$  mmol/L for GDM women would limit LGA and other perinatal complications rates. However, large, well-conducted and randomized controlled trials comparing different BG targets are needed to directly address optimal fasting and postprandial BG targets. Further studies should also assess the risk of maternal hypoglycemia, SGA, insulin use and cost-effectiveness of such modification.

#### *Adjustment of glycemic targets based upon fetal abdominal circumference on third-trimester ultrasound*

Despite reduced perinatal morbidity with interventions to achieve euglycemia in women with GDM, increased prevalence of macrosomia persists in this population. To improve outcomes, 4 randomized controlled trials (327–329) have examined the use of fetal abdominal circumference (AC) as measured sonographically and regularly in the third trimester to guide medical management of GDM. This approach involves using stricter maternal BG targets (FBG  $<4.5$  and 2-hour postprandial BG  $<5.6$  to 6.1 mmol/L), and an increased use of insulin, if needed, when the fetal AC measures  $\geq 75$ th percentile (327–329) or  $\geq 70$ th percentile (330) and conversely relaxed glycemic objectives (FPG  $<5.6$ –6.7 and 2-hour postprandial BG  $<7.8$  to 11.1 mmol/L) when risk of LGA was considered low. A recent meta-analysis has shown that this approach can result in a significant 50% reduction in LGA rate ( $p=0.0017$ , number needed to treat [NNT] 10 women with GDM) compared to standard care, without an increase in SGA rate (331), but caution should be used before extrapolation of these results to routine clinical practice. Indeed, it may be difficult to apply this flexible approach given the extreme glycemic targets that were used, the fact that routine determination of AC is not done or sufficiently reliable, and frequent ultrasounds may not be accessible to most centres. Further analyses are needed to estab-

lish safe stricter and relaxed glycemic targets that should be recommended for women with GDM to limit LGA and SGA rates.

### Monitoring

Frequent SMBG is essential to guide therapy of GDM (331,333). Both fasting and postprandial testing are recommended to guide therapy in order to improve fetal outcomes (89,332). CGMS have been useful in determining previously undetected hyperglycemia, but it is not clear if it is cost effective (334–336). Recent randomized controlled trials suggest that CGM may be of benefit in the treatment of GDM. In a randomized trial, 340 women were randomized to undergo blinded 3-day CGM every 2 to 4 weeks from GDM diagnosis at 24 weeks GA or routine care with SMBG (337). Women using CGM had less glucose variability, less BG values out of the target range, as well as less preeclampsia, primary caesarean section and lower infant birthweight.

In a similar study of 106 women with GDM, given CGM from 24 to 28 weeks or 28 weeks to delivery, excess maternal weight gain was reduced in the CGM group compared to women doing only SMBG, especially in women who were treated with CGM earlier, at 24 weeks GA (338). A1C was lower in the CGM group but not statistically significantly different. More studies are needed to assess the benefits of CGM in this population.

In an effort to control their BG by diet, women with GDM may develop starvation ketosis. Older studies raised the possibility that elevated ketoacids may be detrimental to the fetus (94,339). While the clinical significance of these findings are questionable, it appears prudent to avoid ketosis.

### eHealth medicine: Telehomecare and new technologies for glucose monitoring and healthy behaviour interventions

Use of new technologies and web-based platforms for BG monitoring in pregnant women with diabetes in Canada and worldwide is rapidly increasing. These initiatives allow for 2-way communication with women monitoring and transmitting their BG results in real time to health-care providers for feedback. Studies have demonstrated 38.0% (340) to 82.7% (341) reduction in face-to-face medical visits and decreased insulin use (340) in pregnant women using telehomecare in conjunction with conventional care, without an increase in maternal or perinatal complications. While 4 studies of GDM women (total n=272) have demonstrated comparable glycemic control and pregnancy outcomes (342–345), other studies with type 1 diabetes (346–348) and GDM (348) have shown improved glycemic control and pregnancy outcomes in the group using web-based programs compared to standard care. Enhanced patient empowerment and greater satisfaction with the care received are also reported in groups using new monitoring technology (340–343,345,348,349). However, generalizability of those studies is questionable as these studies were small, conducted in very specific settings and used different types of technologies and e-platforms. Furthermore, acceptance of these interventions by marginalized population subgroups (350) and in remote regions would also be important to determine. Finally, studies assessing cost effectiveness of these measures, both direct (health system resources utilization) and indirect (work absenteeism, parking, daycare fees) are needed.

Systematic reviews of the literature on the use of technology to support healthy behaviour interventions for healthy pregnant women (351) and women with GDM (352,353) showed that good quality trials in this area are few and research on this topic is in its infancy stage. This is evidenced by the focus on intervention acceptance measures, use of small sample sizes, lack of demonstration of causality and lack of examination of long-term effects or follow up.

In summary, new technologies and telehomecare programs have so far shown encouraging results to reduce medical visits and favour

patient empowerment without increasing complication rates in pregnant women with diabetes. In an era of increased prevalence of GDM, well designed and sufficiently powered randomized controlled trials are needed to evaluate the effectiveness of technology as a tool for glucose management, healthy behaviour interventions and a way of relieving health-care system burden.

### Pharmacological therapy

**Insulin.** If women with GDM do not achieve BG targets within 2 weeks of initiation of nutritional therapy and exercise, pharmacological therapy should be initiated (354,355). The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidity (355,356). A variety of protocols have been used, with multiple daily injections (MDI) being the most effective (357). Insulin usually needs to be continuously adjusted to achieve glycemic targets. Although the rapid-acting bolus analogues aspart and lispro can help achieve postprandial targets without causing severe hypoglycemia (356–358), improvements in fetal outcomes have not been demonstrated with the use of aspart or lispro compared to regular insulin (356,357) (see *Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Pharmacological therapy*). Glargine and detemir have primarily been assessed in women with pre-existing diabetes in pregnancy (see *Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Pharmacological therapy*). Randomized trial evidence suggests levemir is safe and may afford less maternal hypoglycemia compared to neutral protamine hagedorn (NPH), while observational studies suggest that glargine, although theoretically less desirable, is also safe.

### Other antihyperglycemic agents

**Metformin.** In several meta-analyses of randomized trials studying the use of metformin compared with insulin in women with gestational diabetes, women treated with metformin had less weight gain (359) and less pregnancy-induced hypertension compared to women treated with insulin (360–365). Infants of mothers using metformin had lower gestational age and less neonatal hypoglycemia. On the other hand, there was conflicting evidence regarding preterm birth, with some studies finding a significant increase with the use of metformin, while others did not. This finding was mainly demonstrated by the Metformin in Gestational diabetes (MiG) trial (366), where there was an increase in spontaneous preterm births rather than iatrogenic preterm births. The reason for this was unclear.

While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta. Results of The Offspring Follow Up of the Metformin in Gestational diabetes (MiG TOFU) trial, at 2 years, showed that the infants exposed to metformin have similar total fat mass but increased subcutaneous fat, suggesting a possible decrease in visceral fat compared to unexposed infants (367). In another follow-up study of infants exposed to metformin during pregnancies with gestational diabetes, children exposed to metformin weighed more at the age of 12 months, and were heavier and taller at 18 months, however, body composition was similar (368) as was motor, social and linguistic development. Studies looking at neurodevelopment showed similar outcomes between exposed and nonexposed infants at 2 years of age (369,370).

In summary, long-term follow up from 18 months to 2 years indicate that metformin exposure in-utero does not seem to be harmful with regards to early motor, linguistic, social, (368), metabolic (367,368) and neurodevelopmental (369,370) outcomes. Longer-term follow up is not yet available.

**Glyburide.** Glyburide has been shown to cross the placenta. In 2 meta-analyses of randomized trials studying the use of glyburide vs. insulin in women with GDM, glyburide was associated with

increased birthweight, macrosomia and neonatal hypoglycemia compared with insulin (361,362). In the same meta-analyses, compared to metformin, glyburide use was associated with increased maternal weight gain, birthweight, macrosomia and neonatal hypoglycemia (361,362). Therefore, the use of glyburide during pregnancy is not recommended as first- or second-line treatment, but may be used as third-line treatment if insulin is declined by the mother and metformin is either declined or insufficient to maintain good glycemic control.

**Acarbose.** There is only 1 small randomized trial looking at the use of acarbose in women with GDM. There was no difference in maternal/fetal outcomes compared to insulin although gastrointestinal side effects were increased (371).

**Other antihyperglycemic agents.** There is no human data on the use of DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors. The use of these noninsulin antihyperglycemic agents is not recommended during pregnancy.

### **Obstetrical Considerations in Women with Gestational Diabetes (See Section Entitled ‘Obstetrical Considerations in Women with Pre-Existing Diabetes and Gestational Diabetes’)**

#### *Intrapartum glucose management*

The primary goal of intrapartum glucose management in women with gestational diabetes is to prevent neonatal hypoglycemia, which is thought to occur from the fetal hyperinsulinism caused by maternal hyperglycemia (372). Longer-term follow-up studies have found that infants with neonatal hypoglycemia had increased rates of neurological abnormalities at 18 months, especially if hypoglycemic seizures occurred or if hypoglycemia was prolonged (373,374) and at 8 years of age with deficits in attention, motor control and perception (375).

#### *Risk of neonatal hypoglycemia is related to maternal BG levels*

Maternal hyperglycemia during labour, even when produced for a few hours by intravenous fluids in mothers without diabetes, can cause neonatal hypoglycemia (376,377). Studies have generally been performed in mothers with pregestational diabetes or insulin-treated GDM. These have been observational with no randomized trials deliberately targeting different levels of maternal glycemia during labour. Most have found that there is a continuous relationship between mean maternal BG levels during labour and the risk of neonatal hypoglycemia with no obvious threshold. Authors have often chosen 2 levels within the range and shown that there is more hypoglycemia with the higher value, but the studies do not arrive at a common value and vary from <4.6 mmol/L to <8.0 mmol/L (378–387). By consensus, we suggest aiming for <7.0 mmol/L during labour and delivery.

#### *Intrapartum insulin management*

Insulin requirements tend to decrease intrapartum (385,386). There are very few studies (although many published protocols) that examine the best method of managing glycemia during labour (387,388). Given the lack of studies, there are no specific protocols that can be recommended to achieve the desired maternal BG levels during labour.

#### *Postpartum*

**Breastfeeding.** Women with GDM should be encouraged to breastfeed immediately after delivery and for at least 4 months postpartum,

as this may contribute to the reduction of neonatal hypoglycemia (211) and offspring obesity (215), and prevent the development of metabolic syndrome and type 2 diabetes in the mother (214,389–397). Longer duration and more intense breastfeeding is associated with less diabetes in the mother with hazard ratios as low as 0.43 (395). Furthermore, offspring that are breastfed for at least 4 months have lower incidence of obesity and diabetes longer term (212). However, GDM is associated with either similar (189) or poor initiation rates (398) compared to those without diabetes, as well as poor continuation rates (189). Factors associated with cessation of breastfeeding before 3 months include breastfeeding challenges at home, return to work, inadequate support, caesarean section and lower socioeconomic status (399). In conclusion, women with GDM should be encouraged to breastfeed as long as possible as intensity and duration of nursing have both infant and maternal benefits (current recommendation by Canadian Paediatric Society is up to 2 years) (217), but more support is needed as this group is at risk for early cessation.

**Long-term maternal risk of dysglycemia.** With the diagnosis of GDM, there is evidence of impairment of both insulin secretion and action (400,401). These defects persist postpartum and increase the risk of impaired fasting glucose, IGT and type 2 diabetes (402,403). The cumulative risk increases markedly in the first 5 years and more slowly after 10 years (404,405). At 3 to 6 months postpartum, risks of dysglycemia are in the 16% to 20% range. While elevated FPG during pregnancy is a strong predictor of early development of diabetes (406–408), other predictors include age at diagnosis, use of insulin, especially bedtime insulin or oral agents, and more than 2 pregnancies (408–410). A1C at diagnosis of GDM is also a predictor of postpartum diabetes (408,411). Any degree of dysglycemia is associated with increased risk of postpartum diabetes (412). After 16 years, 40% of women with prior GDM will develop type 2 diabetes (413). Some women with GDM, especially lean women under 30 years of age who require insulin during pregnancy, progress to type 1 diabetes (414,415). Women with positive autoantibodies (anti-glutamic acid decarboxylase [anti-GAD], anti-insulinoma antigen 2 [anti-IA2]) are more likely to have diabetes by 6 months postpartum (416).

Postpartum testing is essential to identify women who continue to have diabetes, those who develop diabetes after temporary normalization and those at risk, including those with IGT. However, many women do not receive adequate postpartum follow up, and many believe they are not at high risk for diabetes (417–419). Only 14% to 50% return for postpartum testing (419–422) with annual follow-up rates of only 20% (423,424). Proactive contacts increased testing from 33% to 60% (425,426). Despite this finding, more work in this area is needed to improve uptake. One study revealed that, despite email reminders, absolute improvement was only 10% (427).

Women should be screened postpartum to determine their glucose status. Postnatal FBG has been the most consistently found variable in determining women at high risk for early postpartum diabetes (428). However, FPG alone will miss many women with some degree of abnormal glucose tolerance (429–431); therefore, a 75 g OGTT should be done between 6 weeks and 6 months postpartum. Some recent trials have shown that early postpartum testing (day 2 postpartum) may be as good at detecting diabetes as standard testing times; however, follow up in the standard testing group was poor. One study noted a 100% sensitivity and 94% specificity for diabetes detection but not as effective as identifying other forms of glucose abnormalities, and the sample size was small. If this can be confirmed in more rigorous trials, it may be useful to do early postpartum testing in women at high risk for type 2 diabetes or at high risk for noncompliance with follow up (432). A1C does not have the sensitivity to detect dysglycemia



postpartum (433) and, even combined with FBS, did not help improve its sensitivity (434,435).

Women should be counselled that the recurrence rate of GDM is high, from 30% to 84%, in subsequent pregnancies (436,437). Metabolic syndrome has been shown to be more prevalent in women with GDM (438–440) with rates as high as 23%, 3 times age-matched control using IADPSG criteria to diagnose GDM (441). Given the increased risk of CVD (OR 1.51) (442) with metabolic syndrome, consideration should be given to screening for all components of the metabolic syndrome in the postpartum care of women with GDM, especially if there is a family history (443,444). Education on healthy behaviour interventions to prevent diabetes and CVD should begin in pregnancy and continue postpartum (445,446). Awareness of physical activity for prevention of diabetes is low (447), and emphasis on targeted strategies that incorporate women's exercise beliefs may increase participation rates (448). Although 1 study showed women with prior gestational diabetes and IGT reduced their risk of developing diabetes with both a lifestyle intervention or metformin, these women were, on average, 12 years postpartum. More recent intervention studies of women with GDM alone who were closer to the time of delivery were often underpowered and compliance with the intervention was low.

The 2 largest randomized controlled trials to date were conflicting. The Mothers After Gestational Diabetes in Australia (MAGDA) study randomized 573 women within the first year postpartum to a group-based lifestyle intervention vs. standard care. After 1 year they found a 1 kg difference in weight and no difference in waist circumference or FBG (449). However, only 10% of women attended all the sessions, and 34% attended none. In another randomized controlled trial, 260 women were randomized to receive the Mediterranean diet and physical activity sessions for 10 weeks between 3 to 6 months postpartum, and then reinforcement sessions at 9 months, 1, 2 and 3 years. They found that significantly less women developed glycemic disorders in the intervention group (42% vs. 58%) (450). At 3 years, women in the intervention group had a lower BMI and better nutrition but similar rates of physical activity. However, engaging women to adopt health behaviours may be challenging soon after delivery. More studies are needed to explore interventions that may help this population reduce their risk.

*Long-term metabolic impact of fetal exposure to maternal GDM.* Observational studies have linked maternal GDM with poor metabolic outcomes in offspring (451). However, 3 systematic reviews (452–454) have concluded that maternal GDM is inconsistently or minimally associated with offspring obesity and overweight and this relationship is substantially attenuated or eliminated when adjusted for confounders. The HAPO offspring study extended their follow up to 5- to 7-year-olds and found that after adjustment for maternal BMI, higher maternal plasma glucose (PG) concentrations during pregnancy were not a risk for childhood obesity (455). In contrast, a recent cohort found an association between maternal FPG and offspring BMI at 7 years of age that persisted after adjustment for birth weight, socioeconomic status and maternal pre-pregnancy BMI (456). Current evidence fails to support the hypothesis that treatment of GDM reduces obesity and diabetes in offspring. Three follow-up studies of offspring whose mothers were in randomized controlled trials of GDM management found that treatment of GDM did not affect obesity at 4 to 5 years, 5 to 10 years or a mean age of 9 years (457–459). This follow up may be too short to draw conclusions about longer-term impact. However, it is interesting to note that the excess weight in offspring of women with diabetes in the observational work by Silverman et al (460) was evident by 5 years of age. Furthermore, a subanalysis of another trial follow-up study revealed that comparison by age at follow up 5 to 6 vs. 7 to 10 years old did not influence their findings (458).

Association between maternal diabetes and other long-term offspring outcomes, such as childhood academic achievement and autism spectrum disorders (ASD), have been explored in observational studies. Reassuringly, offspring of mothers with pre-existing type 1 diabetes had similar average grades when finishing primary school compared to matched controls (461). Associations between autism and different types of maternal diabetes during pregnancy have been inconsistent and usually disappear or are substantially attenuated after adjustment for potential confounders (462,463). Unspecified antihyperglycemic medications were either not associated with ASD (463) or not independently associated with ASD risk (462,463), but merit further investigation to assess if there are differences in the association between different types of antihyperglycemic agents and ASD.

*Contraception after GDM.* Women with prior GDM have numerous choices for contraception. Risk and benefits of each method should be discussed with each patient and same contraindications apply as in non-GDM women. Special attention should be given as women with GDM have higher risk of metabolic syndrome and, if they have risk factors, such as hypertension and other vascular risks, then IUD or progestin-only contraceptives should be considered (464). The effect of progestin-only agents on glucose metabolism and risk of type 2 diabetes in lactating women with prior GDM merits further study as in 1 population this risk was increased (464,465).

*Planning future pregnancies.* Women with previous GDM should plan future pregnancies in consultation with their health-care providers (466,467). Screening for diabetes should be performed prior to conception to assure normoglycemia at the time of conception (see Screening for Diabetes in Adults chapter, p. S16), and any glucose abnormality should be treated. In an effort to reduce the risk of congenital anomalies and optimize pregnancy outcomes, all women should take a folic acid supplement of 1.0 mg (467).

## RECOMMENDATIONS

### Pre-existing Diabetes

#### Preconception care

- All women of reproductive age with type 1 or type 2 diabetes should receive ongoing counselling on reliable birth control, the importance of glycemic control prior to pregnancy, the impact of BMI on pregnancy outcomes, the need for folic acid and the need to stop potentially embryopathic drugs prior to pregnancy [Grade D, Level 4 (7)].
- Women with type 2 diabetes with irregular menses/PCOS who lose significant weight or are started on metformin or a thiazolidinedione (TZD) should be advised that fertility may improve and be counselled regarding possible pregnancy and receive preconception counselling [Grade D, Consensus].
- Before attempting to become pregnant, women with type 1 or type 2 diabetes should:
  - Receive preconception counselling that includes optimal diabetes management, including nutrition, preferably in consultation with an interprofessional pregnancy team to optimize maternal and neonatal outcomes [Grade C, Level 3 (6,7,6,468)]
  - Strive to attain a preconception A1C  $\leq 7.0\%$  (or A1C  $\leq 6.5\%$  if can safely be achieved) to decrease the risk of:
    - Spontaneous abortion [Grade C, Level 3 (159)]
    - Congenital anomalies [Grade C, Level 3 (7,76,469,470)]
    - Preeclampsia [Grade C, Level 3 (471,472)]
    - Progression of retinopathy in pregnancy [Grade A, Level 1 for type 1 diabetes (25); Grade D, Consensus for type 2 diabetes]
    - Stillbirth [Grade C, Level 3 (77)].
  - Supplement their diet with multivitamins containing 1 mg of folic acid at least 3 months preconception and continuing until at least

- 12 weeks of gestation to prevent congenital anomalies [Grade D, Level 4 (14)]
- d. Discontinue medications that are potentially embryopathic, including any from the following classes:
- ACE inhibitors and ARBs
    - Prior to conception in women with hypertension alone [Grade C, Level 3 (65–67)]
    - Upon detection of pregnancy in women with CKD [Grade D, Consensus]
  - Statins [Grade D, Level 4 (473)].
4. Women on metformin and/or glyburide preconception may continue on these agents if glycemic control is adequate until pregnancy is achieved [Grade C, Level 3 (152,153)]. Women on other antihyperglycemic agents, should switch to insulin prior to conception as there are no safety data for the use of other antihyperglycemic agents in pregnancy [Grade D, Consensus].

#### Assessment and management of complications

5. Women should undergo an ophthalmological evaluation by a vision care specialist during pregnancy planning, the first trimester, as needed during pregnancy after that and, again, within the first year postpartum in order to identify progression of retinopathy [Grade B, Level 1 for type 1 diabetes (25); Grade D, Consensus for type 2 diabetes]. More frequent retinal surveillance during pregnancy as determined by the vision care specialist should be performed for women with more severe pre-existing retinopathy and poor glycemic control, especially those with the greatest anticipatory reductions in A1C during pregnancy, in order to reduce progression of retinopathy [Grade B, Level 1 for type 1 diabetes (25,27); Grade D, Consensus for type 2 diabetes].
6. Women with albuminuria or CKD should be followed closely for the development of hypertension and preeclampsia [Grade D, Consensus].

#### Management in pregnancy

7. Once pregnant, women with pre-existing diabetes should receive care by an interprofessional diabetes health-care team, including diabetes educators (nurse and dietitian), obstetrical care provider, and physician/nurse practitioner, with expertise in diabetes and pregnancy to minimize maternal and fetal risks [Grade C, Level 3 (7)].
8. Once pregnant, women with type 2 diabetes should be switched to insulin for glycemic control [Grade D, Consensus]. Noninsulin antihyperglycemic agents should only be discontinued once insulin is started [Grade D, Consensus].
9. Pregnant women with pre-existing diabetes should:
- Receive an individualized insulin regimen and glycemic targets typically using intensive insulin therapy by basal-bolus injection therapy [Grade A, Level 1B, for type 1 diabetes (73,129); Grade A, Level 1, (129) for type 2 diabetes] or CSII (insulin pump) [Grade C, Level 3 (147) for type 1 diabetes]
  - Strive for target BG values [Grade D, Consensus for all values]:
    - Fasting and preprandial <5.3 mmol/L
    - 1 hour postprandial <7.8 mmol/L
    - 2 hours postprandial <6.7 mmol/L
  - Aim for an A1C of  $\leq 6.5\%$  during pregnancy ( $\leq 6.1\%$  if possible), if can be achieved safely, to lower the risk of late stillbirth and infant death [Grade D, Level 4 (77)]
  - Be prepared to raise BG and A1C targets in the presence of severe hypoglycemia during pregnancy [Grade D, Consensus]
  - Perform SMBG, both pre- and postprandially, to improve pregnancy outcomes [Grade C, Level 3 (76)].
10. Health-care providers should discuss appropriate weight gain at the initial visit and regularly throughout pregnancy [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be individualized based on the Institute of Medicine guidelines by pre-pregnancy BMI to lower the risk of LGA infants [Grade B, Level 2 (120,121)].
11. Aspart, lispro or glulisine may be used in women with pre-existing diabetes to improve postprandial BG [Grade C, Level 2 (104) for aspart; Grade C, Level 3 (132,133,135) for lispro; Grade D, Level 4 (137) for glulisine] and reduce the risk of severe maternal hypoglycemia [Grade C, Level 3 (135) for aspart and lispro; Grade D, Consensus for glulisine] compared with human regular insulin.

12. Detemir [Grade B, Level 2 (474)] or glargine [Grade C, Level 3 (142)] may be used in women with pre-existing diabetes as an alternative to NPH and is associated with similar perinatal outcomes.
13. Women with pre-existing diabetes should start ASA 81\* mg daily at 12–16 weeks' gestation to reduce the risk of preeclampsia [Grade D, Level 4 (48)]. \*81 mg is commonly used in Canada due to its commercial availability, but the optimal dose has yet to be determined. Recent evidence suggests that higher dosage regimens might provide additional efficacy.
14. Women with type 1 and insulin-treated type 2 diabetes who receive antenatal corticosteroids to improve fetal lung maturation should follow a protocol that increases insulin doses proactively to prevent hyperglycemia [Grade D, Level 4 (157)] and DKA [Grade D, Consensus].
15. Women with type 1 diabetes in pregnancy should be offered use of CGM to improve glycemic control and reduce neonatal complications [Grade B, Level 2 (113)].

#### Fetal surveillance and timing of delivery

16. In women with pre-existing diabetes, assessment of fetal well-being should be initiated at 30–32 weeks' gestation and performed weekly starting at 34–36 weeks' gestation and continued until delivery [Grade D, Consensus]. Earlier onset and/or more frequent fetal health surveillance is recommended in those considered at highest risk [Grade D, Consensus].
17. In women with uncomplicated pre-existing diabetes, induction should be considered between 38–39 weeks of gestation to reduce risk of stillbirth [Grade D, Consensus]. Induction prior to 38 weeks of gestation should be considered when other fetal or maternal indications exist, such as poor glycemic control [Grade D, Consensus]. The potential benefit of early term induction needs to be weighed against the potential for increased neonatal complications.

#### Intrapartum glucose management

18. Women should be closely monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0–7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].
19. CSII (insulin pump) may be continued in women with pre-existing diabetes during labour and delivery if the women or their partners can independently and safely manage the insulin pump and they choose to stay on the pump during labour and delivery [Grade C, Level 3 (172) for type 1 diabetes; Grade D, Consensus for type 2 diabetes].

#### Postpartum

20. Insulin doses should be decreased immediately after delivery below prepregnant doses and titrated as needed to achieve good glycemic control [Grade D, Consensus].
21. Women with pre-existing diabetes should have frequent blood glucose monitoring in the first days postpartum, as they have a high risk of hypoglycemia [Grade D, Consensus].
22. For women with pre-existing diabetes, early neonatal feeding should be encouraged immediately postpartum to reduce neonatal hypoglycemia [Grade C, Level 3 (211)]. Breastfeeding should be encouraged to reduce offspring obesity [Grade C, Level 3 (215)] and for a minimum of 4 months to reduce the risk of developing diabetes [Grade C, Level 3 (212)]. Women with pre-existing diabetes should receive assistance and counselling on the benefits of breastfeeding, in order to improve breastfeeding rates, especially in the setting of maternal obesity [Grade D, Consensus].
23. Women with type 1 diabetes should be screened for postpartum thyroiditis with a TSH test at 2–4 months postpartum [Grade D, Consensus].
24. Metformin and/or glyburide may be used during breastfeeding [Grade C, Level 3 (203) for metformin; Grade D, Level 4 (204) for glyburide]. Other noninsulin antihyperglycemic agents should not be used during breastfeeding as safety data do not exist for these agents [Grade D, Consensus].

#### Gestational Diabetes

##### Prevention

25. In women at high risk for GDM based on pre-existing risk factors, nutrition counselling should be provided on healthy eating and prevention of

excessive gestational weight gain in early pregnancy, ideally before 15 weeks of gestation, to reduce the risk of developing GDM [Grade B, Level 2 (225,227)].

#### Screening and diagnosis

26. Women identified as being at high risk for type 2 diabetes should be offered earlier screening with an A1C test at the first antenatal visit to identify diabetes which may be pre-existing [Grade D, Consensus]. For those women with a hemoglobinopathy or renal disease, the A1C test may not be reliable and screening should be performed with an FPG [Grade D, Consensus]. If the A1C is  $\geq 6.5\%$  or the FPG is  $\geq 7.0$  mmol/L, the woman should be considered to have diabetes in pregnancy and the same management recommendations for pre-existing diabetes should be followed [Grade D, Consensus].
  - a. If the initial screening is performed before 24 weeks of gestation and is negative, the woman should be rescreened as outlined in recommendations 28 and 29 between 24–28 weeks of gestation [Grade D, Consensus].
27. All pregnant women not known to have pre-existing diabetes should be screened for GDM at 24–28 weeks of gestation [Grade C, Level 3 (475)].
28. The preferred approach for the screening and diagnosis of GDM at 24–28 weeks is the following [Grade D, Consensus]:
  - a. Screening for GDM should be conducted using the 50 g GCT administered in the nonfasting state with PG glucose measured 1 hour later [Grade D, Level 4 (272)]. A PG  $\geq 7.8$  mmol/L at 1 hour is a positive screen and is an indication to proceed to the 75 g OGTT [Grade C, Level 2 (268)]. A PG  $\geq 11.1$  mmol/L is diagnostic of gestational diabetes and does not require a 75 g OGTT for confirmation [Grade D, Level 4 (272)].
  - b. If the GCT screen is positive, a 75 g OGTT should be performed as the diagnostic test for GDM using 1 of the following criteria:
    - i. Fasting PG  $\geq 5.3$  mmol/L OR
    - ii. 1 hour PG  $\geq 10.6$  mmol/L OR
    - iii. 2 hours PG  $\geq 9.0$  mmol/L [Grade B, Level 1 (273)].
29. An alternative approach to screen and diagnose GDM is the 1-step approach: a 75 g OGTT should be performed (with no prior screening 50 g GCT) as the diagnostic test for GDM using 1 of the following criteria:
  - a. Fasting PG  $\geq 5.1$  mmol/L OR
  - b. 1 hour PG  $\geq 10.0$  mmol/L OR
  - c. 2 hours PG  $\geq 8.5$  mmol/L [Grade B, Level 1 (273)].

#### Management during pregnancy

30. Women with GDM should:
  - a. To improve pregnancy outcomes, strive for target BG values:
    - i. Fasting and preprandial  $< 5.3$  mmol/L [Grade B, Level 2 (85,88)]
    - ii. 1 hour postprandial  $< 7.8$  mmol/L [Grade D, Level 4 (87)]
    - iii. 2 hours postprandial BG  $< 6.7$  mmol/L [Grade B, Level 2 (85)]
  - b. Perform SMBG, both fasting and postprandially, to improve pregnancy outcomes [Grade B, Level 2 (89)]
  - c. For women on insulin therapy, maintain BG levels  $> 3.7$  mmol/L [Grade D, Consensus].
31. Health-care providers should discuss appropriate weight gain and healthy lifestyle interventions regularly throughout pregnancy [Grade D, Consensus]. Recommendations for weight gain for women with GDM should be individualized based on Institute of Medicine guidelines by pre-pregnancy BMI to prevent excessive gestational weight gain and reduce the risk of LGA [Grade B, Level 2 (297,299)], macrosomia and caesarean sections [Grade B, Level 2 (296,297)].
32. Nutritional counselling by a registered dietitian should be provided to women with GDM to help them achieve their nutrition, weight and blood glucose goals [Grade D, Level 4 (306)]. Women with GDM should be encouraged to eat a healthy diet for pregnancy and to replace high-GI foods with low-GI foods to reduce the need for insulin initiation and decrease birth weight [Grade C, Level 3 (315)].
33. If women with GDM do not achieve glycemic targets within 1–2 weeks with nutritional therapy and physical activity, pharmacologic therapy should be initiated [Grade D, Consensus].
  - a. Insulin in the form of basal-bolus injection therapy may be used as first-line therapy [Grade A, Level 1 (129) for insulin]

- b. Rapid-acting analogue insulin aspart, lispro or glulisine may be used over regular insulin for postprandial glucose control, although perinatal outcomes are similar [Grade B, Level 2 (356,357) for aspart and lispro; Grade D, Consensus for glulisine]
- c. Metformin may be used as an alternative to insulin [Grade A, Level 1A (362) for metformin]; however, women should be informed that metformin crosses the placenta, longer-term studies are not yet available, and the addition of insulin is necessary in approximately 40% to achieve adequate glycemic control [Grade D, Consensus].

34. In women with GDM who decline insulin and do not tolerate or are inadequately controlled on metformin, glyburide may be used [Grade B, Level 2 (362)].

#### Fetal surveillance and timing of delivery in GDM

35. Increased frequency of fetal assessment should be considered in women with GDM that is poorly controlled and/or associated with comorbid conditions [Grade D, Consensus].
36. Women with GDM can be offered induction of labour between 38–40 weeks' gestation to potentially reduce the risk of stillbirth [Grade D, Consensus] and the risk of caesarean section [Grade C, Level 2 (167,169)]. Earlier or later induction of labour should be considered based on glycemic control and the presence or absence of other comorbid conditions [Grade D, Consensus].

#### Intrapartum glucose management

37. Women with GDM should be monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0–7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].

#### Postpartum

38. Women with GDM should be encouraged to breastfeed immediately after delivery in order to avoid neonatal hypoglycemia [Grade D, Consensus] and to continue for at least 3–4 months postpartum in order to prevent childhood obesity [Grade C, Level 3 (476)] and diabetes in the offspring [Grade D, Level 4 (476)] and to reduce risk of type 2 diabetes and hypertension in the mother [Grade C, Level 3 (391,395,396,476)].
39. Women should be screened with a 75 g OGTT between 6 weeks to 6 months postpartum to detect prediabetes and diabetes [Grade D, Consensus]. Methods to improve postpartum testing, such as phone calls or email reminders to women with a history of GDM, should be employed to improve screening rates [Grade C, Level 3 (425)].
40. In women who were diagnosed with diabetes in early pregnancy based on A1C (see recommendation 29), if ongoing hyperglycemia is not evident postpartum, a confirmatory test for diabetes with a FPG or 75 g OGTT should be done at 6 to 8 weeks' postpartum [Grade D, Consensus].
41. Women with prior GDM should receive counselling regarding healthy behaviour interventions to reduce the recurrence rate in subsequent pregnancies and reduce their increased risk of type 2 diabetes [Grade C, Level 3 (445,446)].
42. In women with prior GDM who have IGT on postpartum screening, healthy behaviour interventions with or without metformin can be used to prevent/delay the onset of diabetes [Grade B, Level 2 (477,478)].

#### Abbreviations:

A1C, glycated hemoglobin; AC, abdominal circumference; ACE, angiotensin-converting enzyme; aOR, adjusted odds ratio; ARB, angiotensin II receptor blocker; ASD, autism spectrum disorder; BG, blood glucose; BMI, body mass index; BP, blood pressure; CBG, capillary blood glucose; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CrCl, creatinine clearance; CSII, continuous subcutaneous insulin infusion; CV, cardiovascular; CVD, cardiovascular disease; DHC, diabetes health-care; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; FBG, fasting blood glucose; GCT, glucose challenge test; GDM, gestational diabetes; GLP-1, glucagon-like polypeptide-1; GWG, gestational weight gain; GI, glycemic index; IGT, impaired glucose tolerance; IOL, induction of labour; IOM, Institute of Medicine; IUD, intra-uterine device; LDL-cholesterol, low-density lipoprotein cholesterol; LGA, large for gestational age; MDI, multiple daily injections; MI, myocardial infarct; NICU, neonatal intensive care unit; NNT, number needed to treat; NPH, neutral protamine Hagedorn;

OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; PG, plasma glucose; RAAS, renin angiotensin aldosterone system; RR, relative risk; SD, standard deviation; SGA, small for gestational age; SGLT2, sodium-glucose cotransporter-2; SMBG, self-monitoring of blood glucose; TSH, thyroid-stimulating hormone; TZD, thiazolidinedione.

## Other Relevant Guidelines

Screening for Diabetes in Adults, p. S16  
 Organization of Diabetes Care, p. S27  
 Type 2 Diabetes and Indigenous Peoples, p. S296

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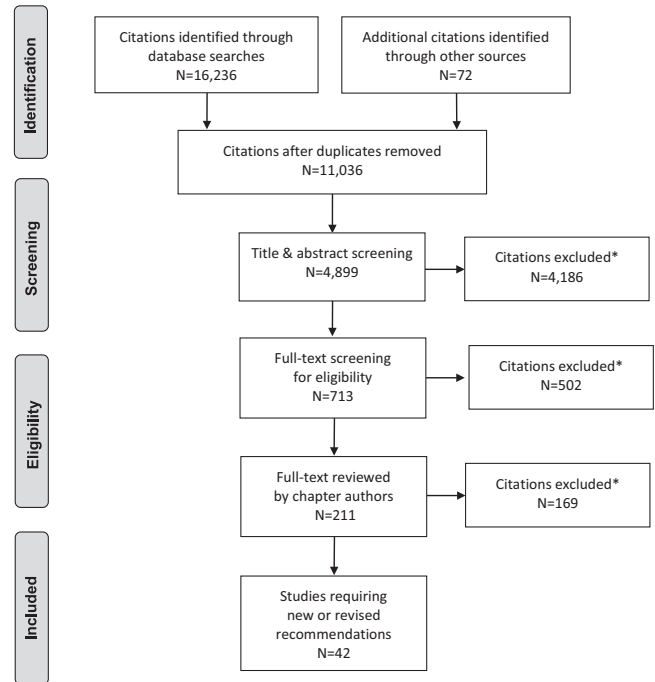
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## Literature Review Flow Diagram for Chapter 36: Diabetes and Pregnancy



\*Excluded based on: population, intervention/exposure, comparator/control or study design

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