Gestational Diabetes Mellitus

By Karen L. Whalen, Pharm.D., BCPS, CDE, FAPhA;
and James R. Taylor, Pharm.D., BCACP, CDE

Reviewed by Bethany L. Murphy, Pharm.D., BCACP, BC-ADM; Steve C. Burkes, Pharm.D., BCPS, CSP; and Nicholas D. Baker, MPH, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Apply data regarding the risks of maternal hyperglycemia to the care of women with gestational diabetes mellitus (GDM).
2. Distinguish the differences between the various screening procedures for GDM.
3. Devise a monitoring plan to maximize maternal and fetal outcomes in patients with GDM.
4. Design an optimal treatment regimen, including nonpharmacologic and pharmacologic therapy, for GDM management.
5. Evaluate the role of oral hypoglycemic agents in GDM treatment.
6. Construct a plan for intra- and postpartum treatment of patients with GDM.

ABBREVIATIONS IN THIS CHAPTER

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
GDM	Gestational diabetes mellitus
LGA	Large for gestational age
NDDG	National Diabetes Data Group
NICE	National Institute for Health and Care Excellence
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test

Table of other common abbreviations.

INTRODUCTION

In the past, any hyperglycemia initially detected during pregnancy was considered gestational diabetes mellitus (GDM), regardless of whether the condition actually existed before the pregnancy or continued after the pregnancy. Today, GDM is diabetes that is diagnosed in the second or, more commonly, third trimester and is distinct from type 1 and type 2 diabetes (ADA 2016a). Diabetes developing during the first trimester is generally considered type 2 diabetes, although it can be type 1 or GDM (ADA 2016a). Because of variations in reporting, the population being studied, and the lack of universal diagnostic criteria, the exact prevalence of GDM is difficult to determine. A recent CDC report found prevalence rates of 4.6% and 9.2%, depending on the data sources used (CDC 2014). A history of GDM is the most significant risk factor for GDM. Other risk factors include Asian, Native American, Pacific Islander, African American, or Hispanic ethnicity; BMI of 25 kg/m^2 or greater; diabetes in a first-degree relative; excessive early gestational weight gain (first-trimester weight gain of 2 kg [4.4 lb] plus second-trimester weight gain per week of 0.6 kg [1.3 lb] for underweight, 0.45 kg [1.0 lb] for normal weight, 0.32 kg [0.7 lb] for overweight, and 0.27 kg [0.6 lb] for women with obesity); macrosomia in a previous pregnancy; maternal age older than 35; and weight gain of more than 5 kg (11 lb) since 18 years of age (Garrison 2015).

Women with GDM are often asymptomatic, so screening is important for detection. In a normal pregnancy, insulin resistance develops in the second trimester and continues until birth. The mechanism is not fully understood but is believed to be related to the production of hormones, cytokines, or adipokines by the placenta. Insulin secretion also increases, resulting in normal glucose concentrations. Gestational diabetes typically develops because of preexisting increased insulin

resistance and diminished insulin secretion. During pregnancy, the imbalance between insulin resistance and secretion may lead to hyperglycemia. Gestational diabetes is associated with maternal and fetal complications. Treatment options include nonpharmacologic therapy, insulin, and oral therapy.

MATERNAL AND FETAL COMPLICATIONS

Maternal Complications

Potential maternal complications associated with GDM include gestational hypertension, preeclampsia, and non-elective cesarean delivery. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was an international, multicenter study designed to assess the risks of adverse outcomes associated with maternal glucose concentrations (HAPO 2008). Subjects had a one-step 75-g oral glucose tolerance test (OGTT) at 24–32 weeks' gestation. Primary outcomes were birth weight greater than 90th percentile, primary cesarean section delivery, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile. Secondary outcomes included preeclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia, and intensive neonatal care. Results showed a continuous graded relationship of risk, with no distinct thresholds, between maternal glucose concentrations and the primary and secondary outcomes. Cesarean delivery was directly correlated with maternal glycemia, with an overall frequency of 23.7%. Another study found a 19.5% rate of non-elective cesarean delivery in women with GDM, compared with 13.5% in women without diabetes (Gorgal 2012). Results of the HAPO study showed 5.9% of patients had gestational hypertension and 4.8% had preeclampsia. Rates of gestational hypertension and preeclampsia in the general population are 3.6%–9.1% and 1.4%–4.0%, respectively (Roberts 2011). Regarding long-term complications, up to 50% of women with GDM will develop type 2 diabetes later in life. On average, this occurs 22–28 years after pregnancy (England 2009; O'Sullivan 1982). Ethnicity and obesity (BMI > 30 kg/m^2) may play a role in the risk and timing of the subsequent diagnosis of diabetes. For example, as many as 60% of Latino women with GDM may develop diabetes within 5 years (Kjos 1995). Other long-term complications include a 2.5- and 1.7-fold increased risk of developing metabolic syndrome and cardiovascular disease, respectively (Gunderson 2009; Shah 2008).

Fetal Complications

Neonates of women with GDM are at increased risk of macrosomia, which is defined as a birthweight over 4000 g, as well as neonatal hypoglycemia, hyperbilirubinemia, birth trauma, respiratory distress syndrome, and shoulder dystocia (Reece 2010). Macrosomia is the most common fetal complication, with a reported incidence of 15%–45%, followed by hyperbilirubinemia in 10%–13% of neonates (Esakoff 2009; Boulet 2003). Hypoglycemia can occur in 3%–5% of infants as a result of increased fetal insulin production in response to maternal hyperglycemia, which can increase the risk of seizures. Shoulder dystocia is a rare, but serious complication that can lead to brachial plexus injury. Long-term complications of infants born to mothers with GDM include increased risk of impaired glucose tolerance, type 2 diabetes, hypertension, obesity, and dyslipidemia (Mitanchez 2014).

Benefits of Treatment

Few well-designed studies have evaluated the benefit of treating GDM. Trials to date have included treatment strategies of self-monitoring blood glucose, medical nutrition therapy, and insulin. Outcomes data using other treatment modalities are lacking. Treatment of GDM reduces the risk of maternal hypertensive disorders by 40% (Hartling 2013). Rates of cesarean delivery are unaffected by treatment. Evidence on maternal long-term complications, such as type 2 diabetes and obesity, is lacking.

A meta-analysis of five randomized clinical trials found that treating GDM results in a 50% reduction in risk of macrosomia in infants, although the absolute mean difference in birth weight was less than 150 g (Hartling 2013). Risk of shoulder dystocia was reduced by 60%, although the overall events were rare (Hartling 2013). No difference was found

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of diabetes
- Laboratory testing and self-monitoring values used in diabetes management (e.g., fasting glucose, A1C)
- Common approaches to controlling diabetes – nutritional therapy, exercise, and medications
- Mechanism of action, dosing, and common adverse effects of metformin and glyburide
- Types of insulin (basal, mealtime) and common insulin dosing strategies
- General knowledge of the risk of medication use during pregnancy

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Diabetes Association. Standards of medical care in diabetes – 2016. Diabetes Care 2016;39(suppl 1):S94-S98.
- NICE Guideline: Diabetes and pregnancy: management from preconception to the postnatal period.

for neonatal hypoglycemia, birth injury, or risk of eventually developing glucose intolerance. Additional studies of maternal and fetal long-term outcomes are needed because data were insufficient to draw firm conclusions.

Some studies have tried to identify whether any risks are associated with treating GDM. Results from four trials found no increase in small-for-gestational-age neonates, rates of neonatal hypoglycemia, or admission to neonatal ICUs associated with treatment (Hartling 2013). Health care costs were minimally affected by treatment, but the treatment groups did have more prenatal visits.

SCREENING AND DIAGNOSIS OF GDM

Women who are at risk of preexisting diabetes should be screened at their first prenatal visit using the diagnostic criteria for nonpregnant adults. This includes overweight women or women with obesity with at least one additional risk factor, such as physical inactivity, family history of diabetes, high-risk ethnicity, history of GDM, hypertension, or hyperlipidemia (Garrison 2015). Otherwise, screening methods can follow the American Diabetes Association (ADA) or American College of Obstetricians and Gynecologists (ACOG) guidelines.

Screening Methods

Screening and diagnosis of GDM may consist of either a one- or a two-step approach (Figure 1-1). The one-step approach was initially recommended by the ADA in 2011 for use in all pregnant women without preexisting diabetes. It involves a 75-g OGTT at 24–28 weeks' gestation. This was based on recommendations from the International Association of Diabetes and Pregnancy Study Group (IADPSG). The IADPSG recommendations were based primarily on the results of the HAPO study. In reviewing the HAPO study, the IADPSG panel defined diagnostic glucose thresholds on the basis of reaching an OR of 1.75 for adverse outcomes, which led to the creation of the one-step glucose thresholds (IADPSG 2010). The OR of 1.75 was used because it identified the average glucose value at which the adverse outcomes of birth weight, cord C-peptide,

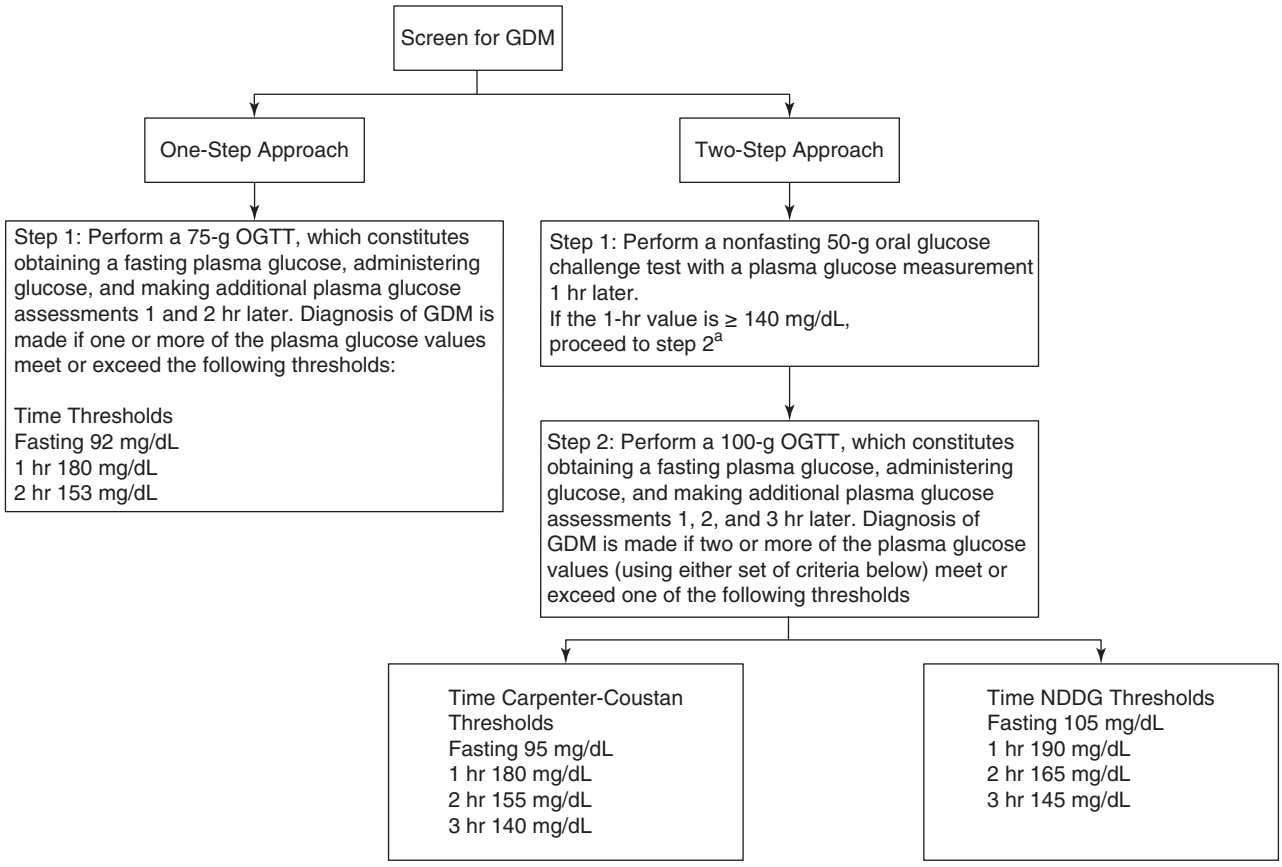

Figure 1-1. Screening and diagnostic criteria for gestational diabetes mellitus

[a]Some clinicians may use a 1-hr threshold of 130 or 135 mg/dL, though the ADA recommends 140 mg/dL. In addition, some clinicians may begin empiric therapy for GDM if the step 1 plasma glucose result is > 200 mg/dL and not proceed to step 2, though the ADA does not include that recommendation in its guidelines.

GDM = gestational diabetes mellitus; NDDG = National Diabetes Data Group; OGTT = oral glucose tolerance test.

Information from: Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician 2015;91:460-7.

and percent body weight were all in the 90th percentile. The two-step approach has been recommended by ACOG and an NIH consensus development program (ACOG 2013).

Controversies Regarding Best Screening Method

The IADPSG and ADA recognize that using the one-step approach would likely increase the number of women with a GDM diagnosis because only one abnormal value is needed for diagnosis. Although this may lead to increased health care costs, the ADA believes that the benefits outweigh these disadvantages. Data are unavailable from randomized controlled trials regarding outcomes for these additional women whose GDM would be diagnosed by the one-step method.

In the two-step approach, two different sets of glucose thresholds exist: Carpenter-Coustan and National Diabetes Data Group (NDDG). The Carpenter-Coustan thresholds are lower than the NDDG thresholds, resulting in higher rates of GDM diagnoses. Use of the Carpenter-Coustan criteria increases diagnosis by 30%–50% (Gokcel 2002; Magee 1993). Comparative trials are limited, making it difficult to recommend one criteria over another. One recent study compared the two diagnostic criteria and their effects on outcomes (Harper 2016b). This was a secondary analysis of a trial involving the treatment of mild GDM in 958 patients. Results showed that treatment with nutritional counseling, dietary therapy, and, in some cases, insulin provided similar reductions in the incidence of pregnancy-induced hypertension, shoulder dystocia, cesarean delivery, and macrosomia, regardless of which two-step diagnostic criteria were used. Clinicians and institutions should select one criteria to use consistently, with local rates of diabetes and availability of resources for managing GDM factored into that decision.

A recent systematic review analyzed 38 studies to assess different diagnostic thresholds for GDM on maternal and fetal outcomes in the absence of treatment for GDM. The results showed that women with GDM, regardless of the diagnostic criteria used, consistently had higher rates of cesarean section, shoulder dystocia, and large for gestational age (LGA) infants. Macrosomia was significantly higher with the two-step approach, but not the one-step approach. The authors concluded that higher glucose thresholds did not consistently have higher maternal or fetal risks, and further research is needed to determine which diagnostic criteria are associated with the best outcomes.

MONITORING IN GDM

Blood Glucose Monitoring

Once a woman has a diagnosis of GDM, routine glucose monitoring should begin. Evidence is lacking regarding the optimal frequency of testing, but the general recommendation is to monitor four times a day (ACOG 2013). This would consist of daily monitoring of fasting glucose and 1 or 2 hours after each meal. Data are insufficient regarding whether 1- versus 2-hour postprandial monitoring is superior. Postprandial glucose control is associated with better overall glycemic control and may be more predictive of maternal and fetal complications. Individuals with GDM that is diet controlled can monitor less often.

Glucose Goals and Other Monitoring Values

Observational studies show that A1C concentrations less than 6%–6.5% are associated with the lowest rates of fetal complications, but trials have not evaluated the risk-benefit of achieving these targets. Hemoglobin A1C concentrations during normal pregnancy fall by as much as 0.5% because of increased RBC turnover (Nielsen 2004). Furthermore, because postprandial glucose is a better indicator of risk of complications, A1C is not as useful. Suggested glycemic targets for patients with GDM, which vary slightly among the various guidelines, are outlined in Table 1-1.

NONPHARMACOLOGIC MANAGEMENT

Nutritional Therapy

Medical nutrition therapy is the cornerstone of treatment for GDM (Metzger 2007). Dietary intervention, in combination with insulin therapy as needed, reduces the risk of LGA

Table 1-1. Recommended Glycemic Targets for Patients with Gestational Diabetes

Guideline	Fasting Glucose (mg/dL)	1-Hr Postprandial Glucose (mg/dL)	2-Hr Postprandial Glucose (mg/dL)
ACOG	≤ 95	< 140	< 120
ADA	≤ 95	≤ 140	≤ 120
Endocrine Society	≤ 95[a]	≤ 140	≤ 120
NICE	< 95	< 140	< 115

[a]The Endocrine Society suggests a lower fasting glucose target of ≤ 90 mg/dL if it is attainable without significant hypoglycemia.
NICE = National Institute for Health and Care Excellence.

infants, fetal macrosomia, preeclampsia, and serious perinatal complications (Landon 2009; Crowther 2005). All women with GDM should receive dietary counseling at the time of diagnosis, preferably provided by a registered dietitian or nutritionist experienced in GDM management. The goals of dietary modification in GDM are to attain the desired level of glycemic control; provide adequate weight gain, which contributes to maternal and fetal well-being; and prevent the development of ketosis (ACOG 2013).

Suggested weight gain during pregnancy for patients with GDM varies according to the pre-pregnancy BMI. The ADA recommends a weight gain of 6.8–11.3 kg (15–25 lb) for overweight women and 4.5–9.1 kg (10–20 lb) for women with obesity (ADA 2016b), and the Endocrine Society suggests similar gestational weight gain, as outlined in the Institute of Medicine (IOM) revised guidelines for weight gain during pregnancy (Blumer 2013; Rasmussen 2009). Table 1-2 provides an overview of recommendations for weight gain in pregnancy, together with suggested caloric intake. Excessive weight gain is associated with a greater risk of fetal macrosomia and should be avoided. A large retrospective cohort study showed that women with GDM who followed IOM guidelines for weight gain had improved perinatal outcomes, and women who had excessive weight gain were more likely to have an LGA infant, preterm delivery, or cesarean delivery (Cheng 2008b). Conversely, women who gained less weight than recommended had a greater risk of delivering a small-for-gestational-age infant. In general, women with obesity women should reduce their pre-pregnancy daily caloric consumption by about 30% while maintaining a minimum caloric intake of 1600–1800 kcal per day (Blumer 2013; ADA 2008). More severe restriction of caloric intake may result in ketosis. Weight loss during pregnancy is not generally recommended (ADA 2008). Weekly weight checks can be used to identify excessive or insufficient weight gain.

Medical nutrition therapy for women with GDM should emphasize distribution of calories, with a focus on restriction of carbohydrates. The ACOG guidelines recommend a caloric distribution of 33%–40% carbohydrates, 20% protein, and 40% fat (ACOG 2013). Strong evidence for the optimal proportion of carbohydrates in GDM is lacking, and the Endocrine Society suggests a slightly less restrictive carbohydrate intake of 35%–45% of total calories (Blumer 2013). Other sources recommend a minimum intake of 175 g of carbohydrates per day, although this is greater than the recommended daily carbohydrate consumption (130 g) for nonpregnant women (Blumer 2013; ADA 2008; IOM 2002). Regardless of the strategy used to determine initial carbohydrate intake in GDM, adjustment of carbohydrate consumption should be ongoing and based on clinical measures such as blood glucose concentrations, ketone concentrations, and weight gain (ADA 2008).

A typical daily meal plan for women with GDM includes three small to moderate-sized meals and two to four snacks, one of which should be at bedtime to prevent the development of ketosis overnight (ADA 2008). Meal plans should consider cultural preferences as well as desired weight gain and level of physical activity (Metzger 2007). A suggested recommendation for caloric distribution across meals and snacks consists of 10% of total calories at breakfast, 30% at lunch, 30% at dinner, and 30% divided between the snacks. In general, carbohydrate intake should be distributed throughout the day to reduce postprandial hyperglycemia, and protein should be included with all meals and snacks to promote satiety. Glucose may be more difficult to control in the morning due to the dawn phenomenon. Therefore, women with GDM may require lower carbohydrate consumption to attain desired glucose concentrations after breakfast compared with other meals. Patients with GDM should be trained in carbohydrate counting, and blood glucose concentrations should be interpreted in the context of food logs that document carbohydrate intake (Metzger 2007). When insulin therapy is needed, consistency of carbohydrate intake with meals and snacks is an important focus (ADA 2008).

Table 1-2. Recommendations for Weight Gain and Caloric Requirements During Pregnancy

Pre-pregnancy BMI (kg/m^2)	Total Weight Gain	Rates of Weight Gain[a] 2nd and 3rd Trimesters	Caloric Requirements
	Range, lb	Mean (range), lb/wk	Range, kcal/kg/day[b]
Underweight (< 18.5)	28–40	1 (1–1.3)	Up to 40
Normal weight (18.5–24.9)	25–35	1 (0.8–1)	30
Overweight (25.0–29.9)	15–25	0.6 (0.5–0.7)	22–25
Obese (≥ 30.0)	11–20	0.5 (0.4–0.6)	12–14

[a]Calculations assume a 1.1- to 4.4-lb weight gain in the first trimester.

[b]Present pregnant weight.

Information from: Rasmussen KM, Yaktine AL; Institute of Medicine (U.S.). Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academies Press, 2009.

In addition to the amount of carbohydrates ingested, the type of carbohydrates is important. Intake of complex carbohydrates is preferred to intake of simple carbohydrates because complex carbohydrates are less likely to cause postprandial hyperglycemia (ACOG 2013). Food sources that are higher in complex carbohydrates tend to have a lower glycemic index, which blunts the rise in postprandial glucose.

A randomized trial of 63 women with GDM compared a low-glycemic index diet with a conventional high-fiber diet with a higher glycemic index (Moses 2009). Women receiving the higher glycemic index diet were significantly more likely to require the addition of insulin therapy. Furthermore, insulin treatment was avoided in about half of these women when they changed to the low-glycemic index diet. Likewise, a systematic review and meta-analysis that included nine randomized controlled trials and 884 women with GDM showed that a low-glycemic index diet was associated with a lower rate of insulin use (relative risk of insulin use 0.77) and lower birth weight infants (mean weight difference –161.9 g) (Viana 2014). In the same study, diets classified as low carbohydrate or characterized by moderate energy restriction (about 33% reduction in caloric intake) were not associated with changes in insulin use or birth weight. None of the diets had a significant effect on maternal or neonatal outcomes such as maternal weight gain, frequency of cesarean delivery, or incidence of fetal macrosomia.

Another small study (n=52) examined the effects of the Dietary Approaches to Stop Hypertension (DASH) diet in women with GDM (Asemi 2014). Women randomized to the DASH diet for 4 weeks during pregnancy were significantly less likely to require cesarean delivery (46.2% vs. 80.8%) or addition of insulin therapy (23% vs. 73%) than were women randomized to the control diet (45%–55% carbohydrates, 15%–20% protein, and 25–30% fat). Infant birth weights in the DASH diet group were also significantly lower (3222.7 g vs. 3818.8 g). The DASH diet is similar to a low-glycemic index diet, with its emphasis on fruits, vegetables, whole grains, and lean meats. According to the available evidence, patients with GDM should be encouraged to select carbohydrate sources with a low glycemic index, such as whole grains, fruits, and vegetables (Box 1-1).

Box 1-1. Glycemic Index of Various Foods

Low glycemic index

- Carrots
- Corn
- Fruits (most)
- Lima beans
- Oat bran
- Peas
- Steel-cut oatmeal
- Stone-ground whole wheat bread
- Sweet potatoes

Moderate glycemic index

- Brown rice
- Couscous
- Quick oats
- Pita bread
- Rye bread
- Whole wheat bread
- Wild rice

High glycemic index

- Bagel
- Bran flakes
- Corn flakes
- Instant oatmeal
- Melon
- Pineapple
- Popcorn
- Pretzels
- White bread
- White rice

Information from: American Diabetes Association. Glycemic Index and Diabetes [homepage on the Internet]. 2013.

Physical Activity

Together with medical nutrition therapy, physical activity is a key component in initial GDM management. Physical activity improves insulin sensitivity and reduces both fasting and postprandial glucose concentrations in patients with diabetes. The ADA, ACOG, and Endocrine Society guidelines recommend a program of moderate exercise consisting of 30 minutes most days of the week for women with GDM who have no medical or obstetric contraindications to physical activity (ACOG 2013; Blumer 2013; Colberg 2010). Examples of moderate exercise include brisk walking, recumbent bicycling, or 10 minutes of seated arm exercises after each meal.

Although many randomized controlled trials support the benefits of physical activity in nonpregnant adults with diabetes, evidence of improved outcomes in GDM is limited. A small randomized trial of 19 women with GDM examined the effects of diet (20% protein, 40% carbohydrate, and 40% fat) and exercise compared with diet alone for 6 weeks (Jovanovic 1989). The exercise regimen consisted of 20 minutes of physical activity three times weekly using an arm ergometer (arm cycle or arm crank) to maintain heart rate in the desired range. Participants in the exercise group had significantly lower fasting glucose (70.1 ± 6.6 vs. 87.6 ± 6.2 mg/dL) and 1-hour plasma glucose concentrations (105.9 ± 18.9 vs. 187.5 ± 12.9 mg/dL) after a 50-g oral glucose challenge. Another small randomized trial evaluated a regimen of diet and exercise consisting of cycling for 45 minutes three times weekly compared with a regimen of diet and insulin therapy (Bung 1991). Mean glucose concentrations, rates of cesarean delivery, infant birth weights, and incidence of fetal macrosomia were comparable between the two groups.

In 2006, a systematic review and meta-analysis of four trials involving 114 women with GDM found that glucose control was improved in patients who participated in an exercise program

such as an arm ergometer or cycling for 20–45 minutes three times weekly compared with those without a specific exercise regimen (Ceysens 2006). Maternal and neonatal outcomes such as need for insulin therapy and fetal macrosomia did not differ in the exercise group. The authors concluded that the evidence was insufficient to advocate for or against an exercise program for women with GDM and recommended further study to better determine the effects of exercise on maternal and fetal outcomes in GDM. Although evidence is limited for improvement in maternal and perinatal outcomes, a regimen of moderate exercise helps control maternal blood glucose and should be recommended for most women with GDM.

DRUG THERAPY FOR GDM

Suggested Thresholds for Initiation

With appropriate lifestyle modification, 70%–85% of women with GDM can achieve adequate glucose control (ADA 2016b). Drug therapy should be considered when medical nutrition therapy and moderate physical activity fail to achieve glucose goals within 1–2 weeks. Little consensus exists regarding the threshold glucose values that should trigger initiation of drug therapy. A systematic review and meta-analysis found no evidence to support that maternal and infant outcomes were affected by the glucose concentration at initiation of drug therapy for GDM (Nicholson 2008).

One approach is to initiate pharmacologic therapy if most glucose values within a 1-week period are elevated (Landon 2009). The ACOG guidelines recommend initiating drug therapy if fasting glucose concentrations are routinely greater than 95 mg/dL, or 1- or 2-hour postprandial concentrations are routinely 140 mg/dL and 120 mg/dL or greater, respectively (ACOG 2013). Another method is to begin drug therapy if two or more values at the same meal (e.g., post-breakfast or post-lunch) in a 2-week period exceed desired glucose concentrations by more than 10 mg/dL (Moore 2010). A third approach involves initiating drug therapy if two or more fasting or postprandial blood glucose values exceed 100 mg/dL or 126 mg/dL, respectively, in a 2-week period (Crowther 2005). Overall, a defined threshold of initiation for drug therapy in GDM does not exist, and clinicians should consider the severity and frequency of hyperglycemia, fetal growth, and patient factors when deciding to initiate pharmacotherapy (Garrison 2015; ACOG 2013).

Insulin

Human insulin crosses the placenta in insignificant amounts and is considered safe for use in pregnancy. Both the ADA and ACOG guidelines recommend insulin as a first-line treatment for GDM uncontrolled by nutritional therapy. The National Institute for Health and Care Excellence (NICE) guideline advises initial treatment with insulin, either with or without metformin, for any patient with a fasting glucose of 7 mmol/L (126 mg/dL) or greater at diagnosis (NICE 2015). The NICE guideline also suggests consideration of insulin, either with or without metformin, for women with complications of GDM such as macrosomia and a fasting glucose of 6.0–6.9 mmol/L (108–125 mg/dL).

Options for basal insulin coverage in GDM treatment include intermediate-acting neutral protamine Hagedorn (NPH) insulin and the long-acting analogs insulin glargine and insulin detemir (Table 1-3). Insulin degludec has not been studied in pregnant women. Because NPH insulin was used in initial studies of GDM, it is the standard with which the long-acting insulin analogs have been compared, and several guidelines continue to recommend its use. Both ACOG and the Endocrine Society suggest the use of NPH insulin for the treatment of women with GDM (ACOG 2013; Blumer 2013), whereas the ADA does not specify a preferred basal insulin (ADA 2016b). In the general nonpregnant population, long-acting insulin analogs are associated with a lower risk of hypoglycemia than NPH insulin, making them an option for GDM management. However, as with any agent for use in pregnant women, the longer-acting insulin analogs needed to overcome safety concerns before use could be endorsed in this specialty population.

Table 1-3. Insulin Preparations Used in the Management of Gestational Diabetes

Type of Insulin Preparation	Onset of Action (hr)	Peak of Action (hr)	Duration (hr)
Mealtime insulin			
Insulin aspart	0.25	1–3	3–5
Insulin lispro	0.25–0.5	1–3	3–5
Regular insulin	0.5–1	2–3	5–7
Basal insulin			
Insulin detemir	1–2	No pronounced peak	8 to ≥ 24
Insulin glargine	1–2	No pronounced peak	11 to ≥ 24
NPH insulin	1–2	4–12	10–19 (up to 24)

Use of insulin detemir in pregnancy was first investigated in women with type 1 diabetes. In a randomized open-label trial of 310 pregnant patients with type 1 diabetes, insulin detemir was compared with NPH insulin, both used in combination with mealtime insulin in a basal-bolus regimen (Hod 2014). Overall, maternal and perinatal outcomes were similar in both groups. No significant safety concerns were identified in the insulin detemir group. In addition, a meta-analysis examining the safety of insulin analogs in pregnancy concluded that the risks of neonatal hypoglycemia or LGA neonates with insulin detemir compared with NPH insulin were not increased in the treatment of type 1 diabetes in pregnancy (Lv 2015). A recent randomized trial of 85 women with GDM found insulin detemir noninferior to NPH insulin for glucose control (Herrera 2015). The trial was not powered sufficiently to detect differences in perinatal outcomes or maternal weight gain.

The Endocrine Society suggests use of insulin detemir in women with known or potential problematic hypoglycemia with NPH insulin (Blumer 2013). In the United States, insulin detemir is rated FDA pregnancy risk category B, and the European Medicines Agency permits its use during pregnancy. The FDA has instituted a change in the pregnancy information required within prescription drug labeling (Pregnancy and Lactation Labeling Rule – PLLR); the current pregnancy risk categories are gradually being phased out in favor of more comprehensive information. Currently, however, the pregnancy risk categories are still in the labeling of many prescription drug products.

A concern with the use of insulin glargine in pregnancy is its increased affinity for the insulin-like growth factor (IGF-1) receptor (Pollex 2011). The IGF-1 receptor is structurally similar to the insulin receptor, and insulin analogs have modifications in amino acid sequence or structure that may increase or diminish the binding affinity for IGF-1 receptors (Jovanovic 2007). Insulin glargine has a 6-fold affinity for the IGF-1 receptor compared with human insulin, and insulin detemir has about one-sixth the affinity. During pregnancy, IGF-1 plays a role in implantation and mediates the effects of human placental growth hormone on the fetus. Thus, disruption of the normal function of IGF-1 raises concerns of potential enhanced mitogenic activity. However, in therapeutic doses, insulin glargine is unlikely to cross the placenta, and studies to date have not shown an increased fetal risk with the use of this agent during pregnancy.

A systematic review and meta-analysis of eight studies involving 702 women with pregestational diabetes (existing type 1 or type 2 diabetes before pregnancy) or GDM who received insulin glargine in pregnancy concluded that fetal outcomes did not differ significantly from those of women treated with NPH insulin (Pollex 2011). A second meta-analysis examining the use of insulin glargine in eight observational studies of pregestational diabetes or GDM showed no significant difference in birth weight, neonatal outcomes, or severe maternal hypoglycemia compared with NPH insulin (Lv 2015). In summary, randomized controlled trials using insulin glargine in GDM are lacking, and insulin glargine should only be used if the benefits outweigh the risk of adverse effects to the mother and fetus.

The rapid-acting analogs insulin aspart and insulin lispro are preferred to regular insulin for mealtime coverage (ACOG 2013). Both analogs improve postprandial glucose control compared with regular insulin and may have a reduced risk of delayed postprandial hypoglycemia (Metzger 2007). The analogs are also more convenient to administer preprandially, as opposed to regular insulin, which should be administered 30 minutes before meals for optimal postprandial coverage (Cheng 2008a). Like the long-acting analogs, the rapid-acting analogs were first studied in pregnancy in type 1 diabetes.

A randomized, open-label trial of 322 patients with type 1 diabetes showed that perinatal outcomes and maternal glucose control with insulin aspart were comparable with regular insulin when used in a basal-bolus regimen (Hod 2008). Similarly, in a meta-analysis of six randomized controlled trials of women with pregestational diabetes or GDM (n=1143), insulin aspart appeared to be as safe as regular insulin, with no significant differences in the rate of fetal macrosomia or cesarean delivery (Lv 2015). The same meta-analysis included a review of nine observational studies of women with pregestational diabetes or GDM (n=1561) treated with insulin lispro or regular insulin and concluded that insulin lispro was associated with a higher rate of LGA infants but a lower risk of severe maternal hypoglycemia than regular insulin. Use of insulin lispro was not associated with an increased rate of fetal macrosomia or cesarean delivery (Lv 2015).

Glulisine is the only rapid-acting insulin without human data in pregnancy. As a result, glulisine is the only rapid-acting analog rated as FDA pregnancy risk category C; aspart and lispro are category B. The Endocrine Society states that insulin glulisine should not be used in pregnancy because it offers no added benefit over other rapid-acting analogs (Blumer 2013). According to the available evidence, the rapid-acting insulin analogs, aspart and lispro, have efficacy and safety comparable with regular insulin. They are preferred in GDM management because of the convenience of mealtime administration and potentially lower risk of delayed hypoglycemia.

Insulin requirements can vary widely during pregnancy, particularly during the second trimester when insulin resistance may rise rapidly (ADA 2016b). Insulin resistance continues to increase into the third trimester and may plateau or diminish slightly near the end of pregnancy. Because most women receive a diagnosis of GDM late in the second trimester or early in the third trimester, variability in insulin requirements should be considered. For women who have mild fasting hyperglycemia, an injection of intermediate- or long-acting insulin (0.15–0.2 unit/kg) at bedtime can be used to control elevated fasting glucose. Mild postprandial elevations in glucose can typically be managed with administration of 2–4 units of rapid-acting insulin before meals. Alternatively, elevated

glucose after lunch may be treated with an intermediate-acting insulin before breakfast (Cheng 2008a).

For women with marked hyperglycemia, several daily injections provide optimal glucose control. A typical starting dose of insulin is 0.7–1 unit/kg/day (Table 1-4), administered in divided doses (ACOG 2013; Hone 2010). Higher insulin doses may be required in women with obesity or multiple gestation pregnancies. Once the total daily insulin dose is calculated, 50% is administered as basal insulin using NPH or long-acting insulin analogs, and the remaining 50% is administered in three preprandial injections of rapid-acting insulin (Hone 2010). According to initial studies with NPH in pregnancy, some sources recommend that if NPH is selected as the basal insulin, it should be divided into three equal doses given before breakfast, before dinner, and at bedtime (Hone 2010). However, a twice-daily regimen of NPH is commonly used for basal control. For women with limited financial resources, a regimen of NPH and regular insulin may be more affordable. Regardless of the initial regimen, the dose should be titrated often, using data from self-monitoring of blood glucose.

Metformin

Because many women with GDM have mild hyperglycemia, treatment with oral medications such as metformin is also an acceptable option when medical nutrition therapy and exercise fail to control glucose adequately. Metformin improves peripheral insulin sensitivity and is not known to cause weight gain or hypoglycemia when used alone (Rowan 2008). In addition, metformin has been used in patients with polycystic ovary syndrome to increase ovulation and enhance fertility, and it may be continued until the end of the first trimester in an attempt to reduce the rate of spontaneous abortion (ACOG 2013; Metzger 2007). Metformin crosses the placenta, and initially, there was concern about using metformin in pregnancy when a small retrospective cohort study of 118 patients found an increased incidence of preeclampsia and perinatal loss with metformin compared with treatment with sulfonylureas or insulin (Hellmuth 2000). These findings were based on patients with GDM or type 2 diabetes who were treated with oral hypoglycemic agents or insulin during pregnancy at a single site in Denmark between 1966 and 1991. However, more recent studies have not noted similar safety concerns with metformin use in pregnancy, and the drug is currently rated as FDA pregnancy risk category B. Management of GDM is an off-label indication of metformin.

Table 1-4. Suggested Starting Dose of Insulin in Gestational Diabetes

Weeks' Gestation	Insulin Dose[a] (unit/kg/day)
0–12	0.7
13–28	0.8
29–34	0.9
35–40	1.0

[a]Present pregnancy weight.

Information from: Hone J, Jovanovic L. Approach to the patient with diabetes during pregnancy. J Clin Endocrinol Metab 2010;95:3578-85.

In 2008, the Metformin in Gestational Diabetes (MiG) trial investigators published the first large randomized controlled trial (n=751) examining metformin use as compared to insulin in GDM treatment (Rowan 2008). The metformin dose was initiated at 500 mg once or twice daily with food and titrated over 1–2 weeks, depending on glycemic goals, to a maximum daily dosage of 2500 mg. No significant differences occurred between the metformin- and insulin-treated groups in the composite outcome of neonatal complications, which included a composite measure of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score less than 7, and prematurity. The incidence of preterm delivery (less than 37 weeks' gestation) was significantly higher with metformin (12.1% vs. 7.6%). As might be expected, the risk of severe neonatal hypoglycemia was significantly lower in the metformin group (3.3% vs. 8.1%). About 45% of the women in the metformin group needed supplemental insulin therapy to achieve glycemic targets (Rowan 2008).

A second randomized controlled trial compared metformin with glyburide for GDM treatment (Moore 2010). Seventy-four women were randomized to glyburide and 75 to metformin, and the primary outcome was glucose control. For patients who were able to maintain glucose control with either drug alone, the mean fasting or 2-hour postprandial glucose concentrations were similar. However, about twice as many women in the metformin group (34.7%) required supplemental insulin to achieve glucose control compared with the glyburide group (16.2%). Mean birth weights were lower in the metformin group, but the study was underpowered to explore other secondary outcomes.

A systematic review and meta-analysis examined maternal and fetal outcomes with metformin compared with insulin in six randomized controlled trials, which included 1362 patients with GDM (Balsells 2015). Maternal outcomes were improved with metformin compared with insulin, with less maternal weight gain and a lower risk of pregnancy-induced hypertension. Fetal outcomes, however, included a lower gestational age at delivery (−0.16 weeks) and an increased risk of preterm delivery with metformin (risk ratio 1.50). Although it did not reach statistical significance, there was a trend toward less neonatal hypoglycemia with metformin. On average, 33.8% of women in the metformin group required supplemental insulin. These findings were supported by an earlier meta-analysis that evaluated a similar set of trials (Gui 2013).

In the earlier meta-analysis, the effects of metformin compared with glyburide in women with GDM were also evaluated

(Balsells 2015). Only two randomized controlled trials (n=349) were available that had studied the two drugs head-to-head for GDM management. Compared with glyburide, metformin was associated with less maternal weight gain (–2.06 kg). In addition, fetal outcomes included lower birth weight, less macrosomia (risk ratio 0.33), and a lower incidence of LGA infants in the metformin group. The treatment failure rates were 26.8% and 23.5% with metformin and glyburide, respectively. Given this analysis, the investigators concluded that glyburide was inferior to metformin in GDM management.

Recommendations for the role of metformin in GDM treatment differ, according to the various guidelines. The ACOG guidelines recommend metformin as an appropriate first-line therapy for GDM management, and the NICE guideline also supports metformin as initial therapy in women with GDM and a fasting glucose below 7 mmol/L (126 mg/dL) at diagnosis (NICE 2015; ACOG 2013). In contrast, the Endocrine Society suggests metformin as an alternative in women who refuse or have contraindications to insulin or glyburide (Blumer 2013). The rationale for this recommendation includes the higher failure rate of metformin and the unknown long-term safety profile in offspring of women treated with metformin. The ADA recommends insulin as a first-line agent and proposes metformin as an acceptable alternative if glucose control is sufficient (ADA 2016b). The ADA cites the slightly higher risk of prematurity and unknown long-term effects on offspring as concerns with metformin use in GDM.

Although metformin has an acceptable safety profile with short-term use in GDM management, it crosses the placenta readily, and the long-term effects of fetal exposure to an insulin-sensitizing agent are unknown. To address these concerns, the MiG trial investigators assessed the potential effects on growth of children exposed to metformin in utero (Rowan 2011). Offspring of women who participated in the MiG trial had body composition measurements at 2 years of age. Overall, the children born to mothers treated with metformin did not differ in height, weight, total fat, or percent body fat compared with children whose mothers were treated with insulin. However, offspring exposed to metformin had a higher amount of subcutaneous fat, as noted in the upper arm circumference and biceps and subscapular skinfolds. The implications of this change in fat distribution are unclear. For instance, it is unknown whether an increase in subcutaneous fat deposition translates to less visceral fat. The intent of the MiG investigators is to reassess these children at later points in life. Thus, additional data are needed to fully assess the long-term safety and outcomes in offspring exposed to metformin in utero. Women who are prescribed metformin for GDM management should be counseled that metformin crosses the placenta and that the long-term effects of fetal exposure to this agent are unknown.

Glyburide

Glyburide has been extensively studied for GDM management. Glyburide is the only sulfonylurea that crosses the placenta to a minimal extent, likely because of high protein binding (Metzger 2007). Depending on the manufacturer, glyburide is rated as FDA pregnancy risk category B or C. Management of GDM is an off-label use of glyburide. When used in GDM treatment, the initial glyburide dose is typically 2.5–5 mg once daily in the morning. The dose is titrated according to glucose readings to a maximum of 20 mg daily, usually given in two divided doses (ACOG 2013). For best efficacy, glyburide should be administered 30–60 minutes before meals, and the drug's activity should be carefully balanced with meals and snacks to minimize the risk of hypoglycemia (Caritis 2013). Supplemental insulin therapy may be required in 5%–20% of patients with GDM managed with glyburide. When selecting therapy, practitioners should consider that glyburide may be less effective in women with higher fasting glucose concentrations at diagnosis and those with a history of GDM or GDM diagnosed before 26 weeks' gestation (Harper 2016a). Although clinical studies show that adequate glucose control can be attained in most patients with GDM treated with glyburide, recent safety analyses have raised concerns about glyburide as a first-line therapy for GDM.

An initial randomized controlled trial that investigated glyburide use in 404 women with GDM found no significant differences in glycemic control or perinatal outcomes in the glyburide-treated group compared with the insulin-treated group, although the study was underpowered to detect differences in less common neonatal complications (Langer 2000). A large retrospective cohort study of women with GDM enrolled in the Sweet Success California Diabetes and Pregnancy Program (n=10,682) examined perinatal outcomes in women who were treated with glyburide compared with insulin therapy (Cheng 2012). In the Sweet Success program, 19.4% of women received glyburide and 80% received insulin therapy. Treatment with glyburide was associated with an increased risk of birth weight greater than 4000 g and admission to the neonatal ICU. A second retrospective cohort study, which investigated perinatal outcomes in GDM through review of a large insurance claims database, had similar findings (Camelo Castillo 2015). Neonates of mothers treated with glyburide (n=4982) had a higher risk of neonatal ICU admission, respiratory distress, and LGA. Although noted study limitations included lack of information on the level of glycemic control and maternal obesity as possible confounding factors, the data suggested the need for additional study regarding the safety of glyburide in GDM. Of interest, the authors noted that the frequency of glyburide use for GDM in the claims database had increased from 7.4% in 2000 to 64.5% in 2011 (Camelo Castillo 2014). A recent systematic review and meta-analysis of seven randomized controlled trials that compared glyburide with insulin in GDM management showed that glyburide was associated with a higher mean birth weight (mean difference 109 g) and an increased risk of macrosomia and neonatal hypoglycemia (Balsells 2015). Given these results and supportive data from

prior analyses, glyburide should not be used not be used as a first-line agent in GDM management if insulin or metformin is available.

The ADA continues to endorse insulin as a first-line agent for GDM management, stating that glyburide may be inferior to insulin and metformin because of the increased risk of macrosomia and neonatal hypoglycemia (ADA 2016b). The NICE guideline recommends consideration of glibenclamide (glyburide) in women intolerant of metformin therapy or those with poor glycemic control on metformin alone who refuse insulin therapy (NICE 2015). In contrast, ACOG supports glyburide as a suitable first-line treatment for GDM, and the Endocrine Society recommends glyburide as an acceptable alternative to insulin therapy, although these recommendations were made before the more recent glyburide safety data (ACOG 2013; Blumer 2013). Women with GDM who are initiated on glyburide should be counseled about the potential increased risk of macrosomia and neonatal hypoglycemia, as well as the risk of maternal hypoglycemia and strategies for managing hypoglycemia with this agent. In addition, they should be informed that glyburide crosses the placenta in trace amounts, and long-term safety data are lacking.

Other Agents

Data with other oral and injectable agents in GDM treatment are limited. The α-glucosidase inhibitor acarbose was studied in one small trial, which randomized women with GDM to receive acarbose (n=19), insulin (n=27), or glyburide (n=24) (Bertini 2005). Eight patients treated with acarbose (42.1%) did not achieve glycemic control, compared with five of the glyburide-treated patients (20.8%). The incidence of LGA infants was 10.5%, 25%, and 3.7% in the acarbose, glyburide, and insulin groups, respectively. In an observational cohort study of women exposed to medications in pregnancy, five women reported treatment with acarbose early in pregnancy, and two of the women had miscarriages (Wilton 1998). Given these data and the GI adverse effect profile of acarbose, it cannot be recommended for GDM treatment. Other agents such as the meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and

Patient Care Scenario

A 34-year-old Hispanic woman at 30 weeks' gestation in her first pregnancy presents for a follow-up visit. She was given a diagnosis of GDM at 28 weeks' gestation, and her fasting glucose at diagnosis was 107 mg/dL. At that time, she was counseled to begin nutritional therapy and a moderate exercise regimen. Given the following glucose values over the past week, what is the best option for GDM management in this patient?

Fasting glucose (mg/dL): 94, 102, 98, 97, 100, 93, 107
One hour after breakfast: 137, 140, 142, 135
One hour after lunch: 132, 141, 148
Two hours after dinner: 129, 120, 118, 124

ANSWER

Drug therapy for GDM is recommended if lifestyle modifications fail to achieve adequate glucose control within 1–2 weeks. The ACOG guidelines support initiating drug therapy for GDM if fasting glucose concentrations routinely exceed 95 mg/dL (five of seven during the past week), 1-hour glucose concentrations routinely exceed 140 mg/dL (three of seven), or 2-hour glucose concentrations routinely exceed 120 mg/dL (two of four). Therefore, the patient is a candidate for GDM drug therapy.

Insulin, glyburide, and metformin are alternatives for GDM management, and given the patient's mild hyperglycemia, an oral medication is a reasonable first choice. The ACOG guidelines recommend metformin as an appropriate first-line therapy for GDM management. The NICE guideline also supports metformin as initial therapy in women with GDM and a fasting glucose below 126 mg/dL at diagnosis, which is consistent with the data available for this patient. Although glyburide might be considered for GDM, recent data have generated concerns regarding its use as a preferred therapy for GDM. In addition to the potential for maternal hypoglycemia, glyburide has been associated with an increased risk of fetal macrosomia and neonatal hypoglycemia compared with insulin. The NICE guideline recommends consideration of glyburide in women intolerant of metformin therapy.

Metformin should be initiated at a dose of 500 mg once or twice daily and titrated over 1–2 weeks, depending on glucose concentrations and patient tolerance. If target glucose concentrations are not achieved with metformin, insulin should be added. The patient should be counseled that many women with GDM treated with metformin may require supplemental insulin to obtain adequate glucose control (20%–45%). In addition, metformin crosses the placenta, and the long-term effects of fetal exposure of metformin are unknown.

1. American College of Obstetricians and Gynecologists (ACOG) Committee on practice bulletins-obstetrics. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol 2013;122:406-16.
2. NICE Guideline: Diabetes and Pregnancy: Management from Preconception to the Postnatal Period. 2015. Available at https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021.
3. Balsells M, Garcia-Patterson A, Sola I, et al. Glibenclamide, metformin and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h102.

sodium glucose cotransporter-2 inhibitors have limited or no human data in pregnancy and should not be considered for GDM management.

OTHER MANAGEMENT STRATEGIES

Fetal Assessment

The need for other management strategies often depends on the severity of maternal hyperglycemia and the ease of glucose control. The ACOG guidelines recommend antenatal testing for poor glycemic control because these pregnancies have a higher likelihood of complications such as stillbirth (ACOG 2013). In general, antenatal testing is usually done in women who require oral drug therapy or insulin for GDM management (Garrison 2015). However, no consensus exists regarding the use of antenatal testing in women with GDM well controlled with nutritional therapy. Omission of antenatal testing in this population may be reasonable if there are no other pregnancy complications (e.g., preeclampsia) or other risk factors for poor pregnancy outcomes, such as advanced maternal age or previous stillbirth.

Specific guidelines detailing the type and timing of antenatal assessments in women with GDM are not available, and ACOG recommends that antenatal testing be conducted in accordance with local standards of practice (ACOG 2013). Many experts recommend that antenatal testing begin at 32 weeks' gestation. Typical testing might include once- or twice-weekly fetal non-stress tests (NSTs) or modified biophysical profiles (Garrison 2015). The NST poses no harm to the fetus and involves the mother wearing one belt to measure fetal heart rate and another to monitor contractions over 20–30 minutes. A normal NST is "reactive," showing that the fetal heart rate accelerates during times of movement. A modified biophysical profile includes the NST, together with an assessment of amniotic fluid volume by ultrasonography. The modified biophysical profile is considered normal if the NST is reactive and there is at least one adequate pocket of amniotic fluid more than 2 cm deep.

Ultrasonography is another fetal assessment that can be used to identify the risk of macrosomia. Many obstetricians use ultrasonography at 36–39 weeks' gestation to assess fetal growth. However, ultrasonography is not a highly sensitive or specific method for identifying LGA infants, and clinical examination may be comparable. The ACOG guidelines recommend that clinicians assess fetal size late in the third trimester using either ultrasonography or clinical examination. In the future, as ultrasound technology continues to advance, ultrasonography may have a more defined role in the fetal assessment of women with GDM.

Obstetric Considerations

Given the potential risks of pregnancies complicated by GDM, timing and route of delivery are important considerations. Unlike in preexisting diabetes, well-controlled trials that examine the optimal timing of delivery in GDM are not available, and evidence-based recommendations cannot therefore be made. The ACOG guidelines suggest that expectant management should be practiced in women with GDM controlled with diet or drug therapy and recommend against delivery before 39 weeks' gestation (ACOG 2013). If glycemic control is poor or other maternal or fetal complications are present, an earlier delivery can be considered. The NICE guideline offers a similar recommendation, suggesting that women with GDM should be advised to give birth before the end of the 40th week of gestation, and elective delivery before this time can be considered in the presence of maternal or fetal complications (NICE 2015). In clinical practice, many obstetricians offer induction of labor for women with GDM at 39–40 weeks' gestation, or at the estimated date of delivery (40 weeks). Because the risk of shoulder dystocia is higher in pregnancies complicated by diabetes, ACOG also suggests that women with GDM with a predicted fetal weight of 4500 g or more be counseled about cesarean delivery as an option to reduce the incidence of birth trauma (ACOG 2013).

Intrapartum Glucose Control

Maternal hyperglycemia during labor and delivery can contribute to the risk of neonatal hypoglycemia (Blumer 2013). Thus, prevention of neonatal hypoglycemia is a primary goal of intrapartum glucose management. Hypoglycemia in the mother should be avoided if a long-acting insulin is used during labor (Cheng 2008a).

Of note, insulin requirements are usually decreased during labor because the woman is typically fasting, and the work of labor requires energy expenditure. Therefore, for women with GDM managed with insulin, it may be reasonable to omit the dose of long-acting insulin or give only one-half of the usual dose on the day of delivery (Garrison 2015; Cheng 2008a).

Both the Endocrine Society and NICE guidelines recommend a target plasma glucose concentration of 72–126 mg/dL during labor and delivery, whereas ACOG recommends a target of 70–110 mg/dL (ACOG 2005). Plasma glucose values should be monitored every 1–2 hours, and intravenous dextrose or insulin infusion should be administered as needed to maintain intrapartum glucose concentrations in the desired range (Blumer 2013). Women with diet-controlled GDM are unlikely to require intrapartum administration of insulin. Glucose concentrations in most women with GDM return to near-normal concentrations shortly after delivery, and glucose-lowering therapies should be discontinued immediately after birth (NICE 2015).

POSTPARTUM MANAGEMENT

Postpartum Screening

Within 24–72 hours of delivery and before returning to community care, women should have a glucose assessment (fasting plasma glucose or self-monitored glucose) to

exclude ongoing hyperglycemia (NICE 2015; Blumer 2013). Because women with a history of GDM are at a greater risk of developing prediabetes or type 2 diabetes, most guidelines recommend screening at 6–12 weeks postpartum using the one-step approach (2-hour 75-g OGTT) previously described (ADA 2016b; ACOG 2013; Blumer 2013). The NICE guideline differs, advocating screening with fasting blood glucose rather than the 2-hour 75-g OGTT, and advises against the routine use of the OGTT (NICE 2015). Studies evaluating the use of A1C, with or without fasting glucose, to diagnose postpartum glucose intolerance have not had consistent results with respect to its sensitivity, and, at least initially, A1C may still be affected by the increased RBC turnover during pregnancy (ADA 2016b; Benhalima 2015).

After the initial postpartum screening, some sources recommend continued use of the 2-hour 75-g OGTT, whereas others, such as the ADA, indicate that A1C, fasting glucose, or the 2-hour 75-g OGTT may be used. Nonpregnant thresholds should be used when doing postpartum screening. Screening should be repeated every 1–3 years and continued lifelong. The frequency of screening may depend on other risk factors for GDM or plans for subsequent pregnancies (ADA 2016b). Patients with identified glucose intolerance should be referred for treatment.

Data from the Nurses' Health Study II showed that the risk of developing diabetes in women with a history of GDM was 40% lower in those who followed healthy eating patterns (ADA 2016b). Furthermore, both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with glucose intolerance and a history of GDM (ADA 2016b). Metformin reduced progression by 40%, whereas lifestyle intervention provided a 35% reduction (Aroda 2015). Thus, women with a history of GDM who are identified with glucose intolerance should be referred for preventive therapy.

Patient Counseling

As stated earlier, women with a history of GDM should be counseled on lifestyle modifications that support weight loss after delivery and reduce the future risk of metabolic syndrome and type 2 diabetes. These patients should also be informed of the importance of repeated screening for glucose intolerance, particularly before considering another pregnancy. The need for contraception should be emphasized to reduce the incidence of unplanned pregnancy. The choice of contraceptive should not be influenced by the history of GDM, but should be based on other medical conditions or contraindications present in the patient. Any contraceptive that is appropriate, given the concomitant medical conditions of the patient, can be considered. In addition, women with a history of GDM should be encouraged to breastfeed because this can assist with weight loss in the postpartum period and may reduce the risk of progression to type 2 diabetes later in life (Garrison 2015; Blumer 2013).

CONCLUSION

Optimal glucose control is key to reducing the risk of maternal and fetal complications in GDM. Most women with GDM can achieve adequate glucose control with nutritional therapy. For patients who do not achieve glycemic control with diet, drug therapy with insulin, metformin, or glyburide is

Practice Points

- **Glycemic targets for GDM are more stringent than for other types of diabetes mellitus and include fasting glucose of 95 mg/dL or less, 1-hour postprandial glucose of 140 mg/dL or less, and 2-hour postprandial glucose of 120 mg/dL or less.**
- **Most women with GDM can achieve glycemic targets with lifestyle modification.**
- **Nutritional therapy for women with GDM should emphasize distribution of calories (33%–40% carbohydrates, 20% protein, and 40% fat), with a focus on restriction of carbohydrates as needed to control glucose.**
- **Nutritional therapy for women with GDM should provide enough caloric intake to promote adequate weight gain. Suggested weight gain and caloric intake during pregnancy is based on pre-pregnancy BMI.**
- **Most women with GDM should engage in moderate exercise for 30 minutes most days of the week.**
- **There is no consensus on when to initiate drug therapy in GDM. In general, therapy should be considered when most glucose values in 1 week exceed glycemic targets. Clinicians should consider the severity and frequency of hyperglycemia, fetal growth, and patient factors when deciding to initiate pharmacotherapy.**
- **ACOG recommends metformin as an appropriate first-line therapy for GDM. NICE also recommends metformin as first-line therapy if the fasting glucose is less than 126 mg/dL at diagnosis.**
- **Women with GDM treated with metformin are more likely to require supplemental insulin than those treated with glyburide.**
- **Glyburide crosses the placenta to a minimal extent. Treatment of GDM with glyburide may be associated with a higher rate of fetal macrosomia and neonatal hypoglycemia.**
- **Glyburide is an appropriate therapy in GDM, especially if intolerance to metformin or refusal of insulin therapy is present.**
- **Insulin is listed as a preferred therapy in all the GDM-related guidelines and should be the agent of choice for women with marked hyperglycemia.**
- **Insulin aspart and insulin lispro are preferred insulins for the management of postprandial glucose. To date, insulin glulisine does not have human data in pregnancy.**
- **Both NPH insulin and insulin detemir are recommended as preferred basal insulins in GDM treatment. Randomized controlled trials with insulin glargine in GDM are lacking.**
- **Women with a history of GDM are at increased risk of type 2 diabetes later in life. They should be screened at 6–12 weeks postpartum and then every 1–3 years. Women who develop glucose intolerance should be referred for treatment.**

indicated. Although most women revert to nondiabetic status after delivery, a significant proportion of women with a history of GDM later develop prediabetes or type 2 diabetes. Pharmacists can play an integral role in GDM management by emphasizing the importance of prenatal care and screening for GDM, educating patients on the risks and benefits of various glucose-lowering agents for GDM, and providing evidence-based and patient-centered recommendations for lifestyle modifications and drug therapy in GDM management. In addition, pharmacists are in a key position to provide counseling on the importance of monitoring and techniques for monitoring the signs and symptoms of hypoglycemia, management of hypoglycemia, and methods to reduce the development of type 2 diabetes in the future.

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Self-Assessment Questions

1. A 39-year-old white woman (height 65 inches, weight 56 kg) has a medical history of asthma and seasonal allergies. Her family history is significant for hyperlipidemia and hypertension. Her current drug therapy includes budesonide MDI, albuterol MDI, and loratadine. Which one of the following best represents a risk factor for gestational diabetes mellitus (GDM) in this patient?

   A. Age
   B. Race
   C. Family history of hyperlipidemia
   D. BMI 20.5 kg/m^2

Questions 2 and 3 pertain to the following case.

The HAPO study was a landmark study to clarify the risks of gestational diabetes and maternal and fetal outcomes. Secondary outcomes included premature delivery, shoulder dystocia, intensive neonatal care, hyperbilirubinemia, and preeclampsia. The following data summarize the association between secondary outcomes and increasing maternal fasting glucose.

	Odds Ratio (95% CI)
Premature delivery	1.05 (0.99–1.11)
Shoulder dystocia	1.18 (1.04–1.33)
Intensive neonatal care	0.99 (0.94–1.05)
Hyperbilirubinemia	1.00 (0.95–1.05)
Preeclampsia	1.21 (1.13–1.29)

2. Which one of the following best summarizes the primary outcome of the HAPO study?

   A. Elevated maternal glucose was associated with higher rates of cesarean section delivery and infant birth weights greater than 90th percentile but unchanged rates of neonatal hypoglycemia and cord C-peptide greater than 90th percentile.
   B. Elevated maternal glucose was associated with higher infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile but unchanged rates of cesarean section delivery.
   C. Elevated maternal glucose was associated with higher rates of cesarean section delivery, infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile.
   D. Elevated maternal glucose was associated with lower rates of cesarean section delivery but higher rates of infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile.

3. Which one of the following best describes the association between increasing maternal fasting glucose and secondary outcomes in the HAPO study?

   A. Increasing fasting glucose was associated with a significant increase in all secondary outcomes, except with no significant effect on intensive neonatal care.
   B. Increasing fasting glucose was associated with a significant increase in shoulder dystocia and preeclampsia and no significant effect on the other secondary outcomes.
   C. Increasing fasting glucose was associated with a significant decrease in intensive neonatal care but a significant increase in all other secondary outcomes.
   D. Increasing fasting glucose was associated with a significant increase in shoulder dystocia, preeclampsia and premature delivery, and no significant effect on the other secondary outcomes.

4. For which one of the following patients (all with no history of GDM) would it be best to screen for diabetes at the first prenatal visit rather than waiting until 24–28 weeks' gestation?

   A. A 30-year-old African American woman with BMI 31 kg/m^2
   B. A 24-year-old Asian woman with BMI 20 kg/m^2
   C. A 34-year-old white woman with BMI 30 kg/m^2
   D. A 35-year-old Hispanic woman with BMI 23.5 kg/m^2

5. Which result will lead to diagnosis of GDM following the one-step approach with a 75-g oral glucose tolerance test (OGTT)?

   A. 1-hour glucose 160 mg/dL
   B. 1-hour glucose 175 mg/dL
   C. 2-hour glucose 150 mg/dL
   D. 2-hour glucose 160 mg/dL

6. A 30-year-old African American woman is at 24 weeks' gestation. Her physician is screening for GDM using the two-step approach, and her step 1 glucose was 160 mg/dL. She then continues to step 2 and has a 100-g OGTT. Using the NDDG criteria, which one of the following would most likely result in a GDM diagnosis?

   A. Fasting glucose 120 mg/dL, 1-hour glucose 180 mg/dL, 2-hour glucose 160 mg/dL, and 3-hour glucose 140 mg/dL

B. Fasting glucose 100 mg/dL, 1-hour glucose 180 mg/dL, 2-hour glucose 170 mg/dL, and 3-hour glucose 135 mg/dL
C. Fasting glucose 115 mg/dL, 1-hour glucose 185 mg/dL, 2-hour glucose 170 mg/dL, and 3-hour glucose 140 mg/dL
D. Fasting glucose 102 mg/dL, 1-hour glucose 178 mg/dL, 2-hour glucose 155 mg/dL, and 3-hour glucose 137 mg/dL

7. A 25-year-old pregnant woman at 28 weeks' gestation recently received a diagnosis of GDM. She has been monitoring her glucose, as instructed, and reports fasting glucose values of 82 and 86 mg/dL and postprandial values of 125 and 135 mg/dL. Which one of the following values best indicates suboptimal control of her glucose, according to the ACOG guidelines?

   A. Fasting glucose 82 mg/dL
   B. Fasting glucose 86 mg/dL
   C. 1-hour postprandial glucose 135 mg/dL
   D. 2-hour postprandial glucose 125 mg/dL

8. Which one of the following pairs of GDM complications is most likely to improve with treatment?

   A. Rate of infant macrosomia and maternal hypertensive disorders
   B. Rate of maternal hypertensive disorders and type 2 diabetes
   C. Rate of infant macrosomia and cesarean delivery
   D. Rate of infant shoulder dystocia and neonatal hypoglycemia

Questions 9–11 pertain to the following case.

H.B. is a 27-year-old woman (height 64 inches, current weight 70 kg [155 lb], pre-pregnancy weight 61 kg [135 lb]) at 28 weeks' gestation. She has just been given a diagnosis of GDM and is to begin lifestyle modification and glucose monitoring.

9. Which one of the following is best to recommend for lifestyle modification for H.B.?

   A. Consume a diet with no more than 20% of caloric intake from fat.
   B. Aim for a total caloric intake of 1600 mg per day.
   C. Eat three meals per day and avoid snacking in between.
   D. Engage in moderate exercise for about 30 minutes most days of the week.

10. Which one of the following is best to recommend for carbohydrate intake in H.B.?

   A. Choose carbohydrates with a low glycemic index, such as whole grains and fruits.
   B. Eat no more than 75 g of carbohydrates per day divided across meals and snacks.
   C. Consume most of the carbohydrate intake early in the day.
   D. Avoid evening snacks containing carbohydrates.

11. One week after starting nutritional therapy, H.B. returns to the clinic. She weighs 70 kg (155 lb), and her glucose values are as follows:

   Fasting: 95, 92, 89, 87, 94, 95
   One hour after breakfast: 150, 138, 154, 148
   One hour after lunch: 136, 126, 118
   Two hours after dinner: 112, 118, 108, 96

   H.B. reports that her typical meals include breakfast – two slices of white bread with peanut butter and apple, or cornflakes with milk and banana; lunch – salad with a glass of milk or iced tea; dinner – chicken or fish with vegetables and rice or couscous; and snacks – fruit, cheese, yogurt, pickles, and hummus and crackers. Which one of the following is best to recommend for H.B.?

   A. Reduce caloric intake to obtain better glycemic control.
   B. Reduce carbohydrate intake at breakfast.
   C. Increase carbohydrate intake with dinner.
   D. Increase carbohydrate intake to promote adequate weight gain.

12. If dietary modifications fail to provide adequate glucose control in GDM, which one of the following patients is the best candidate for metformin, according to the NICE guideline?

   A. 24-year-old with fasting glucose 120 mg/dL at diagnosis and history of GDM in a previous pregnancy
   B. 35-year-old with fasting glucose 137 mg/dL at diagnosis and history of polycystic ovary syndrome (PCOS)
   C. 26-year-old with fasting glucose 127 mg/dL at diagnosis and a multiple gestation pregnancy
   D. 38-year-old with fasting glucose 118 mg/dL at diagnosis and history of stage 3b chronic kidney disease

Questions 13 and 14 pertain to the following case.

F.F. is a 24-year-old woman at 28 weeks' gestation. She received a diagnosis of GDM 2 weeks ago (fasting glucose at diagnosis 110 mg/dL) and has begun nutritional therapy and moderate exercise. F.F.'s glucose values over the past week are as follows:

Fasting glucose (mg/dL): 96, 98, 101, 97, 106, 107, 92
One hour after breakfast: 147, 140, 135, 139
One hour after lunch: 142, 146, 138
Two hours after dinner: 120, 116, 136, 127

13. Which one of the following is best to recommend for GDM management in F.F.?

    A. Give acarbose.
    B. Give glyburide.
    C. Give metformin.
    D. Continue current lifestyle modification.

14. F.F. is concerned about taking drugs for GDM and wants more information on the risks of various medications to her unborn child. Which one of the following is the most important counseling point to provide to F.F.?

    A. Glyburide crosses the placenta to a greater extent than metformin.
    B. Metformin is associated with a greater risk of low blood glucose in the infant than glyburide.
    C. The long-term effects of fetal exposure to both metformin and glyburide are unknown.
    D. Women taking metformin are more likely to require the addition of insulin for GDM.

15. A 26-year-old woman at 30 weeks' gestation presents for a follow-up visit. Having received a diagnosis of GDM 2 weeks ago, she has implemented dietary modification. She has a medical history of PCOS. She reports GI intolerance to metformin, which was used to treat her PCOS, and states that she is afraid of injecting herself. Her glucose logs show an average fasting glucose of 99 mg/dL and averages of 128 mg/dL and 142 mg/dL 1 hour after breakfast and dinner, respectively. Which one of the following is best to recommend for GDM management in this patient?

    A. Give glyburide.
    B. Give metformin.
    C. Give insulin.
    D. Continue dietary modification and advise patient to avoid all carbohydrates.

16. A 33-year-old woman at 31 weeks' gestation (current pregnancy weight 86 kg [189 lb]) was given a diagnosis of GDM 3 weeks ago. Together with nutritional therapy, she has been taking metformin, and the dose has been titrated to 1000 mg twice daily. She is tolerating metformin well, but her glucose logs show moderate hyperglycemia after breakfast and dinner. Which one of the following is best to recommend adding to manage hyperglycemia in this patient?

    A. Glyburide 2.5 mg twice daily before breakfast and dinner
    B. 12 units of neutral protamine Hagedorn (NPH) insulin before breakfast
    C. 3 units of regular insulin before breakfast and dinner
    D. 4 units of insulin aspart before breakfast and dinner

17. A 32-year-old woman with GDM is at 30 weeks' gestation, and her current pregnancy weight is 80 kg (176 lb). She has marked hyperglycemia, and the physician would like to initiate intensive insulin therapy. Which one of the following is the best insulin regimen to recommend for this patient?

    A. 18 units of NPH insulin before breakfast and bedtime and 12 units of insulin aspart before breakfast, lunch, and dinner
    B. 20 units of NPH insulin before breakfast and dinner and 12 units of insulin lispro before breakfast, lunch, and dinner
    C. 36 units of insulin glargine at bedtime and 13 units of insulin glulisine before breakfast, lunch, and dinner
    D. 40 units of insulin detemir at bedtime and 13 units of insulin lispro before breakfast, lunch, and dinner

18. A 30-year-old woman delivered her first child 2 weeks ago. The patient was given a diagnosis of GDM during the pregnancy, and her glucose values returned to normal within 2 days of delivery. Which one of the following is best to recommend for her next diabetes screening, according to the ADA guidelines?

    A. Within the next week, she should have a 2-hour 75-g OGTT.
    B. In 4 weeks, she should have a 2-hour 75-g OGTT.
    C. In 8 weeks, she should have an A1C test.
    D. In 12 weeks, she should have a fasting glucose checked.

19. In a 10-year study, the Diabetes Prevention Program examined the effects of intensive lifestyle modification (ILS) and metformin on preventing diabetes in women with a history of gestational diabetes. Following are some results from the trial that highlight the effects of ILS or metformin on diabetes progression in women with prior GDM.

	Placebo	ILS	Metformin
Incidence of diabetes (cases per 100 person-years)	11.4	7.6	6.8
Reduction in incidence (compared with placebo)		35.2[a]	40.4[a]
Number needed to treat (to prevent one case in 10 years compared with placebo)		11.3	7.2

[a]p<0.05 compared with placebo.

Which one of the following best describes the results of the Diabetes Prevention Program?

A. Treatment with metformin was significantly more effective than ILS in reducing the progression to diabetes in women with a history of GDM.
B. Both metformin and ILS significantly reduced progression to diabetes compared with placebo in women with a history of GDM.
C. Metformin is associated with a 7.2% absolute risk reduction in progression to diabetes in women with a history of GDM.
D. Only one out of 11 women with a history of GDM will progress to diabetes if treated with ILS.

20. A 26-year-old woman had GDM during her recent pregnancy. At her 6-week postpartum visit, she has no signs of glucose intolerance. She would like to have another child in about 2 years but worries about the risk of GDM. Which one of the following is the most important counseling point to discuss with this patient?

A. Because your glucose is normal now, you have a very low risk of developing GDM with your next pregnancy.
B. ILS, together with breastfeeding, can help reduce your risk of developing type 2 diabetes later in life.
C. Taking metformin will reduce the risk of GDM with your next pregnancy by about 40%.
D. You should avoid using oral contraceptives to help reduce your risk of future GDM.