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Gestational diabetes: Optimizing Dx and management in primary care

Understanding risk factors and glucose targets for gestational diabetes can help you identify at-risk patients and improve outcomes for mother and infant.

PRACTICE RECOMMENDATIONS

> Manage gestational diabetes mellitus (GDM) with lifestyle behavior changes first and add insulin as a secondary treatment only if glycemic targets are not being met. (A)

> Treat hyperglycemia in GDM with insulin, not metformin or glyburide; these agents cross the placenta to the fetus.

Strength of recommendation (SOR)

- Good-quality patient-oriented evidence
- **B** Inconsistent or limited-quality patient-oriented evidence
- Consensus, usual practice, opinion, disease-oriented evidence, case series

Gestational diabetes mellitus (GDM), defined as newonset hyperglycemia detected in a pregnant woman after 24 weeks of gestation, affects 4% to 10% of pregnancies in the United States annually¹ and is a major challenge for health care professionals.² During pregnancy, the body's physiologic responses are altered to support the growing fetus. One of these changes is an increase in insulin resistance, which suggests that pregnancy alone increases the patient's risk for type 2 diabetes (T2D). However, several other factors also increase this risk, including maternal age, social barriers to care, obesity, poor weight control, and family history.

If not controlled, GDM results in poor health outcomes for the mother, such as preeclampsia, preterm labor, and maternal T2D.³⁻⁵ For the infant, intrauterine exposure to persistent hyperglycemia is correlated with neonatal macrosomia, hypoglycemia, perinatal complications (eg, preterm delivery, fetal demise), and obesity and insulin resistance later in life.⁴

Primary care physicians (PCPs) are the patient's main point of contact prior to pregnancy. This relationship makes PCPs a resource for the patient and specialists during and after pregnancy. In this article, we discuss risk factors and how to screen for GDM, provide an update on practice recommendations for treatment and management of GDM in primary care, and describe the effects of uncontrolled GDM.

Know the key risk factors

Prevention begins with identifying the major risk factors that contribute to the development of GDM. These include maternal age, social barriers to care, family history of prediabetes, and obesity and poor weight control.

Older age. A meta-analysis of 24 studies noted strong positive correlation between GDM risk and maternal age.⁶ One



Women diagnosed with prediabetes in 1 study were found to have significantly less weight gain during pregnancy compared with patients with normal A1C, suggesting a benefit in early identification and intervention.

of the population-based cohort studies in the meta-analysis examined relationships between maternal age and pregnancy outcomes in women living in British Columbia, Canada (n = 203,414). Data suggested that the relative risk of GDM increased linearly with maternal age to 3.2, 4.2, and 4.4 among women ages \geq 35, \geq 40, and \geq 45 years, respectively.⁷

Social barriers to care. Although the prevalence of GDM has increased over the past few decades,1 from 2011 to 2019 the increase in GDM in individuals at first live birth was significantly higher in non-Hispanic Asian and Hispanic/Latina women than in non-Hispanic White women.8 Data from the Centers for Disease Control and Prevention further suggest that diabetes was more prevalent among individuals with a lower socioeconomic status as indicated by their level of education.9 Ogunwole et al10 suggest that racism is the root cause of these disparities and leads to long-term barriers to care (eg, socioeconomic deprivation, lack of health insurance, limited access to care, and poor health literacy), which ultimately contribute to the development of GDM and progression of diabetes. It is important for PCPs and all health professionals to be aware of these barriers so

that they may practice mindfulness and deliver culturally sensitive care to patients from marginalized communities.

■ Family history of prediabetes. In a population-based cohort study (n = 7020), women with prediabetes (A1C, 5.7%-6.4%) were 2.8 times more likely to develop GDM compared with women with normal A1C (< 5.7%).¹¹ Similar results were seen in a retrospective cohort study (n = 2812), in which women with prediabetes were more likely than women with a normal first trimester A1C to have GDM (29.1% vs 13.7%, respectively; adjusted relative risk = 1.48; 95% CI, 1.15-1.89).¹² In both studies, prediabetes was not associated with a higher risk for adverse maternal or neonatal outcomes.^{11,12}

While there are no current guidelines for treating prediabetes in pregnancy, women diagnosed with prediabetes in 1 study were found to have significantly less weight gain during pregnancy compared with patients with normal A1C,¹² suggesting there may be a benefit in early identification and intervention, although further research is needed.¹¹ In a separate case-control study (n = 345 women with GDM; n = 800 control), high rates of gestational weight gain (> 0.41 kg/wk) were

Most obstetricians use a 2-step method to screen for GDM with an initial 75-g oral glucose tolerance test, followed by a 50-g glucose load test if needed. associated with an increased risk of GDM (odds ratio [OR] = 1.74; 95% CI, 1.16-2.60) compared with women with the lowest rate of gestational weight gain (0.27-0.4 kg/wk [OR = 1.43; 95% CI, 0.96-2.14]).¹³ Thus, it is helpful to have proactive conversations about family planning and adequate weight and glycemic control with high-risk patients to prepare for a healthy pregnancy.

I Obesity and weight management. Patients who are overweight (body mass index [BMI], 25-29.9) or obese (BMI > 30) have a substantially increased risk of GDM (adjusted OR = 1.44; 95% CI, 1.04-1.81), as seen in a retrospective cohort study of 1951 pregnant Malaysian women.¹⁴ Several factors have been found to contribute to successful weight control, including calorie prescription, a structured meal plan, high physical activity goals (60-90 min/d), daily weighing and monitoring of food intake, behavior therapy, and continued patient-provider contact.¹⁵

The safety, efficacy, and sustainability of weight loss with various dietary plans have been studied in individuals who are overweight and obese.16 Ultimately, energy expenditure must be greater than energy intake to promote weight loss. Conventional diets with continuous energy restriction (ie, lowfat, low-carbohydrate, and high-protein diets) have proven to be effective for short-term weight loss but data on long-term weight maintenance are limited.16 The Mediterranean diet, which is comprised mostly of vegetables, fruits, legumes, fish, and grains-with a lower intake of meat and dairy-may reduce gestational weight gain and risk of GDM as suggested by a randomized controlled trial (RCT; n = 1252).¹⁷ Although the choice of diet is up to the patient, it is important to be aware of different diets or refer the patient to a registered dietician who can help the patient if needed.

Reduce risk with adequate weight and glycemic control

Prevention of GDM during pregnancy should focus on weight maintenance and optimal glycemic control. Two systematic reviews, one with 8 RCTs (n = 1792) and another with 5 studies (n = 539), assessed the efficacy and safety of energy-restricted dietary intervention on GDM prevention.18 The first review found a significant reduction in gestational weight gain and improved glycemic control without increased risk of adverse maternal and fetal outcomes.¹⁸ The second review showed no clear difference between energyrestricted and non-energy-restricted diets on outcomes such as preeclampsia, gestational weight gain, large for gestational age, and macrosomia.18 These data suggest that while energy-restricted dietary interventions made no difference on maternal and fetal complications, they may still be safely used in pregnancy to reduce gestational weight gain and improve glycemic control.¹⁸

Once a woman is pregnant, it becomes difficult to lose weight because additional calories are needed to support a growing fetus. It is recommended that patients with healthy pregestational BMI consume an extra 200 to 300 calories/d after the first trimester. However, extra caloric intake in a woman with obesity who is pregnant leads to metabolic impairment and increased risk of diabetes for both the mother and fetus.¹⁹ Therefore, it is recommended that patients with obese pregestational BMI not consume additional calories because excess maternal fat is sufficient to support the energy needs of the growing fetus.¹⁹

Ultimately, earlier intervention—prior to conception—helps patients prepare for a healthier pregnancy, resulting in better longterm outcomes. It is helpful to be familiar with the advantages and disadvantages of common approaches to weight management and to be able to refer patients to nutritionists for optimal planning. When establishing a dietary plan, consider patient-specific factors, such as cultural diets, financial and time constraints, and the patient's readiness to make and maintain these changes. Consistent follow-up and behavioral therapy are necessary to maintain successful weight control.

There are many screening tools, but 1 is preferred in pregnancy

There are several ways to diagnose diabetes in patients who are not pregnant, including A1C, a fasting glucose test, an oral glucose tol-

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erance test (OGTT), or random glucose testing (plus symptoms). However, the preferred method for diagnosing GDM is OGTT because it has a higher sensitivity.²⁰ A1C, while a good measure of hyperglycemic stability, does not register hyperglycemia early enough to diagnose GDM and fasting glucose testing is less sensitive because for most women with GDM, that abnormal postprandial glucose level is the first glycemic abnormality.²¹

When to screen. Blood glucose levels should be checked in all pregnant women as part of their metabolic panel at the first prenatal visit. A reflex A1C for high glucose levels can be ordered based on the physician's preference. This may help you to identify patients with prediabetes who are at risk for GDM and implement early behavioral and lifestyle changes. However, further research is needed to determine if intervention early in pregnancy can truly reduce the risk of GDM.¹¹

Screening for GDM should be completed at 24 to 28 weeks of gestation²⁰ because it is likely that this is when the hormonal effects of the placenta that contribute to insulin resistance set the woman up for postprandial hyperglycemia. Currently, there are no evidence-based guidelines for the use of continuous glucose monitoring prior to 24 weeks of gestation to identify GDM.20 If persistent hyperglycemia is present before 24 weeks of gestation, it is considered evidence of a pre-existing metabolic abnormality and is diagnosed as "pregestational diabetes." Treatment should follow guidelines established for women who had diabetes prior to pregnancy.

How to screen? There is ongoing discussion about what is the optimal screening method for GDM: a 1-step strategy with a fasting 75-g OGTT only, or a 2-step strategy with a 50-g non-fasting glucose load test followed by a fasting 100-g OGTT in women who do not meet the plasma glucose cutoff (TABLE 1).²²⁻²⁴ Hillier et al²⁵ compared the effectiveness of these strategies in diagnosing GDM and identifying pregnancy complications for the mother and infant. They found that while the 1-step strategy resulted in a 2-fold increase in the diagnosis of GDM, it did not lead to better outcomes for mothers and infants when compared with the 2-step

method.²⁵ Currently, the majority of obstetricians (95%) prefer to use the 2-step method.²⁴

Manage lifestyle, monitor glucose

Management of GDM in most women starts with diabetes self-management education and support for therapeutic lifestyle changes, such as nutritional interventions that reduce hyperglycemia and contribute to healthy weight gain during pregnancy.20 This may include medical nutrition therapy that focuses on adequate nutrition for the mother and fetus. Currently, the recommended dietary intake for women who are pregnant (regardless of diabetes) includes a minimum of 175 g of carbohydrates, 71 g of daily protein, and at least 28 g of fiber. Further refinement of dietary intake, including carbohydrate restriction, should be done with guidance from a registered dietitian.²⁰ If the obstetrics team does not include a registered dietitian, a referral to one may be necessary. Regular physical activity should be continued throughout pregnancy as tolerated. Social support, stress reduction, and good sleep hygiene should be encouraged as much as possible.

For successful outcomes, therapeutic lifestyle changes should be coupled with glucose monitoring. The Fifth International Workshop-Conference on Gestational Diabetes Mellitus recommends that women with GDM monitor fasting blood glucose and typically 1-hour postprandial glucose. The glucose goals in GDM are as follows²⁶:

- Fasting glucose < 95 mg/dL (5.3 mmol/L), and either
- 1-hour postprandial glucose < 140 mg/dL (7.8 mmol/L), or
- 2-hour postprandial glucose < 120 mg/dL (6.7 mmol/L).

Importantly, in the second and third trimester, the A1C goal for women with GDM is 6.0%. This is lower than the more traditional A1C goal for 2 reasons: (1) increases in A1C, even within the normal range, increase adverse outcomes; and (2) pregnant women will have an increased red blood cell count turnover, which can lower the A1C.²⁷ In a historical cohort study (n = 27,213), Abell et al²⁸ found that women who have an A1C The A1C goal for women with GDM is lower (6.0%) after the first trimester because any rise in A1C is risky and increased red blood cell count turnover may lower A1C.

TABLE 1

Screening for and diagnosis of GDM²²

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24-28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24-28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the total load is \geq 130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least 2^a of the following 4 plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria)²³:

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 hour: 180 mg/dL (10.0 mmol/L)
- 2 hours: 155 mg/dL (8.6 mmol/L)
- 3 hours: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test.

^a The American College of Obstetricians and Gynecologists notes that one elevated glucose value can be used for diagnosis.²⁴ Reprinted with permission from The American Diabetes Association. Copyright 2022 by the American Diabetes Association.²²

Authors' note: For the 50-g GLT (nonfasting) in the 2-step strategy, there is lack of clear evidence supporting 1 cutoff value over another. Therefore, obstetricians may select 1 consistent cutoff value (130, 135, or 140 mg/dL) for their practice.²⁴

< 6.0% in the second and third trimester have the lowest risk of giving birth to large-for-gestational-age infants and for having preeclampsia.

Add insulin if glucose targets are not met

Most women who engage in therapeutic lifestyle change (70%-85%) can achieve an A1C < 6% and will not need to take medication to manage GDM.²⁹ If pharmacotherapy is needed to manage glucose, insulin is the preferred treatment for all women with GDM.²⁰ Treatment should be individualized based on the glucose trends the woman is experiencing. Common treatments include bedtime NPH if fasting hyperglycemia is most prominent and analogue insulin at mealtimes for women with prominent postprandial hyperglycemia.

Noninsulin agents such as metformin and sulfonylureas are not currently recommended by the American College of Obstetricians and Gynecologists or the American Diabetes Association for use in GDM.^{20,24} Despite being used for years in women with pregestational diabetes, metabolic syndrome, and polycystic ovary syndrome, there is evidence that metformin crosses the placenta and fetal safety has not yet been established in RCTs. The Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study was a longitudinal follow-up study that evaluated body composition and metabolic outcomes in children (ages 7-9 years) of women with GDM who had received metformin or insulin while pregnant.³⁰ At age 9 years, children who were exposed to metformin weighed more and had a higher waist-to-height ratio and waist circumference than those exposed to insulin.30

Sulfonylureas are no longer recommended because of the risk of maternal and

Most women who engage in therapeutic lifestyle change (70%-85%) can achieve an A1C < 6% and will not need to take medication to manage GDM. fetal hypoglycemia and concerns about this medication crossing the placenta.^{24,31,32} Specifically, in a 2015 meta-analysis and systematic review of 15 articles (n = 2509), glyburide had a higher risk of neonatal hypoglycemia and macrosomia than insulin or metformin.³³ For women who cannot manage their glucose with therapeutic lifestyle changes and cannot take insulin, oral therapies may be considered if the risk-benefit ratio is balanced for that person.³⁴

Watch for effects of poor glycemic control on mother, infant

■ Preeclampsia is defined as new-onset hypertension and proteinuria after 20 weeks of gestation. The correlation between GDM and preeclampsia has partly been explained by their shared overlapping risk factors, including maternal obesity, excessive gestational weight gain, and persistent hyperglycemia.³⁵ On a biochemical level, these risk factors contribute to oxidative stress and systemic vascular dysfunction, which have been hypothesized as the underlying pathophysiology for the development of preeclampsia.³⁵

Neonatal macrosomia, defined as a birth weight \geq 4000 g, is a common complication that develops in 15% to 45% of infants of mothers with GDM.36 Placental transfer of glucose in mothers with hyperglycemia stimulates the secretion of neonatal insulin and the ultimate storage of the excess glucose as body fat. After delivery, the abrupt discontinuation of placental transfer of glucose to an infant who is actively secreting insulin leads to neonatal hypoglycemia, which if not detected or managed, can lead to long-term neurologic deficits, including recurrent seizures and developmental delays.³⁷ Therefore, it is essential to screen for neonatal hypoglycemia immediately after birth and serially up to 12 hours.38

■ Postpartum T2D. Poor glycemic control increases the risk of increasing insulin resistance developing into T2D postpartum for mothers.³⁹ It also increases the risk of obesity and insulin resistance later in life for the infant.⁴⁰ A retrospective cohort study (n = 461) found a positive correlation between exposure to maternal GDM and elevated BMI in children ages 6 to 13 years.⁴¹ Kamana et al³⁶ further discussed this correlation and suggested that exposure to maternal hyperglycemia in utero contributes to fetal programming of later adipose deposition. Children may develop without a notable increase in BMI until after puberty.⁴²

Partner with specialists to improve outcomes

Although most women with GDM are managed by specialists (obstetricians, endocrinologists, and maternal-fetal medicine specialists),⁴³ these patients are still seeking care from their family physicians for other complaints. These visits provide key touchpoints during pregnancy and are opportunities for PCPs to identify a pregnancy-related complication or provide additional education or referral to the obstetrician.

Also, if you work in an area where specialists are less accessible, you may be the clinician providing the majority of care to a patient with GDM. If this is the case, you'll want to watch for the following risk factors, which should prompt a referral to specialty care:

- a previous pregnancy with GDM²⁰
- a previous birth of an infant weighing $> 4000 \text{ g}^{44}$
- baseline history of hypertension⁴⁵
- evidence of insulin resistance or polycystic ovary syndrome^{46,47}
- a history of cardiovascular disease²⁰
- a need to treat GDM with pharmacotherapy.⁴⁸

Ensuring a smooth transition after the birth

Optimal communication and hand-offs throughout pregnancy and after delivery will benefit everyone. When the pregnant patient's care has been managed by an obstetrician, it is important to address the following issues during the hand-off:

- · baseline medical problems
- medical screenings and treatments in pregnancy (retinopathy and nephropathy screening)
- aspirin initiation, if indicated
- management of thyroid abnormalities
- management of mental health conditions

CONTINUED

Noninsulin agents, such as metformin and sulfonylureas, are not currently recommended by ACOG or the ADA for use in GDM.

TABLE 2

Postpartum care recommendations²⁰

| 14.21 | Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. \mathbf{c} |
|-------|---|
| 14.22 | A contraceptive plan should be discussed and implemented with all women with diabetes of reproductive potential. (A) |
| 14.23 | Screen women with a recent history of gestational diabetes mellitus at 4-12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. B |
| 14.24 | Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. (\mathbf{A}) |
| 14.25 | Women with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1-3 years. (\mathbf{B}) |
| 14.26 | Women with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. (\mathbf{E}) |
| 14.27 | Postpartum care should include psychosocial assessment and support for self-care. |

A Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered.

B Supportive evidence from well-conducted cohort studies.

C Supportive evidence from poorly controlled or uncontrolled studies.

OGTT).20

visits easier to attend.

E Expert consensus or clinical experience.49

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- postpartum glucose management and T2D screening postpartum
- management of complications identified during pregnancy (retinopathy and nephropathy).

Timing and other elements of postpartum care. The first postpartum screen should occur at 4 to 12 weeks postpartum.

OGTT is recommended instead of A1C at

this time because A1C may still be lowered

by the increased red blood cell turnover

related to pregnancy and blood loss at de-

livery. Because women with GDM have a

50% to 75% lifetime risk of T2D,20 patients

with normal test results should be re-tested

every 1 to 3 years using any of the standard

screening methods (A1C, fasting glucose, or

women to follow-up with their own person-

al health care because they are focused on

the care of their baby. The increased use of

telehealth may make postpartum follow-up

tum visits present another opportunity for

PCPs to screen for diabetes and other post-

partum complications, including depression

and thyroid abnormalities. Visits are also an

opportunity to discuss timely contraception

Visits present opportunities. Postpar-

After delivery it may be difficult for

so as to prevent an early, unplanned pregnancy. Other important aspects of postpartum care are outlined in TABLE 2.^{20,49} JFP

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Postpartum visits present another opportunity to screen for diabetes and other postpartum complications, including depression and thyroid abnormalities.

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