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Clinical Management Guidelines for Obstetrician–Gynecologists

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INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect a limited, focused change to clarify and provide additional information on the pharmacologic treatment of gestational diabetes mellitus.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. However, debate continues to surround the diagnosis and treatment of GDM despite several recent large-scale studies addressing these issues. The purposes of this document are the following: 1) provide a brief overview of the understanding of GDM, 2) review management guidelines that have been validated by appropriately conducted clinical research, and 3) identify gaps in current knowledge toward which future research can be directed.

Background

Definition and Prevalence

Gestational diabetes mellitus is a condition in which carbohydrate intolerance develops during pregnancy. Gestational diabetes that is adequately controlled without medication is often termed diet-controlled GDM or class A1GDM. Gestational diabetes mellitus that requires medication to achieve euglycemia is often termed class A2GDM. Because many women do not receive screening for diabetes mellitus before pregnancy, it can be challenging to distinguish GDM from preexisting diabetes. However, it has been estimated that in 2009, 7% of pregnancies were complicated by any type of diabetes and that approximately 86% of these cases represented women with GDM (1). Additionally, the prevalence of GDM varies in direct proportion to the prevalence of type 2 diabetes in a given population or racial or ethnic group. Caucasian women generally have the lowest rates of GDM. There is an increased prevalence of GDM among Hispanic, African American, Native American, and Asian or Pacific Islander women (2). Gestational diabetes also increases with the same risk factors seen for type 2 diabetes such as obesity and increased age (3). With a greater prevalence of obe-

sity and sedentary lifestyles, the prevalence of GDM among reproductive-aged women is increasing globally.

Maternal and Fetal Complications

Women with GDM have a higher risk of developing preeclampsia (9.8% in those with a fasting glucose less than 115 mg/dL and 18% in those with a fasting glucose greater than or equal to 115 mg/dL) and undergoing a cesarean delivery (25% of women with GDM who require medication and 17% of women with diet-controlled GDM underwent cesarean delivery versus 9.5% of controls) (4, 5). Furthermore, women with GDM have an increased risk of developing diabetes (predominantly type 2 diabetes) later in life. It is estimated that up to 70% of women with GDM will develop diabetes within 22–28 years after pregnancy (6–8). The progression to diabetes also is influenced by race, ethnicity, and obesity. For example, 60% of Latin American women with GDM may develop type 2 diabetes within 5 years of their index pregnancy (9).

The offspring of women with GDM are at increased risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia, and birth trauma. There also is an increased risk of stillbirth, although how much this

is related to glycemic control is debated (10). The results of the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO), an international, multicenter study, demonstrated a continuous relationship between maternal glucose levels on each of the three values of the 75-g, 2-hour oral glucose tolerance test (OGTT) and cesarean delivery, birth weight greater than the 90th percentile, clinical neonatal hypoglycemia, and fetal hyperinsulinemia (11). Other studies have demonstrated that fetal exposure to maternal diabetes contributes to childhood and adult-onset obesity and diabetes in offspring, which is independent of risks associated with obesity and genetic predisposition (12, 13).

Screening Practices, Diagnostic Thresholds, and Treatment Benefits

Historically, screening for GDM consisted of obtaining the patient's medical history and focused primarily on past obstetric outcomes and a family medical history of type 2 diabetes. A 1973 study proposed the use of the 50-g, 1-hour OGTT as a screening tool for GDM (14). This test has since become widely accepted, and 95% of obstetricians in the United States use it as the tool for universal screening of pregnant women (15, 16).

The use of historic factors (family or personal history of diabetes, previous adverse pregnancy outcome, glycosuria, and obesity) to identify GDM will fail to identify approximately one half of women with GDM (17). Although certain factors place women at low risk of GDM, it may not be cost effective to screen that group of women with glucose tolerance testing. However, such low-risk women represent only 10% of pregnant women and identifying those who should not be screened may add unnecessary complexity to the screening process (18). Therefore, in 2014, the U.S. Preventive Services Task Force made a recommendation to screen all pregnant women for GDM at or beyond 24 weeks of gestation (16).

Clinical Considerations and Recommendations

▶ *How is gestational diabetes mellitus diagnosed?*

All pregnant women should be screened for GDM with a laboratory-based screening test(s) using blood glucose levels. Screening for GDM generally is performed at 24–28 weeks of gestation (19). Early pregnancy screening for undiagnosed type 2 diabetes, preferably at the initiation of prenatal care, is suggested in overweight and obese women with additional diabetic risk

factors, including those with a prior history of GDM (see Box 1) (16, 20). However, the best test for early GDM or type 2 diabetes screening is not clear. The testing used to diagnose type 2 diabetes in nonpregnant individuals (ie, a fasting blood glucose followed by a 75-g glucose load and a 2-hour plasma glucose measurement) could be used for early pregnancy screening (21). Many obstetricians or obstetric care providers use the two-step screening process that is used for GDM and start with a 50-g OGTT. The American Diabetes Association (ADA) has noted that measurement of hemoglobin A_{1C} also can be used, but it may not be suitable for use alone because of decreased sensitivity compared with OGTT approaches (20). Even if the results of early testing are negative, GDM screening still is recommended at 24–28 weeks of gestation because of the large proportion of women who had negative early pregnancy screening but who will go on to develop GDM (22). In women who have positive 50-g screening test results, but negative follow-up test results early in pregnancy, it is common to use the follow-up test at 24–28 weeks of gestation without repeating the 50-g screening test.

The two-step approach to testing for GDM that is commonly used in the United States is based on first screening with the administration of a 50-g oral glucose solution followed by a 1-hour venous glucose determination. Women whose glucose levels meet or exceed an institution's screening threshold then undergo a 100-g, 3-hour diagnostic OGTT. Gestational diabetes mellitus is most often diagnosed in women who have two or more abnormal values on the 3-hour OGTT.

Institutional screening thresholds for the 1-hour glucose challenge vary from 130 mg/dL to 140 mg/dL, with a range of sensitivities and specificities reported. However, there are no randomized trials that have examined whether one cutoff is more effective than others. Data regarding the ideal threshold value to screen for gestational diabetes in order to improve pregnancy outcomes also are insufficient, although standardization of a screening threshold has been recommended (23). For example, one cohort study showed that a value of 140 mg/dL had lower false-positive rates and improved positive predictive values across various racial and ethnic groups. This analysis also showed that sensitivities were only marginally improved when using lower thresholds (ie, 130 mg/dL and 135 mg/dL) (24). Using a higher standardized threshold of 140 mg/dL may lower the rate of false-positive screening test results and unnecessary administration of the 3-hour OGTTs, which has been shown to be associated with increased maternal stress and dissatisfaction regarding the process of screening for and diagnosing GDM (25–27). However, in the absence of clear evidence that supports one

cutoff value over another (ie, 130 mg/dL, 135 mg/dL, or 140 mg/dL) for the 1-hour glucose screening test, obstetricians and obstetric care providers may select one of these as a single consistent cutoff for their practice, using factors such as community prevalence rates of GDM when making their decision.

Different cutoffs for the 3-hour OGTT also have been proposed. Table 1 (19, 20) lists the diagnostic thresholds established for the 3-hour OGTT by the National Diabetes Data Group and by Carpenter and Coustan, with the latter using lower thresholds that subsequently result in higher rates of GDM diagnosis (20). In the absence of clear comparative trials, one set of diagnostic criteria for the 3-hour OGTT cannot be clearly recommended over the other. For example, in a cross-sectional study that compared the two sets of criteria in more than 26,000 women found that the diagnosis of GDM increased on average by 50% with the use of the Carpenter and Coustan thresholds (28). However, a study that examined the clinical outcomes showed that the women in whom GDM would have been incrementally diagnosed by the Carpenter and Coustan criteria alone had higher rates of perinatal complications than the women with values below these diagnostic thresholds (29). Women who have even one abnormal value on the 100-g, 3-hour OGTT have a significantly increased risk of adverse perinatal outcomes compared with women without GDM (29). Although a higher level of scrutiny may be focused on this subset of women, further research is needed to clarify the risk of adverse outcomes in patients with one abnormal value on the 100-g, 3-hour OGTT and whether they would benefit from treatment.

Given the benefits of standardization, practitioners and institutions should select a single set of diagnostic criteria, either plasma or serum glucose levels designated by the Carpenter and Coustan criteria or the

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Box 1. Screening Strategy for Detecting Pregestational Diabetes or Early Gestational Diabetes Mellitus ⇐

Consider testing in all women who are overweight or obese (ie, have a body mass index greater than 25 or greater than 23 in Asian Americans) and have one or more of the following additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race or ethnicity (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Have previously given birth to an infant weighing 4,000g (approximately 9 lb) or more
- Previous gestational diabetes mellitus
- Hypertension (140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein cholesterol level less than 35 mg/dL (0.90 mmol/L), a triglyceride level greater than 250 mg/dL (2.82 mmol/L)
- Women with polycystic ovarian syndrome
- A_{1C} greater than or equal to 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (eg, prepregnancy body mass index greater than 40 kg/m^2, acanthosis nigricans)
- History of cardiovascular disease

If pregestational or gestational diabetes mellitus is not diagnosed, blood glucose testing should be repeated at 24–28 weeks of gestation.

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Table 1. Proposed Diagnostic Criteria for Gestational Diabetes Mellitus* ⇐

Status	Plasma or Serum Glucose Level Carpenter and Coustan Conversion		Plasma Level National Diabetes Data Group Conversion	
	mg/dL	mmol/L	mg/dL	mmol/L
Fasting	95	5.3	105	5.8
1 hour	180	10.0	190	10.6
2 hours	155	8.6	165	9.2
3 hours	140	7.8	145	8.0

*A diagnosis generally requires that two or more thresholds be met or exceeded, although some clinicians choose to use just one elevated value.

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plasma levels established by the National Diabetes Data Group, for consistent use within their patient populations. Considerations for selection of one set of diagnostic criteria over the other could include, but are not limited to, the baseline prevalence of diabetes in their specific communities and the availability of resources to appropriately manage women in whom GDM will be diagnosed by any given protocol. This approach, although imperfect, avoids establishment of a single set of diagnostic criteria across all populations based on expert opinion alone.

A one-step approach to establishing the diagnosis of GDM using a 75-g, 2-hour OGTT has been used and promoted by other organizations. For example, in 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended that a universal 75-g, 2-hour OGTT be performed during pregnancy and that the diagnosis of GDM be established when any single threshold value was met or exceeded (fasting value, 92 mg/dL; 1-hour value, 180 mg/dL; or 2-hour value, 153 mg/dL) (30). Overall, using the proposed IADPSG criteria would identify approximately 18% of pregnant women in the United States as having GDM; in some subpopulations, the proportion of women in whom GDM is diagnosed would be even higher. In 2011, the ADA endorsed these criteria while acknowledging that adopting these cutoffs would significantly increase the prevalence of GDM (31). The additional women in whom GDM would be diagnosed may be at a lower risk of adverse outcomes than and may not derive similar benefits from diagnosis and treatment as women in whom GDM was diagnosed by traditional criteria (32). As of 2017, the ADA continues to recognize that there is an absence of clear evidence that supports the IADPSG-recommended approach versus the more traditional two-step screening approach (20).

In 2013, a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Consensus Development Conference on Diagnosing Gestational Diabetes recommended that obstetricians and obstetric care providers continue to use a two-step approach to screen for and diagnose GDM. The report underscored the lack of evidence that the use of the one-step 75-g, 2-hour OGTT to diagnose GDM leads to clinically significant improvements in maternal or newborn outcomes and highlighted the significant increase in health care costs that would result (23). Additionally, a 2015 Cochrane review supported that no specific screening strategy has been shown to be optimal (33). In light of this, the American College of Obstetricians and Gynecologists (ACOG) supports the two-step process and recommends that implications of suggested changes

be studied before they are proposed at a national level. However, individual practices and institutions may choose to use the IADPSG's recommendation, if appropriate, for the population they serve.

▶ *What are the benefits of treating gestational diabetes mellitus?*

The 2005 Australian Carbohydrate Intolerance Study in Pregnant Women trial, the first large-scale (1,000 women), randomized treatment trial for GDM (34) found the treatment was associated with a significant reduction in the rate of the primary outcome, a composite of serious newborn complications (perinatal death, shoulder dystocia, and birth trauma, including fracture or nerve palsy). Treatment also reduced preeclampsia (from 18% to 12%) as well as reduced the frequency of infants who were large for gestational age (LGA) (from 22% to 13%) and who had a birth weight greater than 4,000 g (from 21% to 10%). A subsequent randomized, multicenter treatment trial of 958 women with mild GDM conducted in the United States found that, although there were no differences in the frequency of the primary composite outcome (perinatal death, neonatal hypoglycemia, elevated umbilical cord C-peptide level, and birth trauma), several significant differences in secondary outcomes were observed with treatment, including a lower frequency of LGA infants, lower frequency of birth weight exceeding 4,000 g, and reduced neonatal fat mass (35). Moreover, the rates of cesarean delivery, shoulder dystocia, and hypertensive disorders were significantly reduced in women who were treated for GDM. A U.S. Preventive Services Task Force systematic review underscored the demonstrated benefits of treating GDM and highlighted the reduced risks of preeclampsia, shoulder dystocia, and macrosomia (36). The treatment in such studies has consisted of dietary counseling with specific nutritional approaches (37–39) and exercise (40, 41). Based on this evidence, women in whom GDM is diagnosed should receive nutrition and exercise counseling, and when this fails to adequately control glucose levels, medication should be used for maternal and fetal benefit. It is important to note that in both trials described above, women with elevated glucose values were treated with insulin, not oral agents, when medical nutrition treatment did not control glucose values.

▶ *How should blood glucose be monitored in a woman with gestational diabetes mellitus?*

Once a woman with GDM begins nutrition therapy (dietary counseling), surveillance of blood glucose levels is required to confirm that glycemic control has been

established. However, there is insufficient evidence to define the optimal frequency of blood glucose testing in women with GDM. Based on the data available, the general recommendation is for daily glucose monitoring four times a day, once after fasting and again after each meal.

Mean fasting glucose values may be useful for managing diabetes in pregnant women because they are predictive of increased neonatal fat mass in the women's offspring. Neonatal fat mass has been shown to be associated with the development of childhood obesity and diabetes (42). Another study, a randomized controlled trial that compared the value of preprandial versus postprandial measurements for blood glucose monitoring of women with GDM, showed that use of the 1-hour postprandial measurement was associated with better glycemic control, a lower incidence of LGA infants, and lower rates of cesarean delivery for cephalopelvic disproportion (43). Given this evidence, fasting and postprandial values should be used for monitoring blood glucose in women with GDM. Assessment of postprandial blood glucose can be undertaken at either 1 hour or 2 hours after meals. No study to date has demonstrated the superiority of either approach (44–46), and this may be because postprandial glucose peaks at approximately 90 minutes, between the two time points (47).

Once the patient's glucose levels are well controlled by diet, the frequency of glucose monitoring may be modified depending on gestational age, overall concerns for adherence, and likely need for future adjustments to care. It is unusual to recommend obtaining fewer than two measurements per day.

In addition, no controlled trials have been performed to identify optimal glycemic targets. The ADA and ACOG recommend that fasting or preprandial blood glucose values be below 95 mg/dL and postprandial blood glucose values be below 140 mg/dL at 1 hour or 120 mg/dL at 2 hours to reduce the risk of macrosomia (19). Generally, these values are reviewed weekly; however, when there are many abnormal values, more frequent review is common. Alternatively, with stable, normal values, less frequent review is acceptable.

▶ *What nonpharmacologic treatments are effective in managing gestational diabetes mellitus?*

Most commonly, GDM management begins with the nonpharmacologic approaches of dietary modifications, exercise, and glucose monitoring. A recent meta-analysis of lifestyle modification trials in women with GDM demonstrated a reduction in large-for-gestational-age neonates, *macrosomia* (defined as 4,000 g or more), and neonatal fat mass in neonates born to women randomized to lifestyle interventions (48). Additionally, women randomized to the lifestyle interventions were more likely to meet postpartum weight goals 1 year after pregnancy. Despite these promising findings, the specific dietary and exercise approaches are less well studied.

The goal of medical nutrition therapy in women with GDM is to achieve normal blood glucose levels, prevent ketosis, provide adequate weight gain, and contribute to appropriate fetal growth and development. The ADA recommends nutritional counseling by a registered dietitian and development of a personalized nutrition plan based on the individual's body mass index for all patients with GDM (19). In some clinical settings in which a dietitian is not readily available, a clinician should be able to provide recommendations to the patient based on three major nutritional components: 1) caloric allotment, 2) carbohydrate intake, and 3) caloric distribution.

A diet composed of 50–60% carbohydrates often will result in excessive weight gain and postprandial hyperglycemia. Therefore, it has been suggested that carbohydrate intake be limited to 33–40% of calories, with the remaining calories divided between protein (20%) and fat (40%) (49); however, the actual dietary composition that optimizes perinatal outcomes is unknown. For example, a randomized trial of 99 women with GDM that compared a low-glycemic index nutrition plan with a conventional high-fiber diet found that both produced similar pregnancy outcomes (39). A small, recent randomized trial demonstrated that women with GDM randomized to a complex carbohydrate diet had lower fasting glucose values as compared with those on a conventional diet (50). Given these findings and the results of other treatment trials, complex carbohydrates are recommended over simple carbohydrates because they are digested more slowly, are less likely to produce significant postprandial hyperglycemia, and potentially reduce insulin resistance (38). There is little evidence evaluating or supporting different dietary approaches to the treatment of GDM (37). In practice, three meals and two to three snacks are recommended to distribute carbohydrate intake and to reduce postprandial glucose fluctuations.

Although there are multiple randomized trials that have examined exercise and lifestyle interventions in adults with diabetes who are not pregnant, there are few published exercise trials in women with GDM. Even though most of these published trials have small sample sizes, they do appear to show improvement in glucose levels (40, 51–54). In adults with diabetes

who are not pregnant, exercise—particularly weight training—increases lean muscle mass and improves tissue sensitivity to insulin. In overweight or obese women with GDM, exercise also may be able to improve glycemic control. Therefore, a moderate exercise program is recommended as part of the treatment plan for women with GDM (19). Such a plan should mirror diabetes care in general, and women with GDM should aim for 30 minutes of moderate-intensity aerobic exercise at least 5 days a week or a minimum of 150 minutes per week (31). Simple exercise such as walking for 10–15 minutes after each meal can lead to improved glycemic control and is commonly recommended (55).

▶ *What pharmacologic treatments are effective in managing gestational diabetes mellitus?*

Pharmacologic treatment is recommended when target glucose levels cannot be consistently achieved through nutrition therapy and exercise. However, a systematic review found no conclusive evidence for a specific threshold value at which medical therapy should be started (56). Insulin historically has been considered the standard therapy for GDM management in cases refractory to nutrition therapy and exercise and this has continued to be reinforced by the ADA (19).

Insulin, which does not cross the placenta, can achieve tight metabolic control and traditionally has been added to nutrition therapy if fasting blood glucose levels consistently are greater than or equal to 95 mg/dL, if 1-hour levels consistently are greater than or equal to 140 mg/dL, or if 2-hour levels consistently are greater than or equal to 120 mg/dL. These thresholds largely have been extrapolated from recommendations for managing pregnancy in women with preexisting diabetes. If insulin is used throughout the day in women in whom fasting and postprandial hyperglycemia are present after most meals, a typical starting total dosage is 0.7–1.0 units/kg daily. This dosage should be divided with a regimen of multiple injections using long-acting or intermediate-acting insulin in combination with short-acting insulin. However, if there are only isolated abnormal values at a specific time of day, focusing the insulin regimen to correct the specific hyperglycemia is preferred. For example, in women with only elevated fasting values, nighttime administration of intermediate-acting insulin, such as NPH insulin, may be adequate. Similarly, in women with elevated values only for breakfast postprandial, short-acting insulin before breakfast may be the only insulin needed. Regardless of the starting dosage, subsequent dosage adjustments should be individualized according to the woman's monitored blood glucose levels at particular times of the day. For long-acting and

intermediate-acting insulin, NPH insulin has been the mainstay, but more recently insulin glargine and insulin detemir have been described for long-acting use (57–59). For short-acting insulin, insulin analogues—including insulin lispro and insulin aspart—have been used in pregnancy, and these insulin analogues do not cross the placenta. Insulin lispro and insulin aspart should be used preferentially over regular insulin because both have a more rapid onset of action, enabling the patient to administer her insulin right at the time of a meal rather than 10–15 minutes before an anticipated meal. This provides better glycemic control and helps avoid hypoglycemic episodes from errors in timing (60, 61) (Table 2).

Oral Antidiabetic Medications

Oral antidiabetic medications (eg, metformin and glyburide) increasingly are being used among women with GDM, despite the fact that they have not been approved by the U.S. Food and Drug Administration for this indication (62) and even though insulin continues to be the ADA-recommended first-line therapy (19).

Metformin is a biguanide that inhibits hepatic gluconeogenesis and glucose absorption and stimulates glucose uptake in peripheral tissues. Historically, metformin primarily has been used in women with pregestational diabetes or those with polycystic ovary syndrome and infertility. In women with polycystic ovary syndrome, metformin is often continued until the end of the first trimester, despite only limited evidence to suggest that such use decreases the risks of adverse pregnancy outcomes, including first-trimester loss (63). Metformin crosses the placenta with levels that can be as high as maternal concentrations. The long-term metabolic influence on the offspring is unknown (64); however, one recent study found similar developmental outcomes by 2 years of age (65). This concern about the

Table 2. Action Profile of Commonly Used Insulin Agents ⇐

Type	Onset of Action	Peak of Action (h)	Duration of Action (h)
Insulin lispro	1–15 min	1–2	4–5
Insulin aspart	1–15 min	1–2	4–5
Regular insulin	30–60 min	2–4	6–8
Isophane insulin suspension (NPH insulin)	1–3 h	5–7	13–18
Insulin glargine	1–2 h	No peak	24
Insulin detemir	1–3 h	Minimal peak at 8–10	18–26

Modified from Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstet Gynecol 2003;102:857–68.

fetal exposure to metformin and the absence of long-term neonatal follow-up after in-utero metformin exposure is one reason the ADA continues to recommend that when pharmacologic treatment of GDM is indicated, insulin is considered the preferred treatment for diabetes in pregnancy (19).

In one large trial, 751 women with GDM were randomly assigned to receive insulin therapy or metformin (plus insulin if needed). Both groups experienced similar rates of a composite outcome of perinatal morbidity, consisting of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, prematurity, and low Apgar scores (66). In another prospective trial, women randomized to metformin had lower mean glucose levels, less gestational weight gain, and neonates with lower rates of hypoglycemia than those randomized to insulin (67).

Meta-analyses comparing metformin to insulin have been conflicting dependent upon whether unpublished studies or women with type II diabetes mellitus are included. In an initial meta-analysis that included only published data, the differences between neonates delivered to women randomized to metformin versus insulin were minimal (68, 69). Yet, women randomized to metformin experienced a higher rate of preterm birth (risk ratio [RR], 1.5), but a lower rate of gestational hypertension (RR, 0.53) (68).

In a recent meta-analysis that included unpublished trials, a network meta-analysis was performed (70). This method combines information across multiple treatments simultaneously with the analysis of direct evidence (which comes from studies directly randomizing treatments of interest) and indirect evidence (which comes from studies comparing treatments of interest with a common comparator). The effect size did not demonstrate superiority when metformin was compared with insulin on the outcomes of large for gestational age, macrosomia, neonatal hypoglycemia, or cesarean delivery. Interestingly, in the dichotomous meta-analysis performed, no difference in preterm delivery was demonstrated (RR 1.37, 95%; CI 0.62–3.01). A subsequent meta-analysis with trials that included women with type II diabetes and GDM also noted no increase in preterm delivery (71). Thus, although metformin may be a reasonable alternative approach to treat gestational diabetes, it is important to counsel women about the lack of superiority when compared with insulin, the placental transfer of the drug, and the absence of long-term data in exposed offspring. Additionally, in the aforementioned prospective trials, between 26% and 46% of women who took metformin alone eventually required insulin (66, 67).

The dosage for metformin usually starts at 500 mg nightly for 1 week at initiation, then increases to 500 mg twice daily. Because metformin generally is not used in patients with chronic renal disease, creatinine often is checked at baseline to ensure adequate renal function. The most common adverse effects of metformin are abdominal pain and diarrhea, which are minimized by slowly increasing the dosage. Such adverse effects were reported in 2.5–45.7% of patients enrolled in studies of metformin in pregnancy (68), and it is common to recommend taking the medication with meals to reduce symptoms. If higher doses are needed, the maximum dose is usually 2,500–3,000 mg per day in two to three divided doses. In women who decline insulin therapy or who the obstetricians or obstetric care providers believe will be unable to safely administer insulin, or for women who cannot afford insulin, metformin is a reasonable alternative choice.

Glyburide is a sulfonylurea that binds to pancreatic beta-cell adenosine triphosphate potassium channel receptors to increase insulin secretion and insulin sensitivity of peripheral tissues. It should not be used in patients who report a sulfa allergy. Previous meta-analyses have noted increased risks of macrosomia and hypoglycemia with glyburide compared with insulin in the treatment of GDM (66, 67); whereas a more recent meta-analysis only demonstrated higher rates of neonatal hypoglycemia (72). These worse outcomes are despite the fact that individual trials comparing glyburide with insulin failed to show any significant difference in degree of glycemic control (73–75). Observational studies have reported higher rates of preeclampsia, hyperbilirubinemia, and stillbirth with use of glyburide as compared with insulin, but many other outcomes have not been statistically significantly different (62, 76–81). The common dosage of glyburide is 2.5–20 mg daily in divided doses, although pharmacokinetic studies during pregnancy indicate daily doses up to 30 mg may be necessary to achieve adequate control (82). Additionally, 4–16% (or more) women required the addition of insulin to maintain good glycemic control when glyburide was used as initial treatment (73, 77, 83, 84). Despite the increased use of glyburide over the past decade (62), the evidence indicates that glyburide treatment should not be recommended as a first-choice pharmacologic treatment because, in most studies, it does not yield equivalent outcomes to insulin or metformin.

Concerns also have been raised about the safety of oral antidiabetic agents during pregnancy. For example, although an initial study that analyzed umbilical cord blood revealed no detectable glyburide in exposed pregnancies (73), a subsequent study demonstrated that glyburide does cross the placenta (82). As mentioned previously, metformin also has been found to freely cross the placenta, and the fetus is exposed to concentrations

similar to maternal levels (85). Theoretic concerns include the potential effects of in utero metformin exposure on long-term glucose homeostasis of developing offspring. It also is not yet known whether oral antidiabetic medications affect the progression to type 2 diabetes later in life in women who were treated during pregnancy. A recent Cochrane meta-analysis, reporting data on 7,381 women, that compared insulin versus any type of oral antidiabetic pharmacological therapies noted similar effects on health outcomes. This investigation combined women taking either metformin, glyburide, or both, and acarbose (86). Individually these oral antidiabetic medications have been noted to have different clinical efficacies on maternal and neonatal outcomes with diverse safety profiles, hence pooling these trials may have a confounding effect limiting the conclusions drawn from this meta-analysis. Although current data demonstrate no adverse short-term effects on maternal or neonatal health from oral antidiabetic therapy during pregnancy, long-term outcomes are not yet available. Thus, health care providers should counsel women of the limitations in safety data when prescribing oral agents to women with GDM.

Taking into account that oral antidiabetic medications are not approved by the U.S. Food and Drug Administration for the treatment of GDM, cross the placenta, and lack long-term neonatal safety data; and considering that summaries of the current medical literature note poor trial quality while not being designed to assess equivalence or noninferiority when comparing oral agents to insulin; insulin is considered the preferred treatment when pharmacologic treatment of GDM is indicated. Although this recommendation aligns with the ADA recommendation, ACOG recognizes that clinical situations may occur that necessitate the use of oral agents. As aforementioned, in women who decline insulin or who the obstetricians or obstetric care providers believe will be unable to safely administer insulin, or for women who cannot afford insulin, metformin (and rarely glyburide) is a reasonable alternative choice in the context of discussing with the patient the limitations of the safety data and a high rate of treatment failure that requires insulin supplementation.

▶ *Is fetal assessment indicated in pregnancies complicated by gestational diabetes mellitus?*

Antepartum fetal testing is recommended for patients with pregestational diabetes. Because the increased risk of fetal demise in patients with pregestational diabetes is related to suboptimal glycemic control, it would be expected that women with GDM who have poor glycemic control also would be at increased risk. Therefore, fetal surveillance may be beneficial for women with GDM with poor glycemic control. Additionally, because those women who are treated medically with insulin or oral agents had suboptimal glycemic control at some time, fetal surveillance usually is recommended for these patients as well (87). Antenatal fetal testing in women with poorly controlled or medication-requiring GDM without other morbidities usually is initiated at 32 weeks of gestation. If other factors associated with increased risk of adverse pregnancy outcome are present, it may be reasonable to start surveillance earlier in pregnancy.

Studies have not specifically demonstrated an increase in stillbirth with well-controlled A1GDM before 40 weeks of gestation. Thus, antepartum fetal testing may not be necessary in these women. There is no consensus regarding antepartum fetal testing among women with well-controlled GDM who are not medically treated (A1GDM). If antepartum testing is to be used in such patients, it is generally started later than in women with A2GDM. The specific antepartum test and frequency of testing may be chosen according to local practice; however, because polyhydramnios can result from fetal hyperglycemia, it is common for clinicians to use testing that incorporates serial measures of amniotic fluid.

▶ *What are delivery considerations in pregnancies complicated by gestational diabetes mellitus?*

Women with GDM with good glycemic control and no other complications are commonly managed expectantly until term (88, 89). In most cases, women with good glycemic control who are receiving medical therapy do not require delivery before 39 weeks of gestation. The recent GINEXMAL trial of GDM-only patients randomized women to induction of labor at 38 weeks of gestation versus expectant management up to 41 weeks of gestation (90). Although the study did not achieve its intended sample size, there was no difference in cesarean delivery rates (12.6% versus 11.8%, P=.81) or many other outcomes. There was, however, a higher rate of hyperbilirubinemia in the induced group (10.0% versus 4.1%, P=.03). In a randomized trial in which women with insulin-treated GDM and fetuses believed to be of appropriate weight for gestational age were randomized at 38 weeks of gestation to induction of labor within 1 week or expectant management, there was no difference in cesarean delivery rates (91). However, there was a smaller proportion of LGA infants in the induction group. Furthermore, a multiple time series cohort study showed that there were no significant differences in either macrosomia or cesarean delivery rates among women with insulin-treated GDM who

underwent induction of labor at 38–39 weeks of gestation when compared with expectantly managed historic controls (92). Shoulder dystocia was experienced by 10% of the expectant management group after more than 40 weeks of gestation versus 1.4% in the group with labor induction at 38–39 weeks of gestation. A systematic review later confirmed these findings (93). However, a recent study that compared induction of labor before 40 weeks of gestation with expectant management demonstrated a reduction in cesarean delivery among women with GDM who were induced (94). A decision analysis demonstrated that delivery of women with GDM at 38 weeks or 39 weeks of gestation would reduce overall perinatal mortality without increasing cesarean delivery rates (95). Although persuasive, these data have not been confirmed by large randomized trials. Therefore, the timing of delivery in women with GDM that is controlled with only diet and exercise (A1GDM) should not be before 39 weeks of gestation, unless otherwise indicated. In such women, expectant management up to 40 6/7 weeks of gestation in the setting of indicated antepartum testing is generally appropriate. For women with GDM that is well controlled by medications (A2GDM), delivery is recommended from 39 0/7 weeks to 39 6/7 weeks of gestation.

In contrast, expert opinion has supported earlier delivery for women with poorly controlled GDM (88, 89). But clear guidance about the degree of glycemic control that necessitates earlier delivery is lacking, and the recommendations about timing of delivery lack specific guidance as well (96). In light of this, consideration of timing should incorporate tradeoffs between the risks of prematurity and the ongoing risks of stillbirth. In such a setting, delivery between 37 0/7 weeks and 38 6/7 weeks of gestation may be justified, but delivery in the late preterm period from 34 0/7 weeks to 36 6/7 weeks of gestation should be reserved for those women who fail in-hospital attempts to improve glycemic control or who have abnormal antepartum fetal testing.

Because macrosomia is distinctly more common in women with GDM and because shoulder dystocia is more likely at any given fetal weight in pregnancies complicated by diabetes than in pregnancies not complicated by diabetes (97–99), it is reasonable for clinicians to assess fetal growth by ultrasonography or by clinical examination late in the third trimester to attempt to identify macrosomia among women with GDM. However, data are insufficient to determine whether cesarean delivery should be performed to reduce the risk of birth trauma in cases of suspected macrosomia. Although the use of ultrasonography to estimate fetal weight is common, one recent study found that among cases of ultrasonography-diagnosed LGA infants, only 22% were

LGA at birth (100). Additionally, in women whose fetuses received an LGA diagnosis, the risk of cesarean delivery was increased independent of actual birth weight. It has been estimated that up to 588 cesarean deliveries would be needed to prevent a single case of permanent brachial plexus palsy for an estimated fetal weight of 4,500 g, and up to 962 cesarean deliveries would be needed for an estimated fetal weight of 4,000 g (101, 102). Based on the available data, it is not possible to determine whether the potential benefits of planned cesarean delivery at a given estimated fetal weight are similar for women with GDM and women with preexisting diabetes. Therefore, it appears reasonable to recommend that women with GDM should be counseled regarding the risks and benefits of a scheduled cesarean delivery when the estimated fetal weight is 4,500 g or more (103).

▶ *How should women with a history of gestational diabetes mellitus be screened and counseled postpartum?*

Although the carbohydrate intolerance of GDM frequently resolves after delivery, up to one third of affected women will have diabetes or impaired glucose metabolism at postpartum screening. It has been estimated that between 15% and 70% will develop diabetes (predominantly type 2) later in life (8, 104–107). Another study showed that women with a history of GDM have a sevenfold increased risk of developing type 2 diabetes compared with women without a history of GDM (108). Therefore, screening at 4–12 weeks postpartum is recommended for all women who had GDM to identify women with diabetes, impaired fasting glucose levels, or impaired glucose tolerance (IGT) (Fig. 1) (19). A fasting plasma glucose test and the 75-g, 2-hour OGTT have been used for diagnosing overt diabetes in the postpartum period. Although the fasting plasma glucose test is easier to perform, it lacks sensitivity for detecting other forms of abnormal glucose metabolism. Results of the OGTT can confirm an impaired fasting glucose level and impaired glucose tolerance. Therefore, the Fifth International Workshop on Gestational Diabetes Mellitus recommends that women with GDM undergo a 75-g, 2-hour OGTT in the postpartum period (109). This usually should include a fasting plasma glucose as well.

All women who had GDM should follow up with a primary care physician. Additionally, women with impaired fasting glucose, IGT, or diabetes should be referred for preventive or medical therapy. Women with impaired fasting glucose or IGT may respond to lifestyle modification and pharmacologic interventions to decrease incident diabetes. Women with frank diabetes
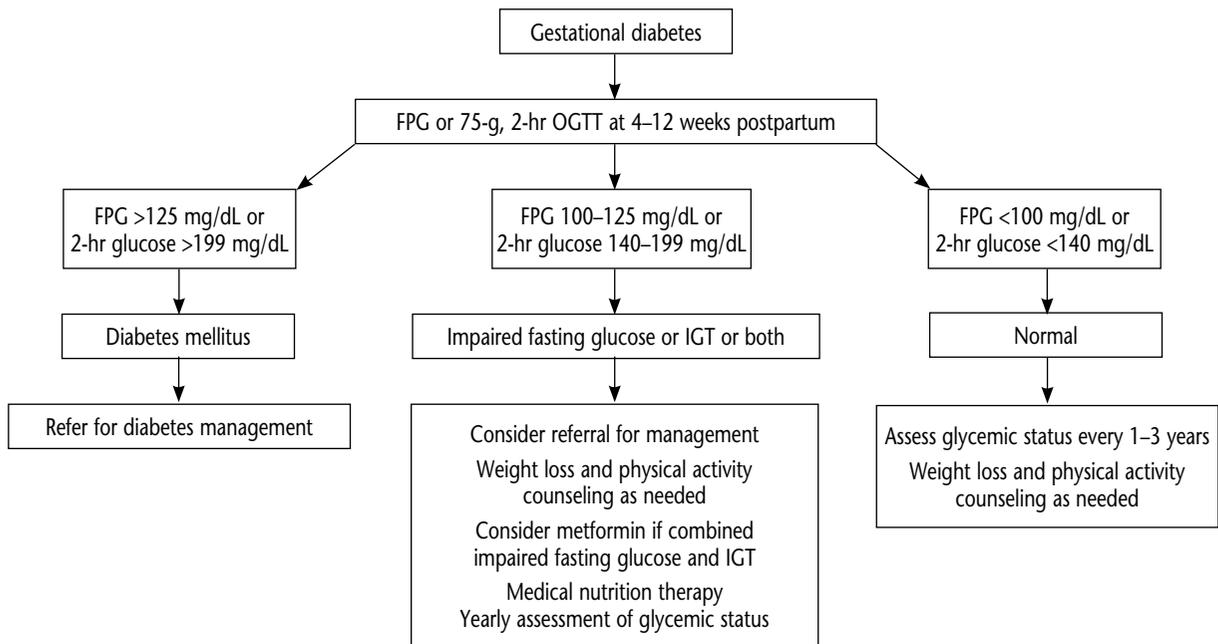
Figure 1. Management of postpartum screening results. Abbreviations: FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance. ⇐

benefit from ongoing intensive medical therapy. The ADA and ACOG recommend repeat testing every 1–3 years for women who had a pregnancy affected by GDM and normal postpartum screening test results (19).

For women who may have subsequent pregnancies, screening more frequently between pregnancies can detect abnormal glucose metabolism before fertilization and provides an opportunity to ensure prepregnancy glucose control (109). Women should be encouraged to discuss their GDM history and need for screening with their obstetricians or obstetric care providers.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

▶ Women in whom GDM is diagnosed should receive nutrition and exercise counseling, and when this fails to adequately control glucose levels, medication should be used for maternal and fetal benefit.

▶ When pharmacologic treatment of GDM is indicated, insulin is considered the preferred treatment for diabetes in pregnancy.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

▶ All pregnant women should be screened for GDM with a laboratory-based screening test(s) using blood glucose levels.

▶ In women who decline insulin therapy or who the obstetricians or other obstetric care providers believe will be unable to safely administer insulin, or for women who cannot afford insulin, metformin is a reasonable alternative choice.

▶ Glyburide treatment should not be recommended as a first-choice pharmacologic treatment because, in most studies, it does not yield equivalent outcomes to insulin.

▶ Health care providers should counsel women of the limitations in safety data when prescribing oral agents to women with GDM.

▶ Women with GDM should be counseled regarding the risks and benefits of a scheduled cesarean delivery when the estimated fetal weight is 4,500 g or more.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- In the absence of clear evidence that supports one cutoff value over another (ie, 130 mg/dL, 135 mg/dL, or 140 mg/dL) for the 1-hour glucose screening test, obstetricians and obstetric care providers may select one of these as a single consistent cutoff for their practice, using factors such as community prevalence rates of GDM when making their decision.

- In the absence of clear comparative trials, one set of diagnostic criteria for the 3-hour OGTT cannot be clearly recommended over the other. Given the benefits of standardization, practitioners and institutions should select a single set of diagnostic criteria, either plasma or serum glucose levels designated by the Carpenter and Coustan criteria or the plasma levels established by the National Diabetes Data Group, for consistent use within their patient populations.

- Once a woman with GDM begins nutrition therapy (dietary counseling), surveillance of blood glucose levels is required to confirm that glycemic control has been established.

- In practice, three meals and two to three snacks are recommended to distribute carbohydrate intake and to reduce postprandial glucose fluctuations.

- Women with GDM should aim for 30 minutes of moderate-intensity aerobic exercise at least 5 days a week or a minimum of 150 minutes per week.

- The timing of delivery in women with GDM that is controlled with only diet and exercise (A1GDM) should not be before 39 weeks of gestation, unless otherwise indicated. In such women, expectant management up to 40 6/7 weeks of gestation in the setting of indicated antepartum testing is generally appropriate.

- For women with GDM that is well controlled by medications (A2GDM), delivery is recommended at 39 0/7 to 39 6/7 weeks of gestation.

- Screening at 4–12 weeks postpartum is recommended for all women who had GDM to identify women with diabetes, impaired fasting glucose levels, or impaired glucose tolerance. Women with impaired fasting glucose, IGT, or diabetes should be referred for preventive or medical therapy. The ADA and ACOG recommend repeat testing every 1–3 years for women who had a pregnancy affected by GDM and normal postpartum screening test results.

- Women with GDM should be counseled regarding the risks and benefits of a scheduled cesarean delivery when the estimated fetal weight is 4,500 g or more.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/GestationalDiabetes.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. These resources may change without notice.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990 and May 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I   Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III   Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.