Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment

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Gestational diabetes mellitus (GDM) is a common disorder affecting ~ 7% of pregnancies each year. It can have a much higher incidence in certain minority populations with a greater predisposition to diabetes. The disorder is characterized by carbohydrate intolerance that begins or is first recognized during pregnancy. The prevalence of GDM varies in direct proportion to the prevalence of type 2 diabetes for a given ethnic group or population.

When and how to screen for GDM has been debated in the literature for decades. Several studies have suggested grouping patients by low, moderate, and high risk for developing GDM. Currently, and after extensive deliberation, universal screening of all pregnant women is recommended by some groups; however, the American Diabetes Association (ADA) recommends screening of only moderate- and high-risk pregnancies. Recognizing and treating GDM results in lowering of maternal and fetal complications. Patients with GDM are at higher risk for excessive weight gain, preeclampsia, and cesarean sections. Infants born to mothers with GDM are at higher risk for macrosomia, birth trauma, and shoulder dystocia. After delivery, these infants have a higher risk of developing hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia, and subsequent obesity and type 2 diabetes. In addition, having a history of GDM puts the mother at risk for development of type 2 diabetes or recurrent GDM in the future. Some recent data suggest an increased risk of cardiovascular disease, as well.

Screening
Fifty years ago, screening for GDM was done by taking patients’ history alone. In 1973, Mahan and O’Sullivan proposed using the 1-hour 50-g oral glucose tolerance test (OGTT) for screening.

Several studies have suggested placing patients into risk categories based on history, as demonstrated in Table 1. Risk factors for GDM include being overweight before pregnancy (BMI > 25 kg/m²), having a first-degree relative with diabetes, previous glucose intolerance, previous macrosomia or large-for-gestational-age baby, polycystic ovarian syndrome, age > 25 years, and being a member of an ethnic group with high prevalence of GDM. Multiparous women have a very high prevalence of GDM (~ 13%).

At patients’ first antenatal visit,
outcomes. Previously, Williams et al. studied 25,118 deliveries to determine whether following the ADA recommendations not to screen women who are <25 years of age, have normal body weight, are not members of a high-risk racial or ethnic group, and have no family history of diabetes would result in missed GDM diagnoses. They found that ~10–11% of women who delivered would never have been screened for GDM, and they were missing 4% of women with GDM.

For higher-risk patients, screening is warranted earlier in pregnancy. Patients with symptoms of overt severe hyperglycemia, such as polyuria and polydipsia, may be diagnosed with a random blood glucose test result ≥ 200 mg/dl. An earlier diagnosis should trigger suspicion of preexisting type 1 or type 2 diabetes and should be investigated and managed appropriately. Screening for glycosuria has been used in the past, but given the poor sensitivity and specificity, the recent U.K. National Institute of Clinical Excellence guidelines did not recommend continuation of screening for glycosuria.

Screening with a fasting blood glucose test has been shown to have a sensitivity of 70–90% and a specificity of 50–75% and is therefore not considered an adequate screening method. In fact, one study by Kousta et al. found that a single fasting glucose screen failed to identify 60% of women with abnormal 2-hour blood glucose levels. Metzger et al. found that a 1-hour 50-g OGTT value ≥ 140 mg/dl would have an ~80% sensitivity and a proportion of women with a positive test of 14–18%. Using a cutoff value of ≥130 mg/dl increases sensitivity to ~90%. A positive test requires further diagnostic testing.

**Diagnosis**

When diagnosing GDM, clinicians must keep in mind that patients may in fact have 1) undiagnosed type 2 diabetes, 2) mild abnormal glucose tolerance before pregnancy that worsens in pregnancy because of increased insulin resistance, 3) normal glucose tolerance before pregnancy that becomes abnormal with advancing gestation, or 4) undiagnosed type 1 diabetes when pregnancy coincides with the prodromal phase of type 1 diabetes (rare). It is estimated that ~1 in 10,000 women will become pregnant in the prodromal phase of type 1 diabetes.

One study described five screening criteria to determine whether a patient is presenting with latent autoimmune diabetes in adults (LADA). These include 1) age of diabetes onset <50 years; 2) acute symptoms of polyuria, polydipsia, and/or weight loss; 3) personal history of autoimmune disease; 4) family history of autoimmune disease; and 5) BMI < 25 kg/m². This study found that 75% of patients with LADA but only 24% of those with type 2 diabetes had two or more criteria. Family history of type 2 diabetes has not been shown to distinguish between LADA and type 2 diabetes and should not be used to exclude LADA.

As stated previously, women with a positive 50-g OGTT need further diagnostic testing with either the 75- or the 100-g OGTT. There is a debate in the literature over which test is a better diagnostic tool. Both tests are administered after an overnight fast of at least 8 hours but not more than 14 hours and after at least 3 days of unrestricted diet including ≥150 g of carbohydrate per day.

Patients need to remain seated and should not smoke throughout the test. If using the 100-g OGTT, the cutoff values should be fasting < 95 mg/dl, 1-hour ≥ 180 mg/dl, 2-hour ≥ 155 mg/dl and 3-hour ≥ 140 mg/dl (Tables 2 and 3). Two or more abnormal values must be measured for the test to be considered a positive diagnostic test. When using the 2-hour 75-g OGTT, the cutoffs are the same at 1 and 2 hours. Again, two or more abnormal values are needed for a positive diagnosis. However, studies have shown that mothers with only one abnormal value are at increased risk for macrosomic infants and other morbidities.

In a recent position statement by the ADA, a cutoff of 140 mg/dl was found to have ~80% sensitivity, and a cutoff of 130 mg/dl had a sensitivity of 90%. Either threshold is acceptable. In patients who are considered to be at high risk, it may be more cost-effective to proceed directly to diagnostic testing instead of initial screening.

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<thead>
<tr>
<th>Table 2. Screening for GDM with the 50-g OGTT*</th>
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<td><strong>Serum glucose cutoff point</strong></td>
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<td>&gt; 140 mg/dl</td>
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<td>&gt; 130 mg/dl</td>
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<td><em>Recommendations as adapted by Metzger et al.</em></td>
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<th>Table 3. Diagnosis of GDM</th>
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<td><strong>Time of measurement</strong></td>
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<td>Random</td>
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<td>3 hour postchallenge</td>
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Pathophysiology

Pregnancy is a condition characterized by progressive insulin resistance that begins near midpregnancy and progresses through the third trimester. In late pregnancy, insulin sensitivity falls by ~ 50%.17 Two main contributors to insulin resistance include increased maternal adiposity and the insulin desensitizing effects of hormones produced by the placenta. The fact that insulin resistance rapidly decreases post-delivery suggests that the major contributors are placental hormones.

The placenta produces human chorionic somatomammotropin (HCS, formerly called human placental lactogen), bound and free cortisol, estrogen, and progesterone. HCS stimulates pancreatic secretion of insulin in the fetus and inhibits peripheral uptake of glucose in the mother.18 As the pregnancy progresses and the size of the placenta increases, so does the production of the aforementioned hormones, leading to a more insulin-resistant state. In nondiabetic pregnant women, the first- and second-phase insulin responses compensate for this reduction in insulin sensitivity, and this is associated with β-cell hypertrophy and hyperplasia.19 However, women who have a deficit in this additional insulin secretory capacity develop GDM. β-Cell dysfunction in women diagnosed with GDM may fall into one of three major categories: 1) autoimmune, 2) monogenic, or 3) occurring on a background of insulin resistance (as is most common).19 The loss of the first-phase insulin response leads to postprandial hyperglycemia, whereas impaired suppression of hepatic glucose production is responsible for fasting hyperglycemia when present.

Because insulin does not cross the placenta, the fetus is exposed to the maternal hyperglycemia. At the 11th or 12th week of gestation, the fetal pancreas is capable of responding to this hyperglycemia.20 The fetus thus becomes hyperinsulinemic, which in turn promotes growth and subsequent macrosomia.

Autoimmune and Monogenic Diabetes in Women Diagnosed With GDM

Lean patients are less likely to be insulin resistant than overweight or obese patients; autoimmune or monogenic forms of diabetes should be considered in such patients, who can rapidly develop overt diabetes after pregnancy. This should prompt physicians to evaluate for circulating autoantibodies to various islet cell proteins. One study21 that included > 5.7 years of follow-up found that 4.6% of these patients developed type 1 diabetes, and 5.3% developed type 2 diabetes. Two-thirds of those who developed type 1 diabetes tested positive for islet cell antibodies (ICAs), whereas 56% had autoantibodies to GAD.21 Women who developed type 1 diabetes were significantly younger. Also, mutations that cause several types of maturity-onset diabetes of the young (MODY) have been found in women with GDM. These monogenic forms of GDM account for < 10% of GDM cases.22

Maternal and Fetal Complications

Maternal complications. Antepartum morbidity in women with GDM mostly consists of higher risk for development of hypertensive disorders and pre-eclampsia.21 However, some of this risk may also be related to the underlying risk factors for GDM, such as obesity and older maternal age. Women with GDM have moderate to high risk of nongestational diabetes in the first several years postpartum. This risk is particularly high in women with marked hyperglycemia, obesity, and a diagnosis of GDM earlier than 24 weeks gestation.24

A study25 of 302 women followed with OGTTs 11 years found that the 8-year postpartum diabetes risk was 52.7%. The risk was nearly 100% within a few years postdelivery in islet autoantibody-positive women, followed by islet autoantibody-negative women who required insulin therapy, and then women who were obese. Risk was lowest in nonobese, islet autoantibody-negative women with GDM who did not require insulin, reaching 14% by 8 years postdelivery.25

A study by Carr et al.26 examined whether GDM increases the risk of cardiovascular disease (CVD) in women with a family history of type 2 diabetes. Researchers found that these women not only had a higher prevalence of CVD (15.5 vs. 12.4%), but also were more likely to have experienced CVD events at a younger age.

Several studies have reviewed the ethnic differences in perinatal outcome of GDM. Neonates born to Native-Hawaiian/Pacific-Islander mothers and Filipino mothers had four and two times the prevalence of macrosomia, respectively, when compared with neonates born to Japanese, Chinese, and Caucasian mothers. There were no ethnic differences observed in the prevalence of fetal demise, fetal anomalies, shoulder dystocia, fetal distress, birth asphyxia, polycythemia, respiratory distress syndrome, or sepsis in neonates.27

Other maternal risks include the need for cesarean section and birth trauma. Fetal complications. Fetuses born to mothers with GDM have higher risks of developing macrosomia, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia, hypertrophic cardiomyopathy, and hypocalcemia, and these complications have been reported with varying frequency.28 Macrosomia is the most common morbidity, occurring in 15–45% of infants exposed to hyperglycemia.29 This occurs when there is delivery of excess glucose to the fetus as a result of maternal hyperglycemia, in turn stimulating fetal hyperinsulinemia, which leads to increased growth. Other maternal factors that may contribute to fetal macrosomia include obesity and high concentrations of lipids and amino acids.28 In subjects with preexisting diabetes, 1-hour postprandial glucose levels were more predictive of fetal macrosomia than were fasting values.30

Not only are there immediate risks to the fetus, but infants exposed to maternal diabetes in utero have an increased risk of diabetes and obesity in childhood and adulthood.31 A study in Pima Indians32 demonstrated that fetal exposure to an
abnormal glucose environment, such as that which is present in GDM, independently increases the risk of the offspring subsequently developing glucose intolerance and diabetes. In addition to macrosomia and risk for obesity and development of glucose intolerance later in life, infants of mothers with GDM are at increased risk of serious birth injury and neonatal intensive care unit admissions.13 Studies indicate that the magnitude of fetal-neonatal risks is proportional to the severity of maternal hyperglycemia.41

**Treatment**

Past studies have compared the effects on outcomes of treating GDM with conventional treatment (diet and exercise) versus pharmacological intervention. Several studies have concluded that women who do not meet established goals with diet and exercise alone have more favorable outcomes with pharmacological intervention. Crowther et al.42 found in a study of 1,000 women with GDM that the rate of serious perinatal complications, defined as death, shoulder dystocia, bone fracture, and nerve palsy, was reduced from 4 to 1% in the 490 women in the intervention group.

Monitoring blood glucose at home is important to tailoring specific treatment and making adjustments as needed. Several studies have shown that monitoring four times daily leads to more favorable glycemic control.43 Patients should be instructed to check premeal and 2-hour postmeal glucose levels in addition to recording the grams of carbohydrate they consume.

Monitoring for fasting ketonuria in the morning will help guide the level of carbohydrate restriction. Studies have reported an inverse association between maternal ketosis in the second and third trimesters and psychomotor development and intelligence in offspring when looking at children 3–5 years of age44 and through 9 years of age.45 The Fourth International Workshop Conference on Gestational Diabetes Mellitus46 recommends maintaining blood glucose concentrations at < 95 mg/dl before meals and < 140 and 120 mg/dl 1 and 2 hours after meals, respectively.

Women with 1-hour postprandial blood glucose levels within the normal range experience fewer incidences of neonatal hypoglycemia, macrosomia, and cesarean delivery.46 Although the majority of women will achieve adequate glycemic control with diet and exercise alone, ~ 30–40% require pharmacological treatment.47 When choosing therapies with patients, physicians should always consider efficacy, safety, and patient acceptance. Options begin with diet and exercise for most patients if they are not severely hyperglycemic at diagnosis. If this fails, the two main options in addition to diet and exercise are insulin therapy and the sulfonylurea glyburide. Women requiring treatment with insulin or glyburide in their third trimester require nonstress fetal testing and biophysical profiles by their obstetricians.

*Diet and exercise.* Patients benefit significantly by receiving dietary counseling to learn to count carbohydrates and plan meals. The ADA recommends that women of normal weight in the second half of pregnancy consume 30–32 kcal/kg body wt. Carbohydrate intake should be ~ 40% of total calories and should be selected from carbohydrate foods with a low glycemic index.48 In overweight women, this requirement should be reduced to 25 kcal/kg.49 Excessive calorie restriction can be monitored by checking for fasting ketonuria, especially when there is a caloric restriction > 30%.

*Insulin.* For decades, human insulins were the only insulin options available for the treatment of GDM. The recent advent of newer insulin analogs that mimic physiological insulin action calls for more information regarding the safety and applicability of their use in GDM.

The insulin analogs lispro and aspart have been identified in the past several years as an alternative to insulin therapy for the treatment of GDM. Its primary action is to enhance insulin secretion. Glyburide does not significantly cross the placenta.40 Several studies have found that glyburide serves as a suitable alternative to insulin for treatment of GDM with similar perinatal outcomes. A survey performed by the American College of Obstetricians and Gynecologists found that 13% of obstetricians and maternal-fetal medicine specialists were using glyburide as a first-line agent in the treatment of women with GDM who failed to achieve glucose control with diet. A disadvantage to taking glyburide is that it sometimes takes > 1 week to observe the effect of titration. However, it is inexpensive and less invasive than...
insulin and has been found to be as effective as insulin therapy for GDM treatment. Langer et al. found that glyburide was as effective as insulin for the treatment of GDM in 404 patients, despite severity of disease when fasting plasma glucose on a glucose tolerance test was between 95 and 139 mg/dl. More than 80% of GDM patients were found to achieve the established levels of control with glyburide; 71% of patients required an average dose of 10 mg of glyburide daily. There was no significant difference in neonatal birth weight, metabolic complications, and composite outcome between the two groups. Chmait et al. studied 69 patients with GDM who failed dietary therapy and were then treated with glyburide. Treatment failure was defined as inadequate glycemic control on 10 mg of glyburide twice daily. The failure rate was 18.8%. Glyburide success was predicted if dietary failure occurred after 30 weeks or fasting blood glucose levels were <110 mg/dl and 1-hour post-prandial levels were >140 mg/dl. This study was done in a predominantly (87%) Hispanic population.

Markers for advancement to insulin include inadequate glycemic control, severe restriction of carbohydrates and calories (as demonstrated by ketonuria) necessary to meet glycemia goals, and a fetus that is large for gestational age. Glyburide is contraindicated in those with an allergy to sulfa. The main risk of taking glyburide, as with insulin, is hypoglycemia.

Metformin. The biguanide metformin during pregnancy has mostly been studied in the first 12 weeks of gestation for patients with polycystic ovary syndrome (PCOS). Preliminary studies have shown that in women with PCOS, metformin may be safe and may reduce risk of miscarriage and development of GDM when used for the entire pregnancy. Metformin may also have a role in therapy for GDM; a multicenter trial is underway in New Zealand to address this question.

Postpartum follow-up. Maternal insulin requirements drop markedly in the postpartum period. Because patients with GDM have a high risk of developing type 2 diabetes, it is important to continue screening these patients. Poor insulin secretion during pregnancy is predictive of diabetes after delivery. Patients should attempt to minimize insulin resistance through exercise, maintenance of normal weight, and avoidance of drugs that induce insulin resistance.

The ADA has recommended 1) an annual fasting blood glucose test, 2) a 6-week postpartum 75-g 2-hour OGTT, and 3) contraception to ensure that patients will not conceive in the face of marked hyperglycemia, which could lead to increased congenital malformations and dysorganogenesis. Patients who had GDM in a previous pregnancy have a 33–50% likelihood of recurrence in a subsequent pregnancy.

Given the well-known sequelae of diabetes, which include macro- and microvascular disease and cardiovascular disease, it is important to recognize the risk and prevent the development of diabetes in the future in women with GDM. In the Diabetes Prevention Program, intensive lifestyle modification to promote weight loss and increase physical activity resulted in a 58% reduction in the relative risk of type 2 diabetes in adults with impaired glucose tolerance. In another study with 1,079 participants aged 25–84 years, weight loss was the dominant predictor of reduced diabetes risk. Every kilogram of weight loss resulted in a 16% reduction in risk.

Summary

GDM is associated with a myriad of fetal and maternal complications. Identifying women with GDM through screening at appropriate gestational age given their risk is crucial to avoiding unfavorable outcomes. It is important for providers to explore the possibility of unmasked type 2 diabetes or even type 1 diabetes caught in the prodromal phase in women with GDM, especially if overt hyperglycemia is present early in pregnancy.

Several agents that are both efficacious and safe are being used to treat women with GDM if diet and exercise fail; these include human insulin, insulin analogs, and glyburide. Studies are underway to test the safety and efficacy of metformin in pregnancy.

Women with GDM need to be followed postpartum and monitored for type 2 diabetes to reduce the risks for complications of diabetes and to avoid conception of future pregnancies in the setting of uncontrolled hyperglycemia.

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FEATURE ARTICLE


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