Introduction

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy, and its rate has continued to increase in the United States. Currently, it affects approximately 1 in 10 or 380,000 pregnant women per year, and nearly 90% of cases of diabetes in pregnancy represent GDM. The prevalence of the condition has more than doubled among non-White, overweight, and low-income women in the last decade in an environment of increasing maternal age, obesity, and sedentary living. In this clinical review, we provide an overview of the epidemiology, screening, and clinical management of GDM.

GDM impact on adverse pregnancy outcomes, and treatment to reduce risk

GDM more than doubles the risk of perinatal morbidity and mortality, and this risk progressively increases with the severity of hyperglycemia and decreases with treatment, including both lifestyle changes and pharmacotherapy. For the infant, maternal hyperglycemia may cause fetal hyperinsulinemia, which results in excessive fetal growth (macrosomia, large for gestational age), birth trauma, neonatal hypoglycemia, delayed lung development, and fetal hypoxia. For the mother, GDM increases the risk of shoulder dystocia, cesarean delivery, and preeclampsia. Historically, the criteria employed to diagnose GDM were based on the likelihood of developing type 2 diabetes later in life rather than on identifying those at the highest risk of adverse perinatal outcomes due to glucose intolerance. The landmark Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study helped establish internationally agreed-upon diagnostic criteria for GDM among more than 25,000 pregnancies. This study demonstrated that increasing hyperglycemia defined by elevations in the 3 values of a 75-g, 2-hour oral glucose tolerance test (GTT) were associated with a progressively increasing risk of a large-for-gestational-age infant at birth, cesarean delivery, rising fetal C-peptide levels, and neonatal adiposity. HAPO’s results led the International Association of Diabetes and Pregnancy Study Groups (IADPSG) task force to recommend a 1-step test for GDM screening. However, after a systematic review of the findings, the National Institutes of Health Consensus Development Conference on diagnosing GDM found insufficient evidence of maternal or perinatal benefit to adopt 1-test screening and, rather, continued to endorse a 2-step approach to screening and diagnosis.
When and how to screen for GDM

GDM is a state restricted to pregnant women whose impaired glucose intolerance is first discovered in pregnancy. Most of these women will have normal fasting glucose levels; hence, a glucose challenge is required to unmask this state. Historically, risk factors including a family history of diabetes, history of macrosomia or stillbirth, obesity, chronic hypertension, and maternal age were used to screen women at the highest risk of GDM. The problem is that more than half of women with an abnormal GTT lack any risk factors.

The American College of Obstetricians and Gynecologists (ACOG) recommends universal screening for all pregnant women. Screening generally is performed between 24 and 28 weeks when the “diabetogenic state” of pregnancy has been established. Two commonly used screening strategies include a 1-step test as endorsed by IADPSG versus a 2-step test as endorsed by ACOG (Table 1). A 1-step test includes a 75-g, 2-hour oral GTT in which a GDM diagnosis can be made when a single value was met or exceeded. A 2-step test involves an initial 50-g glucose challenge test followed by a 3-hour, 100-g oral GTT. The initial 50-g glucose challenge can be performed while fasting or after having eaten. A plasma value between 130 to 140 mg/dL is generally used as a threshold for performing a 3-hour oral GTT. To diagnose GDM based on the 3-hour GTT, ACOG endorses either the National Diabetes Data Group (NDDG) criteria or the less stringent Carpenter and Coustan criteria. Regardless of either set of criteria, if any 2 or more than 4 oral GTT values exceed established thresholds, the diagnosis of GDM is confirmed.

Results from multiple studies have demonstrated that although a larger number of women (nearly double) may be identified as having GDM using IADPSG 1-step criteria compared with 2-step criteria (17% vs 9%). However, the frequency of hypertensive disorders of pregnancy, primary cesarean delivery, and large-for-gestational-age infants, and the perinatal composite outcome were not different between the testing groups. The findings of this study highlight that whereas a 1-step screen may detect more women with GDM than a 2-step screen, there may be no apparent maternal or perinatal benefit overall to this approach.

Finally, ACOG recommends screening earlier in pregnancy for women with

### Table 1

<table>
<thead>
<tr>
<th>IADPSG 1-step Versus 2-step Detection of GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 step¹</td>
</tr>
<tr>
<td>Screening 50 g, 1 hour</td>
</tr>
<tr>
<td>75-g GTT, 2 hours</td>
</tr>
<tr>
<td>Fasting glucose</td>
</tr>
<tr>
<td>82 mg/dL</td>
</tr>
<tr>
<td>130 mg/dL</td>
</tr>
<tr>
<td>1-hour glucose</td>
</tr>
<tr>
<td>180 mg/dL</td>
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<tr>
<td>160 mg/dL</td>
</tr>
<tr>
<td>2-hour glucose</td>
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<tr>
<td>153 mg/dL</td>
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<tr>
<td>155 mg/dL</td>
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<tr>
<td>3-hour glucose</td>
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<tr>
<td>145 mg/dL</td>
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¹A 1-step diagnosis is made if 1 value is met or exceeded.
²A 2-step diagnosis is made when any 2 values of the GTT are met or exceeded.

GDM, gestational diabetes mellitus; GTT, glucose tolerance test; IADPSG, International Association of Diabetes and Pregnancy Study Groups; NDDG, National Diabetes Data Group.
a history of GDM, impaired glucose metabolism, or cardiovascular disease who have delivered an infant weighing 4000 g or more, are overweight or obese, have a first-degree relative with diabetes, and are members of high-risk racial and ethnic groups. An easy approach to diagnose diabetes in early pregnancy is to obtain an HbA1c level. A value greater than or equal to 6.5% is consistent with a diagnosis of type 2 diabetes regardless of pregnancy and does not require further testing. Women with an HbA1c level between 5.7% and 6.4%, which is consistent with impaired glucose tolerance, should undergo a diagnostic oral GTT, as 1 in 4 may later develop GDM. Those with an HbA1c level less than 5.7% can undergo routine screening at 24 to 28 weeks. For those with an HbA1c level less than 5.7% but with risk factors, it is prudent to obtain a GCT as the HbA1c level may only be moderately predictive of early GDM compared with 2-step screening.7

**Firstline treatment for GDM: lifestyle intervention**

The mainstays of GDM treatment begin with lifestyle interventions, including nutritional counseling, dietary changes, and daily exercise, with the goal of decreasing postprandial hyperglycemia (Table 2).8 Dietary and nutrition changes may include limiting carbohydrates to less than 40% of calories, increasing complex relative to simple carbohydrates. Recommended daily exercise includes 30 minutes of moderate-intensity aerobic exercise at least 5 days a week. Of note, a majority of women with GDM may be obese, and 2009 Institute of Medicine gestational weight gain recommendations do not make specific recommendations with regard to women with GDM.

Findings from 2 important trials over the last 20 years have shown that lifestyle interventions for GDM provide both maternal and infant benefits. The Australian Carbohydrate Intolerance Study in Pregnant Women was a multicenter, 10-year, randomized controlled trial (RCT) of 1000 women that demonstrated a significant reduction in the primary composite (perinatal death, neonatal hypoglycemia, elevated cord C-peptide level, or birth trauma) with treatment versus standard care. However, they did find a decrease in the risk of fetal overgrowth, neonatal fat mass, shoulder dystocia, cesarean delivery, and hypertensive disorders of pregnancy.9 Taken together, these 2 studies demonstrate the benefit of treatment of even mild carbohydrate intolerance during pregnancy.

Once the patient commences an appropriate diet and exercise plan, close surveillance of blood glucose levels is necessary to ensure glycemic control is maintained. This is generally accomplished with patients performing daily self-monitored blood glucose checks, including a fasting level and 3 postprandial measurements 1 or 2 hours after each meal. The target glycemich thresholds of fasting glucose are less than 95 mg/dL, 1-hour postprandial glucose less than 140 mg/dL, and 2-hour postprandial glucose less than 120 mg/dL (Table 3). ACOG and ADA recommend the same thresholds for both GDM and pregestational diabetes.10 Once women achieve and maintain good glycemic control, the frequency of testing can be decreased. If these targets cannot be met and the majority of fasting and/or postprandial values are elevated, then pharmacotherapy is recommended.

Of note, for women with pregestational diabetes, glucose monitoring is increasingly being done using continuous glucose monitoring (CGM). This technology is currently not being widely used for GDM, though emerging data suggest that CGM can identify specific times of the day that are not identified with routine blood glucose monitoring, such as nocturnal hyperglycemia, which may be associated with an increased risk of adverse perinatal outcomes.12

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**Table 2**

Lifestyle Recommendations for Women With GDM

1. **MEALS AND SNACKS:**
   3 meals and 3 snacks per day

2. **CALORIES:**
   30-35 kcal/kg normal body weight, 2000-2400 kcal/day

3. **COMPOSITION:**
   carbohydrate, 40%-50% complex high fiber; protein, 20%; fat, 30%-40% (< 10% saturated)

4. **EXERCISE:**
   30 minutes of moderate-intensity aerobic exercise at least 5 days a week

5. **GESTATIONAL WEIGHT GAIN:**
   Follow Institute of Medicine guidelines.

Modified from Gabbe’s Obstetrics: Normal and Problem Pregnancies. 8th ed.
When to initiate pharmacotherapy and which medication to use

The challenge is that at least 1 in 4 women with GDM do not respond to lifestyle intervention, including diet and exercise, and require pharmacotherapy to achieve euglycemia.

The optimum threshold for initiating pharmacologic therapy has not been established. Most clinicians initiate pharmacotherapy when 30% to 50% or more of finger-stick values are above the target range (fasting and 2-hour postprandial glucose ≥ 95 mg/dL and ≥ 120 mg/dL, respectively) in the past week. Both the ACOG and ADA recommend insulin as first-line therapy because it does not cross the placenta and improves perinatal outcomes. The Society for Maternal-Fetal Medicine recommends either metformin or insulin as reasonable first-line options.

Although weight-based insulin regimens by trimester of pregnancy can be used, for which online calculators are readily available, a simpler approach for clinical practice is to initiate a single dose of long-acting neutral protamine Hagedorn (NPH) or insulin detemir at bedtime to treat fasting hyperglycemia. Shorter-acting insulin lispro or aspart can be used to target postprandial hyperglycemia. In our practice, we typically start with 12 to 20 U NPH insulin in the morning and 10 U NPH at bedtime. Then, 5 to 10 U of short-acting insulin lispro or aspart can be used to address mealtime excursions. For a patient for whom fasting hypoglycemia is the sole indication for pharmacotherapy, the authors start with a single injection of bedtime long-acting insulin.

Oral hypoglycemic agents including metformin and glyburide have increasingly become a popular alternative to injectable insulin over the past 2 decades. Historically, glyburide, a sulfonylurea, had been a frequently used oral agent for GDM. Metformin, a biguanide, lowers both basal and postprandial glucose, and is the preferred first-line agent to treat type 2 diabetes outside of pregnancy. An oral option may be preferable to frequent injections due to convenience, lower cost, ease of administration, and better adherence. Insurance coverage and cost of insulin have increasingly been problems, particularly for publicly insured patients. In many areas, this has restricted the available insulin formulary. Great controversy remains about the use of oral agents for GDM. Persistent concerns exist about the efficacy of oral agents for preventing adverse neonatal outcomes compared with insulin and the fact that oral agents (metformin and glyburide), unlike insulin, cross the placenta. We have found that, in practice, women with fasting hyperglycemia (> 115 mg/dL) will generally fail to achieve adequate glycemic control with oral agents.

In the landmark Metformin in Gestational Diabetes (MiG) trial, results of which were published in 2008, Rowan and colleagues randomized 761 women with GDM to either insulin or metformin. They noted that the risk of the composite outcome (neonatal hypoglycemia, respiratory distress, birth trauma, preterm birth, and need for phototherapy in the infant) was observed in about one-third of women in both groups. Of note, more than 40% of women receiving metformin required supplemental insulin to achieve adequate glycemic control. In 2018, Senat and colleagues randomized 914 women to either insulin or glyburide, and noted similar improvements in glycemia with each regimen. However, the frequency of macrosomia and neonatal hypoglycemia were similar between both groups. Several meta-analyses suggest that oral agents, particularly metformin,

### Table 3: Target Plasma Glucose Levels in Pregnancy

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Glucose level (mg/dL)</th>
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<tbody>
<tr>
<td>Before breakfast “fasting”</td>
<td>60 to &lt; 95</td>
</tr>
<tr>
<td>Before lunch, dinner, and bedtime snack</td>
<td>60-105</td>
</tr>
<tr>
<td>1 hour after meals</td>
<td>&lt; 140</td>
</tr>
<tr>
<td>2 hours after meals</td>
<td>&lt; 120</td>
</tr>
<tr>
<td>2 AM to 6 AM</td>
<td>&gt; 60</td>
</tr>
</tbody>
</table>
are equivalent, if not superior, in preventing adverse neonatal outcomes.\textsuperscript{18,19} However, important limitations of the included studies are unclear diagnostic criteria and inability to adjust for impact of severity of hyperglycemia on treatment outcomes; poorly characterized heterogeneous populations, often from low- and middle-income countries, unclear criteria for supplemental insulin, and small sample size.

Whether metformin places exposed children and mothers at higher risk of metabolic disease after delivery remains to be fully answered. In contrast to insulin, which does not cross the placenta, metformin poses a real concern due to the theoretic potential for developmental programming of metabolic dysfunction for children exposed in utero. MiG trial investigators reported that in a subset of children at a 5 to 7-year follow-up, those exposed to metformin had a higher body mass index (BMI; ie, were heavier) than those exposed to insulin.\textsuperscript{20} A recent meta-analysis affirmed that at 2 years, children exposed to metformin had higher BMIs compared with those exposed to insulin.\textsuperscript{21} Addressing the long-term safety of oral agents for GDM therefore remains an important research priority.

### Antepartum and delivery management

Women with well-controlled GDM are at low risk of intrauterine fetal demise, and hence routine antepartum fetal testing is generally not initiated for uncomplicated diet-controlled class A1 GDM. But for women with a hypertensive disorder, prior stillbirth, or suspected macrosomia, fetal testing is undertaken. Additionally, women on pharmacotherapy with either insulin and/or oral agents (class A2) undergo at least weekly fetal testing beginning at 32 weeks’ gestation.

With regard to timing of delivery, many obstetricians have extrapolated the increased risk of stillbirth in women with type 1 and 2 diabetes to those with GDM; hence, women with GDM on pharmacotherapy are generally advised to undergo induction by week 39. The ACOG currently recommends that for women with well-controlled GDM with...
diet alone (class A1) delivery be considered at 39 + 0 to 40 + 6 weeks. For those patients receiving pharmacotherapy (class A2), delivery should be considered at 39 + 0 to 39 + 6 weeks. If glycemic control is suboptimal, then delivery should be considered at 37 + 0 to 38 + 6 weeks. As a guideline, for women with preexisting diabetes, scheduled cesarean delivery to prevent birth trauma is offered to those with suspected macrosomia (4500 g or greater at birth) or a history of prior shoulder dystocia.

**Postpartum screening for type 2 diabetes and effect of GDM on future health**

Women with GDM have a higher risk of developing glucose intolerance later in life, or an approximately 7-fold increased risk of developing type 2 diabetes compared with those without GDM. Among Hispanic women, nearly two-thirds may develop type 2 diabetes in 5 years after the index GDM pregnancy. By the time of postpartum testing between 6 and 12 weeks after delivery, about 1 in 3 women will receive a diagnosis of overt type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance. The risk of subsequent type 2 diabetes increases when diabetes is diagnosed earlier in pregnancy or when maternal fasting glucose levels are higher. Some of these women may represent cases of unidentified preexisting type 2 diabetes.

Both the ADA and ACOG recommend postpartum glucose testing using either a fasting plasma glucose or a 75-g, 2-hour oral GTT at 4 to 12 weeks after delivery for a pregnancy complicated by GDM (Table 4). And although thereafter the optimal testing frequency remains to be established, the ADA supports repeat testing every 3 years for women with prior GDM and normal postpartum screening results. The problem is that only about 1 in 5 women with GDM undergo postpartum screening, and innovative strategies are needed to increase its uptake.

Women should also be counseled about the risk of recurrence of GDM in a subsequent pregnancy, which may be as high as 40%. Important ways to decrease the risk of type 2 diabetes include breastfeeding, lifestyle changes, and pharmacotherapy with metformin. GDM may be associated with an increased risk of childhood obesity and subsequent metabolic dysfunction in the infant. The extent to which fetal programming of metabolic function in GDM has an intergenerational effect that can be modified by treatment remains to be answered.

**Conclusions**

GDM is one of the most common medical complications of pregnancy, and its frequency has nearly doubled in the last decade in an obesogenic environment. GDM doubles the risk of perinatal morbidity and mortality. All pregnant women should be screened for GDM, and currently a 2-step screening approach is most commonly used. First-line treatment includes lifestyle interventions, but nearly 1 in 4 women will require pharmacotherapy. Insulin is generally the preferred first-line pharmacotherapy, but further research is needed with regard to the efficacy and safety of oral agents, particularly metformin. Antenatal testing is generally initiated in the late third trimester, with delivery often recommended by the 39th week. All women with GDM should be screened for glucose intolerance and type 2 diabetes in the postpartum period with follow-up based on their 75-g oral GTT results.

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**FOR REFERENCES VISIT contemporaryobgyn.net/GDM**