Diabetes & Pregnancy: Management Guide

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*Diabetes & Pregnancy: Management Guide* is supported by an educational grant from Novo Nordisk Inc. It has been approved by the American Association of Diabetes Educators (AADE) for pharmacists, nurses, and dietitians.
The following program is a recorded presentation by Carol Homko, RN, PhD, CDE.

Dr. Homko is a nurse and certified diabetes educator, with almost 35 years of experience in diabetes education and management. She established the Diabetes and Pregnancy Program at Temple University Hospital in 1991 and continues to maintain an active clinical practice there. At the present time, Dr. Homko is an Associate Research Professor in the Departments of Medicine, Division of Endocrinology/Metabolism/Diabetes and Obstetrics and Gynecology at the Temple University School of Medicine.

For the past twenty years, her primary research has focused on GDM and pregnancies complicated by pre-existing diabetes. She has published widely in peer-reviewed journals and has authored multiple chapters on the management of pregnancies complicated by diabetes including AADE’s Core Curriculum for Diabetes Education (4th edition) and a contributor to AADE’s Diabetes Education Review Guide. Dr. Homko lectures frequently to local, national, and international audiences of health professionals. She is actively involved with the American Diabetes Association and the American Association of Diabetes Educators at both the local and national levels. Dr. Homko is a past chair of the Pregnancy/Reproductive Health AADE Specialty Practice Group.
The goal of this knowledge-based program is to provide information and guidance on the management of diabetes (both preexisting and gestational) before, during, and after pregnancy.

The objectives are:

- Discuss the prevalence and impact of diabetes in pregnant women
- Describe new diagnostic criteria for gestational diabetes mellitus (GDM) and the implications of these criteria
- Describe preconception care in women with preexisting diabetes
- Describe the management of GDM and preexisting diabetes
DEFINITIONS AND EPIDEMIOLOGY
### Major Types of Diabetes

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Autoimmune destruction of pancreatic beta-cells, resulting in almost complete insulin deficiency</td>
</tr>
<tr>
<td>Type 2</td>
<td>Heterogeneous metabolic dysfunction involving insulin resistance and defects in insulin secretion</td>
</tr>
<tr>
<td>GDM</td>
<td>Carbohydrate intolerance of variable severity with onset during pregnancy</td>
</tr>
</tbody>
</table>

GDM = gestational diabetes mellitus.

The 3 major types of diabetes are preexisting type 1 diabetes, preexisting type 2 diabetes, and gestational diabetes mellitus (GDM).

Preexisting type 1 diabetes is characterized by autoimmune destruction of pancreatic beta-cells, resulting in almost complete insulin deficiency.

Preexisting type 2 diabetes is a heterogeneous metabolic dysfunction involving both insulin resistance and defects in insulin secretion.

GDM is currently defined as carbohydrate intolerance of variable severity with onset during pregnancy. GDM is the only type of diabetes that occurs only during pregnancy. When a woman with type 1 or type 2 diabetes becomes pregnant, the condition is described as “preexisting diabetes and pregnancy.”
An important shift in the epidemiology of diabetes is taking place in the US, and preexisting diabetes is complicating an increasing proportion of pregnancies.

The charts on this slide show the results of a retrospective study of more than 175,000 California women who had a singleton delivery of at least 20 weeks gestation between 1999 and 2005. During the study period, the prevalence of preexisting diabetes compared to GDM more than doubled, from 10% to 21%. In this cohort, preexisting diabetes complicated 1.3% of all pregnancies, while GDM complicated 7.5% of pregnancies.

The increasing proportion of pregnancies complicated by type 2 diabetes in the US is a cause for great concern. Although GDM is associated with negative consequences for fetal development, the risk to the fetus is considerably greater in a pregnancy marked by poorly controlled preexisting diabetes.
According to current data from the Centers for Disease Control and Prevention (CDC), type 2 diabetes accounts for about 90% to 95% and type 1 diabetes accounts for about 5% of all diagnosed cases of diabetes in the US.

As this graph shows, the ratio of cases of preexisting type 1 to preexisting type 2 diabetes in pregnancy differs from this overall ratio and has changed dramatically over the last 3 decades. For the entire US, the estimated ratio of type 1 to type 2 diabetes was 3:1 in 1980, 1:2 in 1988, and 1:8 in 2009.

Several factors explain these changes. First, an increasing number of asymptomatic but high-risk adolescents and young adults are being screened for type 2 diabetes. Therefore, many cases of early-onset type 2 diabetes that would once have been undetected are now being diagnosed. Furthermore, because of the ongoing obesity epidemic in the US, women are increasingly likely to develop diabetes during their childbearing years. Owing to changing immigration patterns, an increasing proportion of young women in the US belong to ethnic groups in which type 2 diabetes is particularly prevalent.
This slide shows screening guidelines for GDM that are recommended by the American College of Obstetricians and Gynecologists (ACOG) as of May 2012. According to these guidelines:

- Risk assessment should be conducted at the first prenatal visit to evaluate patients at high risk for developing GDM. Women at high risk should have their glucose level measured.
- Women at average risk for GDM and those who have not been identified as having an abnormal glucose tolerance before 24 weeks of gestation should have a screening test at week 24 to 28 of gestation.
- A random 50-gram 1-hour oral glucose challenge can be administered without regard for the time of day or the interval since the last meal.
- If the plasma glucose is less than 140 mg/dL, GDM is not present; however, high-risk individuals may be rechecked later in the pregnancy.
- If the plasma glucose is 140 mg/dL or greater, further testing is required.
- Although women at low risk for GDM are not routinely screened, they may be screened on the basis of clinician assessment.
- Low-risk women are those who meet all of the following criteria: less than 25 years of age; no history of poor obstetrical outcome; no first-degree family history of diabetes; normal weight or underweight prior to pregnancy; membership in a low-risk ethnic group.

As we will discuss, a different approach to GDM screening has been proposed in response to the findings of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study.
This slide shows guidelines for the diagnosis of GDM at weeks 24–28 that are still recommended by ACOG as of May 2012. According to these guidelines, there are 2 options for screening women for GDM at weeks 24 to 28 postconception.

The first option is a 2-step approach. Step 1 is to perform an initial screening by measuring plasma or serum glucose 1 hour after a 50-gram load. Using a threshold of 140 mg/dL or greater identifies approximately 80% of women with GDM, while using a threshold of 130 mg/dL or greater identifies approximately 90% of women. Step 2 is to perform a diagnostic 100-gram oral glucose tolerance test (OGTT) on a separate day in women who exceed the chosen threshold on the 50-gram screening.

The second option is to perform a diagnostic 100-gram OGTT in all women to be tested at weeks 24 to 28. This test should be performed in the morning, after an overnight fast of at least 8 hours. The one-step approach may be preferred in clinics with a high prevalence of GDM.

Whichever option is chosen, at least 2 of the following plasma glucose values must be found: fasting, ≥95 mg/dL; 1-hr, ≥180 mg/dL; 2-hr, ≥155 mg/dL; 3-hr ≥140 mg/dL.

As we will discuss, a different approach to the diagnosis of GDM has been proposed in response to the findings of the HAPO Study.
The HAPO Study is a landmark investigation of the association between maternal hyperglycemia and adverse pregnancy outcomes. It included more than 25,000 women at 15 centers in 9 countries and was conducted between 2000 and 2006. The objective of the study was to clarify the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that found in overt diabetes.

Primary outcomes were birth weight above the 90th percentile for gestational age, primary cesarean delivery, clinical neonatal hypoglycemia, and cord-blood C-peptide level above the 90th percentile. “Primary” cesarean delivery meant that the women had not had a prior cesarean section. The C-peptide level was evaluated because it indicates the presence of fetal hyperinsulinemia and is a reliable marker of fetal beta-cell dysfunction.

As shown on the slide, each measure of glycemia was divided into 7 glucose categories, so that the 1-h and 2-h plasma glucose (PG) measures reflected data for approximately the same number of women in each category as did the fasting plasma glucose (FPG) measure.
These graphs show 2 of the primary results of the HAPO study: the frequency of birth weight greater than the 90th percentile for gestational age and the frequency of primary cesarean delivery.

The study showed that with increasing maternal glucose levels, the frequency of each primary outcome increased.

For FPG level, for example, the frequency of birth weight greater than the 90th percentile was 5.3% in the lowest glucose category and 26.3% in the highest category. The frequency of primary cesarean delivery was 13.3% for the lowest glucose category and 27.9% for the highest category.

Compared to women in glucose category 1 for FPG, women in category 7 were 5 times more likely to have a child whose birth weight was above the 90th percentile and 1.6 times more likely to have a primary cesarean section.
These graphs show the other primary results of the HAPO Study: the frequency of clinical neonatal hypoglycemia and the frequency of cord-blood serum C-peptide greater than the 90th percentile.

Again, the study showed that with increasing maternal glucose levels, the frequency of each primary outcome increased.

For FPG, the frequency of clinical neonatal hypoglycemia was 2.1% in the lowest glucose category and 4.6% in the highest category. The frequency of cord C-peptide level greater than the 90th percentile was 3.7% in the lowest glucose category and 32.4% in the highest category.

Compared to women in category 1 for FPG, women in category 7 were twice as likely to have an infant with clinical neonatal hypoglycemia and 7.7 times more likely to have an infant whose cord-blood serum C-peptide was greater than the 90th percentile.
The International Association of Diabetes and Pregnancy Study Groups (IADPSG) was formed in 1998 to facilitate collaboration between regional and national groups with a major focus on diabetes and pregnancy, such as the American Diabetes Association (ADA) and ACOG. After reviewing the results of the HAPO study and other study data, an IADPSG consensus panel developed a paper entitled “Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy,” which was published in *Diabetes Care* in 2010.

The 2 major recommendations of the consensus panel are summarized on this slide. First, women at high risk for GDM should be screened in the first trimester; if found to have diabetes using standard criteria, they should be diagnosed with overt, not gestational, diabetes.

Second, all women not known to have prior diabetes will undergo a 75-g OGGT between 24 and 28 weeks. The diagnostic cut-points, based on the results of the HAPO Study, are ≥92 mg/dL for FPG, ≥180 mg/dL for 1-hour plasma glucose (PG), and ≥153 mg/dL for 2-hour PG. Only 1 abnormal value is needed for a diagnosis of GDM, and a 50-gram oral glucose tolerance (OGT) screening test is not needed.

The goal of the IADPSG is for every diabetes and obstetric association throughout the world to adopt their recommendations for screening and GDM diagnosis. As of May 2012, they have been adopted by the ADA but not by ACOG. In the fall of 2012, the National Institutes of Health plans to hold a consensus development conference to determine the optimal approach to GDM screening and diagnosis in the US.
As the ongoing epidemic of obesity and diabetes had led to more cases of type 2 diabetes in women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased. Therefore, the ADA has adopted the IADPSG recommendation that women with risk factors for type 2 diabetes be screened for diabetes using the standard diagnostic criteria shown on the slide. Screening should be performed at the first prenatal visit.

Risk factors for diabetes are a body mass index (BMI) ≥25 kg/m² and 1 or more of the following additional risk factors: physical inactivity; first-degree relative with diabetes; high-risk race/ethnicity (eg, African American, Latino, Native American, Asian American, or Pacific Islander); woman who previously delivered a baby weighing >9 lb or who was diagnosed with GDM; hypertension (blood pressure [BP] ≥140/90 mmHg or on therapy for hypertension); HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL; woman with polycystic ovarian syndrome (PCOS); A1C ≥5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing; other clinical conditions associated with insulin resistance, such as acanthosis nigricans; and history of cardiovascular disease (CVD).
This slide presents the screening and diagnostic criteria for GDM at 24 to 28 weeks’ gestation that have been adopted by the ADA in response to the recommendations of the IADPSG.

Using these new diagnostic criteria significantly increases the prevalence of GDM, primarily because only 1 abnormal PG value, not 2, is sufficient to make the diagnosis. Other changes are that the OGTT utilizes 75 grams of glucose, not 100 grams, and that results are recorded after 1 hour and 2 hours, not after 1 hour and 3 hours. The 50-gram screening test has also been discontinued.

Some experts have complained that the new criteria “medicalize” pregnancies previously categorized as normal. However, emerging evidence indicates that women diagnosed using the new criteria—even if they would not have been diagnosed by previous criteria—have increased rates of poor pregnancy outcomes that are similar to those of women diagnosed with GDM by earlier criteria.

The ADA also accepted the IADPSG recommendation to test women at high risk for diabetes in the first trimester to determine whether they have undiagnosed type 2 diabetes.
Wide variations in the frequency of GDM are reported in the medical literature. Until recently, it has been impossible to determine how much of this variation is attributable to differences in GDM diagnostic criteria or other methodological differences and how much is due to actual geographic variations in the frequency of GDM. An analysis of data from the HAPO study, in which GDM was defined by IADPSG criteria, found that the frequency of GDM does indeed vary by location. The analysis reported data for the overall HAPO population and for 15 study centers throughout the world. This graph shows GDM frequencies for the total population, the 4 US centers, and the center with the lowest frequency.

The overall frequency of GDM was 17.8%. The highest rate, 25.5%, was reported in Bellflower, California, and the lowest rate, 9.3%, was reported in Beersheba, Israel. In addition to the California site, frequencies were reported for the 3 other US sites: Cleveland, Ohio (25.0%), Chicago, Illinois (17.3%), and Providence, Rhode Island (15.5%). The reasons for these geographic variations are not currently known, although the investigators speculated that differing frequencies of obesity and degrees of abnormal glucose metabolism in the general populations of study sites may have played a role.
The correct statement is: __________.

a. the HAPO Study found a strong association between elevated maternal glucose levels and adverse pregnancy outcomes
b. using the IADPSG criteria, fewer women would be diagnosed with GDM
c. a study using the IADPSG criteria found that GDM currently affects almost 10% of US pregnancies
d. preexisting diabetes is complicating a decreasing proportion of US pregnancies
Answer to Checkpoint 1

The correct answer is a.

The HAPO Study found a strong association between elevated maternal glucose levels and adverse pregnancy outcomes.

The correct answer is a.

The HAPO Study found a strong association between elevated maternal glucose levels and adverse pregnancy outcomes.
GESTATIONAL DIABETES
The pathophysiology of GDM is complex and incompletely understood.

Overcoming the normal insulin resistance of pregnancy requires a compensatory increase in insulin secretion to maintain maternal glucose concentrations within the normal range. When pancreatic beta-cells are unable to compensate for this insulin resistance, GDM ensues.

Women with GDM have both increased insulin resistance and decreased insulin secretion. In GDM, the insulin response to a glycemic stimulus is about half that of normal pregnancy. GDM is increasingly regarded as a stage in the evolution of type 2 diabetes.
Risk Factors for GDM

✓ Family history of diabetes
✓ Obesity (BMI >30 kg/m²)
✓ Increased age (>35 y)
✓ History of abnormal glucose metabolism or PCOS
✓ Previous poor obstetric outcome or GDM
✓ Member of high-risk ethnic group
✓ Previous LGA or macrosomic infant
✓ Low birth weight

BMI = body mass index. LGA = large for gestational age; PCOS = polycystic ovarian syndrome. 

Risk factors for GDM include:

• A family history of diabetes
• Obesity, defined as a BMI greater than 30 kg/m²
• Age greater than 35 years
• History of abnormal glucose metabolism or polycystic ovarian syndrome (PCOS)
• Previous adverse obstetric outcome or GDM
• Membership in a high-risk ethnic group, including African American, Native American, Hispanic/Latino, Asian, or Pacific Islander populations
• Previous delivery of a large-for-gestational-age or macrosomic infant
• Low birth weight

Additional risk factors are lack of physical activity and high intake of saturated fats, red and processed meat, refined grain products, and sweets. Short stature and cigarette smoking have also been linked to the development of GDM in some, but not all, studies.
This slide shows current glycemic goals recommended by the ADA for women with GDM. The premeal goal is ≤95 mg/dL. The postmeal goal is either a 1-hour postmeal value of ≤140 mg/dL or a 2-hour postmeal value of ≤120 mg/dL.
Medical nutrition therapy (MNT) is the cornerstone of treatment for GDM. A woman with GDM should receive nutritional counseling by a registered dietitian (RD) whenever possible or by a qualified health care provider with experience in GDM management. A referral to a dietitian should be made within 48 hours of the GDM diagnosis, and the initial visit should take place within 1 week of the referral.

The meal plan should fulfill minimum nutrient requirements for pregnancy as set by the Institute of Medicine (IOM) and achieve glycemic goals without inducing weight loss or ketonemia. The plan should be culturally appropriate and individualized to take into account the patient’s weight gain, physical activity, and nutrition goals.

Nutrition interventions should emphasize overall healthy food choices, portion control, and cooking practices that can be continued postpartum and that may help to prevent later type 2 diabetes and obesity.

The basis of MNT for GDM involves a carbohydrate-controlled meal plan. Carbohydrate should generally be distributed into 3 small- to moderate-sized meals and 2 to 4 snacks. Consumption of foods high in total carbohydrate or sucrose, such as regular soft drinks, is not recommended.
Meal Planning

✓ Follow carbohydrate consumption guidelines
  • Breakfast: 15–45 g
  • Lunch and dinner: 45–75 g (each)
  • Snacks: 15–45 g

✓ Avoid highly processed carbohydrates
✓ Assess plan by testing BG after eating
✓ Incorporate nutrient-rich carbohydrates
✓ Shift milk and fruit to snacktime
✓ Consider adding 1–2 oz protein with breakfast or snacks to help maintain total calorie intake

Meal plans should be individualized for women with GDM, but some general practices are widely applicable. Plans often recommend the following carbohydrate ranges:

• Breakfast: 15 to 45 grams
• Lunch and dinner: 45 to 75 grams (each)
• Snacks: 15 to 45 grams

Most women find that the postbreakfast blood glucose (BG) goal is the most difficult value to achieve because of elevated hormone levels in the morning. Therefore, carbohydrate intake should be limited to 15 to 45 grams at breakfast. Breakfast cereals are often discouraged because most contain more than 45 grams of carbohydrate. Furthermore, breakfast cereals and other highly processed foods are more likely to raise postmeal glucose levels than less processed, high-fiber foods.

In their eagerness to control their carbohydrate consumption, women may cut back on nutrient-rich carbohydrates such as fruit, milk, and starches. Meal plans often shift milk and fruit from mealtime to snacktime so that the woman can eat a larger portion of starch during meals.

Eating 1 to 2 ounces of protein with breakfast or a snack is a good way to add calories without compromising glucose levels.
Both the ADA and ACOG support the use of self-monitoring of blood glucose (SMBG) in GDM. Women should monitor their BG at least 4 times daily: once in the morning (fasting) and 1 to 2 hours after each meal. An important role of SMBG in patients with GDM is determining whether glucose-lowering drug therapy is needed. It also guides the titration of glucose-lowering medication.

The benefit of A1C testing for women with GDM has not been established.

Women who have insufficient food intake or are losing weight should monitor their urine or blood ketones. Insufficient food intake may result from an inappropriate meal plan, not following the prescribed meal plan, nausea, vomiting, or intentionally undereating to control BG levels. Eating too little or at prolonged intervals may cause a shift from carbohydrate to fat metabolism, leading to rises in urine and blood ketones.
Physical Activity

- Engage in moderate-intensity physical activity for ≥30 min/day*
- Monitor intensity
- Avoid supine position
- Minimize risk of losing balance and fetal trauma
- Monitor BG closely and adjust insulin and carbohydrate intake
- Maintain hydration
- Be alert for warning signs

*In the absence of contraindications.

Regular physical activity is important because it improves BG control, reduces cardiovascular risk factors, and improves well being. In the absence of contraindications, pregnant women with diabetes should be encouraged to engage in moderate-intensity physical activity for at least 30 minutes per day. To avoid overexertion, women should monitor the intensity of their activity. In practical terms, a person engaging in moderate physical activity can talk, but not sing, during the activity.

All pregnant women should choose activities that avoid the supine position and minimize the risks of loss of balance and fetal trauma.

Women with diabetes need to monitor their BG levels before and after physical activity. They should also perform SMBG during the activity if they experience symptoms of hypoglycemia. It is important for them to understand how to adjust their carbohydrate intake and insulin dosing based on the results of SMBG. Maintaining adequate hydration before, during, and after physical activity is also essential.

Pregnant women need to be alert for warning signs that indicate they should immediately stop exercising and seek medical attention. These include excessive shortness of breath, chest pain, dizziness, headache, calf pain or swelling, vaginal bleeding, leakage of amniotic fluid, and painful uterine contractions.
Contraindications to Aerobic Exercise

✓ Hemodynamically significant heart disease or restrictive lung disease
✓ Incompetent cervix
✓ Multiple gestation
✓ Persistent 2nd/3rd trimester bleeding
✓ Placenta previa after 26 weeks
✓ Premature labor or ruptured membranes
✓ Preeclampsia or uncontrolled hypertension


Absolute contraindications to aerobic exercise during pregnancy include hemodynamically significant heart disease, restrictive lung disease, or having an incompetent cervix. Aerobic exercise is also contraindicated in women who are carrying twins and are at risk for preterm labor or for any woman carrying more than 2 fetuses. Additional contraindications are persistent second- or third-trimester bleeding, placenta previa after 26 weeks’ gestation, premature labor or ruptured membranes during the current pregnancy, and preeclampsia or uncontrolled hypertension.

In addition, there are several relative contraindications to aerobic exercise during pregnancy. These are poorly controlled seizure disorder, hyperthyroidism, hemoglobin <10 g/dL, extreme obesity (BMI ≥35 kg/m²), heavy smoking (>20 cigarettes per day), and a history of previous spontaneous abortions (SABs) or preterm births.
As part of its drug evaluation process, in 1975 the US Food and Drug Administration (FDA) began to assign systemically absorbed drugs to 1 of 5 Pregnancy Categories. As shown in the table, drug classifications are based on safety data from adequate, well-controlled human studies, human adverse reaction reports (ARRs) from investigational and/or marketing experience, data from animal reproduction studies, and a calculation of the drug’s risk/benefit ratio. Categories are A through D and X.

The most favorable Pregnancy Category is A, indicating that adequate, well-controlled human studies have failed to demonstrate fetal risk. The least favorable category is X, indicating that the drug causes fetal abnormalities in animals and/or humans and that its risks outweigh its benefits in pregnant women. Drugs in category X are contraindicated during pregnancy, while drugs in categories C and D should be avoided unless no alternative treatment is available and the therapeutic benefit clearly outweighs the risk.

Pregnancy Categories have not been assigned to many drugs introduced in the 1970s and 1980s, such as some of the human insulin products used today.

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**US FDA Pregnancy Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate, well-controlled human studies have failed to demonstrate fetal risk</td>
</tr>
<tr>
<td>B</td>
<td>No fetal risk in animal studies and no adequate, well-controlled human studies, <strong>OR</strong> adverse fetal effects in animal studies, but adequate, well-controlled human studies have failed to demonstrate fetal risk</td>
</tr>
<tr>
<td>C</td>
<td>Adverse fetal effects in animals, no adequate, well-controlled studies in humans, but benefits may outweigh risks <strong>OR</strong> no animal studies or adequate, well-controlled human studies, but benefits may outweigh risks</td>
</tr>
<tr>
<td>D</td>
<td>Evidence of fetal risk based on human studies or ARRs, but benefits may outweigh risks</td>
</tr>
<tr>
<td>X</td>
<td>Fetal abnormalities in animal or human studies, and/or ARRs document fetal risk, and risks outweigh benefits</td>
</tr>
</tbody>
</table>

### Insulins Used in Pregnancy

<table>
<thead>
<tr>
<th>Product</th>
<th>PC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermediate- and Long-Acting (Basal)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>NA</td>
<td>Traditionally the basal insulin of choice</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>B</td>
<td>New category based on favorable data in open-label study vs NPH insulin (N = 310)</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>C</td>
<td>Not currently recommended during pregnancy</td>
</tr>
<tr>
<td><strong>Rapid- and Short-Acting (Bolus, Prandial)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>B</td>
<td>A bolus insulin of choice</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>C</td>
<td>Not currently recommended during pregnancy</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>B</td>
<td>A bolus insulin of choice</td>
</tr>
<tr>
<td>Regular human</td>
<td>NA</td>
<td>Use of rapid-acting insulin analog preferred</td>
</tr>
</tbody>
</table>

*NA = not applicable; PC = Pregnancy Category.*


Considerations in selecting an insulin for use during pregnancy are the type of coverage needed, the insulin delivery system to be used, extensive experience with older human insulins, and the Pregnancy Categories of the insulin analogs.

Although, as an older product, it does not have a Pregnancy Category, NPH insulin has been safely used for many years in pregnant women who need basal insulin. However, the role of NPH insulin as the basal insulin of choice during pregnancy may change in view of a recent FDA decision. In March 2012, the FDA changed the Pregnancy Category of insulin detemir from C to B following review of positive data from an open-label study in which 310 women received insulin detemir or NPH insulin. As of May 2012, insulin glargine remains in Pregnancy Category C, and therefore should not normally be used during pregnancy.

As with NPH insulin, short-acting regular human insulins have not been assigned to a Pregnancy Category, but have been safely used in pregnant women for many years. However, the rapid-acting insulin analogs are generally preferred over human insulins because of their more desirable pharmacokinetic profiles. Among the rapid-acting insulin analogs, the 2 products in Pregnancy Category B—insulin aspart and insulin lispro—are preferred over insulin glulisine, which is currently in category C.
Insulin Therapy in GDM

✓ Initiated when FPG >105 mg/dL or PPG is elevated and food/carbohydrate intake cannot be reduced
✓ Regimen determined by SMBG
  • If only PPG levels are elevated, prandial insulin may suffice
  • If FPG is also elevated, intermediate- or long-acting insulin may be required
✓ Insulin types
  • Human insulin (regular, NPH) widely used
  • Clinical trials support safety and efficacy of insulin aspart and insulin lispro
  • Insulin detemir now Pregnancy Category B

PPG = postprandial glucose.  

The ADA recommends that insulin therapy be initiated when FPG exceeds 105 mg/dL or postprandial plasma glucose (PPG) is elevated and the patient’s food or carbohydrate intake cannot be reduced without weight loss or excessive caloric restriction.

There is no generally accepted protocol for starting insulin therapy in GDM, and SMBG should guide the doses and timing of the insulin regimen. Prandial insulin may suffice if only PPG levels are elevated, but an intermediate or long-acting insulin may be required if FPG values are also above goal.

The type(s) of insulin used are determined by the health care provider based on individual patient characteristics. Regular human insulin and NPH insulin have traditionally been used in GDM, but clinical trials have shown that insulin aspart and insulin lispro are also safe and effective in this population. As previously noted, both of these rapid-acting insulin analogs are in Pregnancy Category B. The Pregnancy Category of the long-acting insulin analog insulin detemir has recently been changed to B, providing another potential option for basal coverage in addition to NPH insulin.
**Glucose-Lowering Agents Other Than Insulin**

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Minimal amounts cross placenta</td>
</tr>
<tr>
<td></td>
<td>In RCTs, similar outcomes to those reported with insulin or metformin</td>
</tr>
<tr>
<td>Metformin</td>
<td>Crosses placenta, but metformin (± supplemental insulin) not associated</td>
</tr>
<tr>
<td></td>
<td>with more perinatal complications than insulin alone in MiG Study.</td>
</tr>
<tr>
<td></td>
<td>Maternal BG values similar in metformin and insulin groups in MiG Study</td>
</tr>
<tr>
<td>Other oral agents, injectables</td>
<td>Should not be used to treat GDM at present time due to lack of evidence.</td>
</tr>
<tr>
<td>other than insulin</td>
<td></td>
</tr>
</tbody>
</table>

MiG = Metformin in Gestational Diabetes; RCT = randomized controlled trial.

Data from randomized clinical trials support the use of glyburide, a second-generation sulfonylurea, and metformin, a biguanide, to treat GDM. Neither agent is specifically approved for use in GDM, but both are in Pregnancy Category B. Studies have shown that minimal amounts of glyburide cross the placenta. In randomized controlled trials, outcomes of women treated with glyburide were generally similar to those of women treated with insulin or metformin.

Although metformin crosses the placenta, the Metformin in Gestational Diabetes (MiG) Study showed that treatment with metformin (alone or with supplemental insulin) is not associated with a higher rate of perinatal complications than treatment with insulin alone. Maternal BG values were similar in the metformin and insulin groups, although some differences were statistically significant in favor of metformin.

Other oral glucose-lowering agents and injectable agents other than insulin should not be used to treat GDM at the present time due to lack of evidence.
Women’s Risks After GDM

✔ 30–84% will develop GDM in a future pregnancy
✔ Type 2 diabetes
  - 40–60% will develop within 5–15 y
  - 7-fold higher risk than for women without GDM
  - Among women with IGT, incidence was 17.1%/y with, 9.8%/y without GDM
  - Independent predictors: elevated FPG, high BMI, insulin use

Among women with a history of GDM, 30% to 84% will develop GDM in a future pregnancy. Non-Hispanic white women are less likely than members of minority populations to develop recurrent GDM.

During the 5 to 15 years after their first GDM episode, between 40% and 60% of women will develop type 2 diabetes. A meta-analysis found that women with a history of GDM were 7 times more likely to develop type 2 diabetes than women with no history of GDM. In the Diabetes Prevention Program trial, which enrolled patients with IGT, the rate of progression to type 2 diabetes was 17.1% per year in women with a history of GDM and 9.8% per year in women without a history of GDM. Independent predictors of developing type 2 diabetes after GDM are elevated FPG, high maternal BMI before or during pregnancy, and insulin use. Insulin use during GDM indicates that a severe metabolic derangement is present.
Postpartum Screening and Interventions

✔ Screen women for persistent diabetes at 6–12 weeks postpartum
  • Use nonpregnant OGTT diagnostic criterion (2-h PG ≥200 mg/dL)
  • Do not use A1C because of prepartum treatment

✔ Screen women for diabetes or prediabetes at least every 3 years

✔ Women with prediabetes should receive lifestyle interventions or metformin to prevent overt diabetes

Because some cases of GDM may represent preexisting undiagnosed type 2 diabetes, the ADA “Standards of Medical Care in Diabetes” recommend that women with a history of GDM should be screened for diabetes 6 to 12 weeks postpartum, using the nonpregnant OGTT criterion. By this criterion, diabetes is diagnosed when the 2-hour PG level is at least 200 mg/dL. (A FPG value of ≥126 mg/dL can also be used to diagnose diabetes.) Since most women with GDM receive prepartum treatment for hyperglycemia, the A1C is an unreliable screening tool at the postpartum visit.

Women with a history of GDM should be screened for the development of diabetes or prediabetes at least every 3 years for the rest of their lives. ADA criteria for prediabetes are IFG, defined as FPG from 100 mg/dL to 125 mg/dL, impaired glucose tolerance IGT, defined as a 2-hour PG value in the 75-g OGTT of 140 mg/dL to 199 mg/dL, or an A1C of 5.7% to 6.4%.

According to the ADA Standards, lifestyle interventions or metformin should be offered to women with a history of GDM who develop prediabetes.
Given their high risk for developing type 2 diabetes, women with a history of GDM require careful long-term management. They should be encouraged to:

- Begin and continue breastfeeding, because of its benefits for mother and child
- Use contraception that is appropriate during breastfeeding and does not increase diabetes risk
- Follow a MNT plan developed in consultation with a dietitian
- Reduce weight to prepregnancy or to goal weight
- Engage in regular physical activity, with a goal of at least 150 minutes of moderate-intensity exercise per week
- Consider initiating drug therapy to increase insulin sensitivity if IGT persists after a good-effort trial of lifestyle changes for 6 to 12 months
- Have regular monitoring for cardiovascular risk factors, following guidelines used for the general population

The most appropriate contraceptive choices for this population are intrauterine devices containing copper or levonorgestrel, or low-dose combination oral contraceptives. Long-term use of progesterone-only contraceptives should be avoided, because they are associated with a 3-fold increased incidence of progression to diabetes. Lifestyle modifications are usually sufficient to improve insulin sensitivity. In the infrequent cases when lifestyle changes do not have the desired effect, clinical trial data support the use of metformin, pioglitazone, or acarbose to improve insulin sensitivity and reduce the incidence of type 2 diabetes.
Follow-up for Children

Child is at long-term risk for:
- Obesity
- Insulin resistance
- Glucose intolerance
- Type 2 diabetes
- GDM (female)
- Dyslipidemia
- Hypertension
- Other CVD

To reduce risk for poor outcomes:
- Educate parents about long-term risks
- Encourage mother to breastfeed
- Advise family to consume healthy diet and remain active
- Monitor child’s growth and development

CVD = cardiovascular disease.


Children born to mothers who had GDM have an increased risk of becoming obese and of developing insulin resistance, IGT, and type 2 diabetes. Females are at increased risk for developing GDM during their own pregnancies. Dyslipidemia, hypertension, and other types of CVD may also develop.

To reduce the risk for poor outcomes, parents need to be educated about the long-term health risks to their child. As mentioned previously, the mother should be encouraged to breastfeed, since breastfeeding is negatively associated with overweight in early childhood.

It is important for health care providers to advise the entire family to eat a healthy diet and remain active.

Providers should also monitor the growth and development of children born to mothers with GDM, paying special attention to their weight, metabolic status, and the emergence of dyslipidemia and other cardiovascular risk factors.
Key Recommendations

- Screen for GDM at 24–28 weeks’ gestation
- Maintain glycemic control through MNT and physical activity
- Use SMBG to ascertain need for drug therapy and guide dose titration
- Treat with insulin, glyburide, or metformin if necessary
- Reevaluate maternal glucose tolerance at 6–12 weeks postpartum
- Provide ongoing monitoring and management for mother and child

Key recommendations for the diagnosis and management of GDM include the following.

Women should be screened for GDM at 24 to 28 weeks’ gestation, using new diagnostic criteria based on the findings of the HAPO Study.

It is important for women diagnosed with GDM to maintain glycemic control through MNT and physical activity. SMBG should be used to ascertain the need for drug therapy and to guide dose titration. Women can be treated with insulin, glyburide, or metformin if necessary.

Women should be reevaluated for glucose intolerance at 6 to 12 weeks postpartum. Because women with a history of GDM and their children are at increased risk for metabolic and other disorders, health care providers need to provide ongoing monitoring and management for both the mother and her child.
The correct statement is: __________.

a. most women with GDM have normal insulin secretion
b. the premeal BG target for women with GDM is ≤95 mg/dL
c. oral glucose-lowering agents should not be used to treat GDM
d. the A1C test should be used to assess glucose tolerance at 6–12 weeks postpartum
The correct statement is b.

The premeal BG target for women with GDM is ≤95 mg/dL.
PREEXISTING DIABETES AND PREGNANCY
Before the discovery of insulin, the rate of maternal mortality in pregnancies complicated by preexisting diabetes was as high as 44%, and perinatal mortality was approximately 60%. Since then, the outlook for pregnant women and their children has improved dramatically. The most dramatic progress occurred during the past 3 decades, because of an increasing emphasis on maternal glucose control and better fetal surveillance and neonatal care.

Despite these improvements, this graph shows that the odds for adverse maternal and neonatal outcomes remain substantially higher in pregnancies complicated by diabetes than in other pregnancies. For example, the odds of having a SAB during the first trimester are 2 times higher and the odds of delivering a child with a congenital anomaly are 3.3 times higher in a pregnancy complicated by preexisting diabetes than in pregnancies without diabetes. A major reason why the odds of adverse outcomes remain elevated is that, as in the general population, more than 50% of pregnancies in women with preexisting diabetes are unplanned. Therefore, glucose levels at conception and during the first weeks of pregnancy, when organogenesis is taking place, may be extremely high.
Pregnancy Complicates Diabetes Management

- Placental hormones, growth factors, and cytokines cause progressive insulin resistance
- Insulin resistance enhances DKA risk
- Insulin-induced hypoglycemia has more rapid onset during pregnancy
- Women with type 2 diabetes often start pregnancy with marked insulin resistance and obesity


Pregnancy profoundly affects the management of diabetes. Placental hormones, growth factors, and cytokines cause a progressive increase in insulin resistance during the second half of pregnancy, necessitating intensive MNT and frequently adjusted insulin administration to prevent hyperglycemia that would be dangerous to the fetus.

Insulin resistance enhances the risk of diabetic ketoacidosis (DKA) in response to the stress of concurrent illnesses or drugs used to manage obstetrical complications.

Insulin-induced hypoglycemia has a more rapid onset during pregnancy and occurs with increased frequency in pregnant women, especially those with type 1 diabetes. Furthermore, there is an increased risk of severe hypoglycemia during early pregnancy in women with type 1 diabetes.

Women with type 2 diabetes often start pregnancy with marked insulin resistance and obesity, adding to the difficulty of attaining optimal glycemic control.
Preconception counseling for the woman with preexisting diabetes should begin at the onset of puberty and continue until permanent sterilization or menopause. A planned pregnancy is a major objective of counseling, and the health care provider should review with the woman her options for contraception and help her choose the one most appropriate for her situation. The provider needs to explain to the woman the risks of pregnancy to herself and to her developing baby. It is essential for the woman to understand that normalizing BG levels before and during the early weeks of pregnancy significantly reduces the risks of SABs and congenital anomalies. She also needs to understand that with continued optimal glucose control throughout pregnancy, the risks of developing further complications are significantly decreased.

The provider must advise the woman of her own personal risks when undertaking pregnancy, emphasizing her need to be evaluated for the presence of diabetes complications and other general medical problems before conception. Genetics is another important aspect of preconception counseling, and it is important for the provider to explain that although the risk of developing type 1 or 2 diabetes is higher for the child of a mother with diabetes than for the general population, the risks are not high enough to advise a woman against pregnancy on genetic grounds. The provider must also convey the psychological and financial commitments that the woman and her family will be undertaking during the pregnancy.
Prepregnancy Assessment

- History and physical examination
- Gynecologic evaluation
- Special studies
  - EKG, treadmill
  - Neuropathy testing
- Laboratory evaluation
  - A1C
  - Urinalysis and culture
  - 24-h urine for CrCl, total protein, and microalbumin
  - Thyroid panel: free T4, TSH, anti-microsomal antibodies

CrCl = creatinine clearance; EKG = electrocardiogram; T4 = thyroxine; TSH = thyroid-stimulating hormone.


After taking a detailed history focusing on the woman's diabetes, the health care provider should perform a careful physical examination, paying special attention to diabetes-related complications and other organ-system abnormalities not directly related to diabetes, especially hypertension.

An eye examination must be performed through dilated pupils by an ophthalmologist. If this examination reveals preproliferative retinopathy or macular edema, laser photocoagulation and other appropriate treatments should be undertaken and the woman's retinal status stabilized before pregnancy. Similarly, evaluations to determine the patient's renal status and the presence of autonomic and peripheral neuropathies are important. If the woman has had diabetes for more than 10 years or diabetes in combination with hypertension for any period of time, the provider should consider ordering an electrocardiogram (EKG). More extensive cardiac testing may be indicated if the woman has a history of chest pain. The woman should also have a neurological assessment and lower-extremity examination for evidence of vascular disease, neuropathy, deformity, or infection.

The women should undergo a careful gynecologic examination to rule out infection, structural abnormalities, and infertility. In addition to lab tests related to the woman's general medical status, the provider should order the tests shown on the slide.
The discovery of certain diabetes-related complications may serve as absolute or relative contradictions to pregnancy. If the woman is found to have ischemic cardiac disease, the risks of maternal mortality are high and the woman should be counseled against undertaking pregnancy. She should also be asked to consider permanent sterilization.

As already mentioned, a woman with active proliferative retinopathy needs to delay the pregnancy until an ophthalmologist can treat her eye disease and confirm that the retinopathy has stabilized.

If the woman displays significant renal disease (serum creatinine >2 mg/dL and/or creatinine clearance <50 mL/min), she should be warned about the high risk of infant mortality and morbidity associated with this complication. Similarly, significant proteinuria (>300 mg/24 h), especially when accompanied by hypertension that does not respond adequately to treatment, is associated with poor pregnancy outcomes. Heavy proteinuria (>2 g/24 h) is a potential contraindication. A woman who has undergone renal transplantation may be able to undertake pregnancy successfully if her medical status is otherwise stable, although the risk remains significant.

Severe gastroenteropathy, characterized by persistent nausea, vomiting, and/or diarrhea, is a relative contraindication. In this situation, metabolic control and nutrition for both the woman and her developing baby are difficult to maintain.
Psychosocial Issues

- Screen women for depression and disordered eating
- Use structured psychotherapy for first-line treatment of mild depression
- Continue or initiate drug therapy for MDD
- Provide intensified interventions for women with anorexia nervosa
- Offer individualized CBT to women with bulimia or binge-eating disorder


Psychological disorders, which can affect glycemic control, are detectable in up to one third of patients with diabetes, including pregnant women. Psychological assessment and treatment should be incorporated into routine care rather than waiting for identification of a specific problem or deterioration in psychological status. It is especially important to screen pregnant women for depression and disordered eating, and to refer patients with these disorders to a mental health clinician.

Structured psychotherapy can be a useful first-line therapy for mild depression, but pharmacotherapy is needed for severe depression. The risk of fetal exposure to untreated major depressive disorder is considered a greater danger than fetal exposure to antidepressant drugs.

Many eating disorders are common in young women with type 1 or type 2 diabetes. Important management principles include addressing the factors that may have triggered the expression of disordered eating, involving the family in treatment, teaching the use of regular meal and snack times and responding to hunger and satiety cues, encouraging nondeprivational approaches to eating, providing intensified interventions for women with anorexia nervosa to ensure adequate prenatal nutrition and fetal development, and using specifically adapted cognitive behavior therapy for women with bulimia or binge-eating disorder.
Prepregnancy Management: Goals and Team

- Goal is to normalize BG levels before conception
- Diabetes care team
  - Primary care physician
  - Endocrinologist
  - High-risk obstetrician
  - Certified diabetes educator
  - Social worker
  - Registered dietitian
  - Pediatrician or neonatologist

Once a woman has undergone prepregnancy counseling and assessment and her fitness for safely undertaking a pregnancy has been established, her health care provider should outline a plan for prepregnancy management. The goal of prepregnancy management is to normalize BG levels before conception.

The woman can then be introduced to the team concept of patient management. Ideally, the diabetes team should include a primary care physician, an endocrinologist, an obstetrician skilled in high-risk obstetrics, a certified diabetes educator, a social worker, a registered dietitian, and a pediatrician or neonatologist.
In preparation for pregnancy, the woman should have an individual consultation with a registered dietitian, who will work with her to develop a meal plan with a calorie content that will help her attain or maintain glycemic control and manage her weight. To reduce the risk of neural tube defects, it is important for the provider to prescribe a prenatal vitamin containing at least 400 μg of folate. The provider should also encourage adequate intake of all vitamins and minerals through a well-balanced diet of fruits, vegetables, whole grains, low-fat dairy products, and lean protein.

The women should continue or begin an intensive insulin regimen, using either basal-bolus or insulin pump therapy. If the patient has been treated with oral hypoglycemic agents, these must be discontinued and insulin initiated.

Instruction in an appropriate exercise routine will enhance the woman’s physical fitness and help her to maintain optimal BG control.

If the woman is not familiar with SMBG techniques, these must be taught. The patient should test her BG levels frequently, before and 1 hour after meals, to assess the adequacy of her insulin regimen. Based on the woman’s BG log, the diabetes team can prescribe adjustments in diet, insulin, or exercise that will help her to achieve euglycemia. The patient and her partner must be reminded about the signs, symptoms, and management of hypoglycemia, and the partner should be instructed in the use of glucagon. If achieving glucose control or hypoglycemia is a frequent problem, the provider should consider using continuous glucose monitoring to obtain a 24-hour view of the woman’s glucose patterns.

The woman should put into practice general principles of good health. These may include cessation of smoking, alcohol intake, and unnecessary drugs.
This slide shows current glycemic goals recommended by the ADA for women with preexisting type 1 or type 2 diabetes who become pregnant.

Recommended ranges are 60 to 99 mg/dL for premeal, bedtime, and overnight BG and 100 to 129 mg/dL for peak postprandial glucose (PPG).

The A1C goal is less than 6.0%.

Note that these are optimal glycemic goals, to be pursued if they can be attained without excessive hypoglycemia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premeal, bedtime, and overnight BG</td>
<td>60–99 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial glucose</td>
<td>100–129 mg/dL</td>
</tr>
<tr>
<td>A1C</td>
<td>&lt;6.0%</td>
</tr>
</tbody>
</table>

*Optimal glycemic goals, to be pursued if they can be attained without excessive hypoglycemia.

ADA. *Diabetes Care*. 2012.
In a pregnant woman with diabetes, an adequate diet and appropriate weight gain are critical for maintaining maternal body tissues and for achieving optimal fetal growth and development. After smoking, inadequate gestational nutrition is the most important risk factor for intrauterine growth restriction (IUGR) and low birth weight.

To optimize the process of nutritional planning, a registered dietitian should help the patient to set up a system for recording food intake, BG levels, and insulin doses and timing. With this information in hand, the patient and dietitian can collaboratively develop a MNT plan that is consistent with IOM guidelines for nutrient intake, calorie consumption, and weight gain. The plan should also reflect the patient's dietary preferences and financial resources. Either the food exchange system or carbohydrate counting may be used.

As mentioned earlier, women capable of becoming pregnant should consume 400 μg/day of folate. During the periconception and prenatal periods, the dose should be increased to 600 μg/day. A prenatal supplement of vitamins and minerals should be considered for women with preexisting diabetes.

Food and/or insulin adjustments should be made in conjunction with the diabetes team, especially if problems such as hyperglycemia, hypoglycemia, urinary ketones, weight loss, or excessive weight gain are identified.
Increased insulin resistance and lipolysis raise the risk of DKA during pregnancy. Although DKA usually occurs in patients with type 1 diabetes, it can also arise in pregnant women with type 2 diabetes. Therefore, all women with preexisting diabetes who are planning pregnancy or are already pregnant should be educated about DKA prevention and symptoms.

Nausea, vomiting, abdominal pain, fever, and small oral intake are all suggestive of DKA. Pregnant women should perform urine ketone measurements when they are sick or when their BG levels remain above 200 mg/dL and promptly report positive values to their health care provider. Up to 30% of pregnant women with DKA have BG levels that are only moderately elevated (<250 mg/dL).

DKA is best managed in critical care units of hospitals with experience in monitoring high-risk pregnancies. Treatment protocols for DKA are based on correcting volume depletion, supplying insulin by infusion, carefully monitoring and correcting electrolyte imbalances, and identifying and treating precipitating factors. Continuous fetal heart rate monitoring and biophysical tests are used to assess fetal wellbeing when DKA occurs after 24 weeks’ gestation. Once DKA is corrected, fetal vital signs generally return to normal.
The risk of hypoglycemia increases during pregnancy, and women with a history of frequent hypoglycemia or hypoglycemia unawareness before pregnancy are at heightened risk. Some of the classic signs of hypoglycemia, including anxiety, nausea, palpitations, tremor, sweating, warmth, confusion, dizziness, headache, hunger, and weakness, may be difficult to distinguish from pregnancy symptoms. Hypoglycemia unawareness is prevalent, although it is at least partially reversible by several weeks of meticulous avoidance of iatrogenic hypoglycemia.

Protocols to minimize the occurrence of maternal hypoglycemia include intensive education of patients and significant others, frequent SMBG, proper timing of adequate meals and snacks, correct administration of insulin doses, and careful management of physical activity. There is some evidence that use of insulin analogs, especially with insulin pump therapy, reduces the frequency of maternal hypoglycemia.

Mild hypoglycemia should be treated with 15 grams of carbohydrate, such as 8 ounces of milk or 4 to 5 glucose tablets. Fifteen minutes after treatment, SMBG should be performed to ensure that the BG level has returned to normal. If not, another 15 grams of carbohydrate should be given.

When a woman experiences severe hypoglycemia and is unable to swallow, a family member or coworker should inject 1 mg glucagon subcutaneously and call an emergency service for help.
Hypertension, a major risk factor for CVD and microvascular complications, occurs frequently in women with diabetes. Hypertension often results from underlying nephropathy in people with type 1 diabetes, while it usually coexists with other cardiometabolic risk factors in individuals with type 2 diabetes. Blood pressure (BP) goals during pregnancy are 110 to 129 mmHg for systolic BP and 65 to 79 mmHg for diastolic BP. These goals are recommended because they strike an appropriate balance between contributing to long-term maternal health and promoting fetal growth. Lower BP levels may be associated with impaired fetal growth.

Prepregnancy management includes transitioning women treated with ACE inhibitors or angiotensin receptor blockers (ARBs) to other antihypertensive medications, since both ACE inhibitors and ARBs can cause fetal damage, especially when taken during the last 6 months of pregnancy. (Drugs in both of these classes are Pregnancy Category C during the first trimester and Category D during the second and third trimesters.) A woman who becomes pregnant while taking an ACE inhibitor or ARB should discontinue it immediately and contact her health care provider.

Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which might reduce uteroplacental perfusion. However, many experts believe that a woman who is taking a thiazide when she becomes pregnant can continue treatment, ideally at a reduced dose. When thiazide therapy is desirable, pregnant women should receive an agent from Pregnancy Category B, such as chlorthalidone or hydrochlorothiazide, instead of one from Category C, such as bendroflumethiazide or trichlormethiazide.
Hypertensive disorders affect more than 20% of pregnancies complicated by diabetes. This slide shows the system for classifying these disorders that was developed by the National High Blood Pressure Education Program Working Group and widely accepted by other medical organizations. The system differentiates hypertensive disorders based on when the symptoms manifest and the presence of proteinuria. The various disorders also vary in their severity. The symptoms of gestational hypertension are usually mild, while preeclampsia and chronic hypertension are often life-threatening conditions.

Preeclampsia, which consists of hypertension that develops after 20 weeks of gestation and is accompanied by proteinuria, is one of the most severe complications experienced by pregnant women with diabetes. It is associated with placental abruption, cerebral hemorrhage, coagulation abnormalities, and maternal and fetal death. Unless it is successfully treated, preeclampsia can progress to eclampsia, which is characterized by seizures and coma. Because termination of pregnancy is the most effective treatment, preeclampsia often leads to preterm delivery, with its associated problems. In patients with chronic hypertension, superimposed preeclampsia often develops early in pregnancy, with an especially severe clinical presentation.
Diabetic Nephropathy

✓ Major risk factor for fetal growth restriction, superimposed preeclampsia, premature delivery, and stillbirth
✓ Optimal BG and BP control improves outcomes
✓ Patient should consult with RD about protein restriction
✓ Refer patient with severe manifestations to center specializing in DN during pregnancy


A diagnosis of overt diabetic nephropathy (DN) during pregnancy is presumed when there is persistent albuminuria (≥300 mg/day) or proteinuria (≥500 mg/day) before 20 weeks’ gestation and no evidence of infection or other renal or urinary tract disorders.

DN during pregnancy is a major risk factor for fetal growth restriction, superimposed preeclampsia, premature delivery, and stillbirth. The incidence of these complications may be minimized by optimal BG and BP control.

A woman with overt nephropathy should consult with a RD about how to safely restrict the amount of protein in her diet and how to control sodium intake to help regulate BP. Protein intake in a pregnant woman with diabetes is 1.1 g · kg body weight−1 · day−1. A nutrition assessment will help guide necessary restrictions, yet ensure a healthy food intake.

A patient should be referred to a center experienced in the care of diabetic renal disease and pregnancy when the glomerular filtration rate has fallen below 60 mL/min per 1.73 m² or difficulties have occurred in the management of hypertension.
Dyslipidemia may emerge or become more severe during pregnancy. Statins, which are usually the agents of choice for dyslipidemia, cause severe fetal harm or death and are contraindicated in pregnancy (category X). Because of the risks associated with statins, they should be discontinued before pregnancy and should not be prescribed for postpubertal girls and women who are not committed to using reliable contraception.

Exercise and MNT may provide adequate lipid control during pregnancy. Using plant sterol-containing margarines, such as Benecol® or Take Control®, can help with cholesterol lowering. Following a Mediterranean diet, which includes plant-based oils, high levels of fiber, abundant fruits and vegetables is also beneficial. To help regulate triglyceride levels, both the ADA and the American Heart association recommend that all individuals consume 2 weekly servings of fish containing high levels of omega-3 fatty acids, such as salmon, herring, lake trout, or albacore tuna. Fish with a high potential for mercury contamination, such as shark, swordfish, jack mackerel, and tilefish, must be avoided during pregnancy. Fish oil capsules are an alternative source of omega-3 fatty acids for women with inadequate fish intake.

When hypercholesterolemia does not respond adequately to lifestyle modification, use of a bile acid-binding resin is recommended. These nonabsorbed lipid-lowering drugs, which are in Pregnancy Category B, are considered the safest agents for use in pregnant women. Colesevelam (Welcho®) is generally considered to be the best tolerated and most effective member of this class.
Tests that monitor fetal status are performed at the health care provider’s discretion, based on individual needs. Ultrasound monitoring is the most commonly performed test. It is used during the first trimester to estimate the delivery date; during the second trimester to identify structural abnormalities; and during the third trimester, as needed, to assess fetal growth and development and to measure amniotic fluid levels. In early pregnancy, ultrasound can identify malformations such as neural tube defects. Serial ultrasound can detect growth patterns, helping to identify infants that are large or small for gestational age. Assessing the fetal response to maternal GDM by ultrasound measurement of fetal abdominal circumference in the second and early third trimesters can provide information that assists with management decisions.

α-Fetoprotein is a maternal blood test that can identify a fetus who may have a neural tube defect. The risk of these defects is 10 to 20 times greater in women with diabetes than in the general population.

If delivery is to be induced before 39 weeks, amniocentesis is performed late in the third trimester to assess lung maturity. In women over the age of 35, this procedure is also performed late in the first trimester to identify chromosomal abnormalities associated with birth defects. A limitation of amniocentesis is that it is associated with a high rate of false-positive results.
Other tests used to monitor fetal status are nonstress tests (NSTs), biophysical profiles, and fetal activity tests. A NST screens for fetal compromise. It should be performed at week 32 in women with preexisting diabetes and between weeks 35 and 40 in women with GDM. A limitation is that false-positive results are common.

The biophysical profile, a combination of a NST and an ultrasound evaluation, is often conducted when NST results are inconclusive. This reliable test is usually performed at week 32 in women with preexisting diabetes. When used in women with GDM, it is usually performed between weeks 35 and 40.

Depending on individual circumstances, NSTs and biophysical profiles may be conducted on a biweekly, weekly, or daily basis.

Fetal activity testing is a simple, inexpensive, and convenient method of monitoring fetal wellbeing that usually begins at about 32 weeks’ gestation. In fetal activity testing, the pregnant woman uses kick counting and other variables to measure fetal movements over a given time period.
In pregnancy complicated by diabetes, appropriate management during labor and delivery increases the safety of the mother and infant.

Continuous fetal heart rate monitoring should be used because of increased risks of fetal hypoxia and acidosis during labor. Recommended methods are external Doppler or internal (scalp electrode) monitoring.

Maternal BG levels should be maintained between 70 and 100 mg/dL to reduce the risk for neonatal hypoglycemia. To ensure that glucose levels remain in this range, the glucose level is measured at least hourly.

To maintain euglycemia, women with preexisting diabetes may receive a continuous infusion of insulin and/or glucose during labor. Many different protocols for intrapartum insulin administration have been developed.
Many fetal and neonatal complications can occur in pregnancies complicated by diabetes. These complications can often be prevented or their severity reduced when patients maintain near-normal BG levels before and during pregnancy. Hypoglycemia in the newborn (BG <35 mg/dL) is the most common neonatal metabolic complication. When maternal diabetes is poorly controlled, the fetus receives more glucose than needed for normal growth and secretes additional insulin to compensate for this excess glucose. After delivery, the glucose supply decreases but the baby continues to secrete large amounts of insulin. The result is neonatal hypoglycemia, which is usually treated by early feeding and, if necessary, by intravenous glucose administration.

Hypocalcemia and hypomagnesemia can cause transient hypoparathyroidism during the first 2 to 4 days of life. Neonatal hypomagnesemia is caused by magnesium depletion in mothers with suboptimal BG control. Hypocalcemia is secondary to hypomagnesemia and hypophosphatemia.

Fetal polycythemia, or high red blood cell count, is associated with increased erythropoietin levels. This complication is thought to be secondary to chronic intrauterine hypoxia, which is caused by hyperglycemia and hyperinsulinemia.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency (%)</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>10–25</td>
<td>Excessive insulin secretion by neonate</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>≤33</td>
<td>Magnesium depletion in mothers with suboptimal BG control</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>≤50</td>
<td>Hypermagnesemia, hyperphosphatemia</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>5–6</td>
<td>Intrauterine hypoxia caused by hyperglycemia and hyperinsulinemia</td>
</tr>
</tbody>
</table>

This slide summarizes other fetal/neonatal complications associated with maternal hyperglycemia. Cardiomyopathy, a rare but severe complication, results from the anabolic effect of hyperinsulinemia. Hyperbilirubinemia has multiple causes, including increased hemolysis and ineffective erythropoiesis, increased bruising, and delayed liver enzyme maturation.

Respiratory distress syndrome (RDS) is a life-threatening disorder associated with preterm delivery, heart or respiratory system anomalies, and hypoglycemia. The incidence of RDS in infants of mothers with diabetes has decreased in recent decades due to a focus on glycemic control during pregnancy, a greater likelihood of extending gestation beyond 38 weeks, and improved monitoring techniques.

The incidence of stillbirth has also declined in recent years, although there is much room for improvement. A French study whose results were published in 2003 found that the perinatal mortality rate of infants born to mothers with preexisting diabetes was 4.4%, compared to 0.7% in the general population. Stillbirths accounted for 79% of perinatal deaths in the study cohort. Only 40% of women who participated in the study had received preconception care.
The weight of a neonate with macrosomia is more than 4000 grams (8.8 lb) or above the 90th percentile for gestational age. Macrosomia is the most common fetal complication of GDM, with an incidence of 10% to 45%. It also occurs in pregnancies complicated by preexisting type 1 or type 2 diabetes.

The incidence of macrosomia is increasing in the US and other developed countries, probably because of rising rates of obesity and diabetes. Heavier mothers have bigger babies. Macrosomia mainly affects the fetal heart, liver, and subcutaneous fat. Common neonatal complications associated with macrosomia are shoulder dystocia, fractured clavicles, and brachial plexus injury. Macrosomia increases the demand for oxygen. Therefore, asphyxia, which is linked to difficult labor and delivery, may result. Macrosomia also increases the likelihood for surgical delivery. The adverse consequences of macrosomia do not end with the perinatal period. Children born with this condition are at increased risk for developing obesity and type 2 diabetes later in life.
Bell and colleagues recently reported on the epidemiology of congenital anomalies in children born to mothers with preexisting diabetes. This population-based cohort study used data from more than 400,000 singleton pregnancies in the north of England between 1996 and 2008.

The study showed that periconception A1C and the presence of prepregnancy nephropathy were the only independent predictors of these anomalies. The investigators found that for each percentage increase in A1C above 6.3%, the odds of a pregnancy being affected by congenital anomaly increased by 30%. The odds ratio (OR) was 1.3. There was no evidence of risk reduction below an A1C of 6.3%, but there were very few cases in this range.

Prepregnancy nephropathy was associated with a greater than 2-fold increased risk of congenital anomaly. The OR was 2.5.

In univariate analysis, low socioeconomic status and lack of folic acid supplementation were significant predictors of congenital anomaly, but these effects were attenuated below significance when adjustment was made for hyperglycemia.
As part of their study of congenital anomalies, Bell and colleagues compared the relative risk (RR) of a congenital anomaly in pregnancies complicated by preexisting diabetes compared to pregnancies without diabetes.

The incidence of congenital anomalies was 2.3% in pregnancies without diabetes, 8.2% in pregnancies complicated by preexisting type 1 diabetes, and 5.8% in pregnancies complicated by preexisting type 2 diabetes. The 2.4% difference in the frequency of congenital anomalies in pregnancies complicated by type 1 or type 2 diabetes was not statistically significant. (Note that some investigators have reported higher frequencies of congenital anomalies in children with type 2 diabetes than in those with type 1 diabetes. Other studies of congenital anomalies associated with preexisting diabetes did not differentiate between type 1 and type 2 diabetes.)

As the graph from the Bell study shows, the RR for any congenital anomaly was 3.3 times higher and the risk of a nonchromosomal anomaly was 3.8 times higher in pregnancies affected by preexisting diabetes. In contrast, the risk of a chromosomal anomaly was similar in pregnancies with and without preexisting diabetes (RR = 1.2). Compared to women without diabetes, women with diabetes were at highest risk of having a child with a musculoskeletal disorder (RR = 13.0). These data reinforce the importance of planning a pregnancy and achieving excellent glucose control before conception.
Most of the congenital anomalies observed in infants of mothers with preexisting diabetes involve the cardiovascular, musculoskeletal, central nervous, gastrointestinal (GI), or genitourinary system. Anomalies in infants born to diabetic mothers are more likely to be multiple, severe, and fatal than those found in infants of mothers without diabetes. Some of the congenital anomalies most strongly associated with diabetes are heart anomalies, such as ventricular septal defect and tetralogy of Fallot, caudal regression syndrome (which is also called caudal dysplasia sequence), situs inversus, GI atresias, and neural tube defects, such as anencephaly and spina bifida.

A ventricular septal defect is a hole in the wall that separates the 2 lower chambers (ventricles) of the heart. Tetralogy of Fallot is a condition caused by a ventricular septal defect in combination with 3 other cardiac abnormalities. Caudal regression syndrome is a structural disorder characterized by abnormal development of the lower spine. Situs inversus is a structural anomaly in which the positions of the major visceral organs are reversed. GI atresia is the absence or closure of a normal opening or tubular structure within the GI system, such as an imperforate anus. Although neural tube defects are numerically rare, the infant of a mother with preexisting diabetes has a greater than 5-fold risk of being born with such a defect compared to the infant of a mother without diabetes.
Maintaining glycemic control during the postpartum period is essential for women with preexisting diabetes. A sharp temporary drop in the maternal insulin requirement occurs immediately after delivery, with a gradual rise to about one third to one half of pregnancy levels over several days. Therefore, the mother should be monitored carefully and insulin adjusted accordingly during the early postpartum period. Although glycemic goals may be relaxed somewhat following delivery, approaching those of nonpregnant women with diabetes (A1C <7.0%), patients should be encouraged to strive for an A1C as close to normal as possible without significant hypoglycemia. For at least 6 months after delivery, women should perform SMBG 3 to 7 times daily to enable them to achieve glycemic goals that are consistent with low rates of postpartum complications and successful lactation.

Early recognition and treatment of maternal complications such as thromboembolism, hemorrhage, and cardiomyopathy are vital. Women with preexisting diabetes have a risk of infection following cesarean delivery that is 1.9 times greater than that of women without diabetes. Because women with type 1 diabetes have a 10% to 23% risk of postpartum thyroiditis, they should be screened for thyroid disease at 3 and 6 months postpartum. All women, including those with diabetes, should be screened for postpartum mood disturbances.
Breastfeeding

- Education begins with preconception counseling
- Consume ≥1800 kcal/day
- Supplements
  - Vitamin D for infants
  - B6 for many women
- Tailor to lactation requirements
  - Glucose-lowering agents
  - Treatments for hypertension, dyslipidemia, thyroid disease, depression


Women with diabetes should be strongly encouraged to breastfeed. Beginning in the preconception period, it is important for health care providers to educate women about the benefits of breastfeeding for at least 12 months, and lactation counseling should be provided during the third trimester of pregnancy.

Women who are breast-feeding need to consume at least 1800 kcal/day and avoid low-calorie diets and weight-loss medication. Once lactation is established, it is safe for overweight women to balance their caloric intake with physical activity to achieve a maximum monthly weight loss of 2 kg (4.4 lbs).

All breastfed infants should receive vitamin D supplements, and women may benefit from vitamin B6 supplements. Infants of mothers with diabetes need to be tested for iron deficiency and treated accordingly. Glucose-lowering agents for women with type 2 diabetes and treatments for dyslipidemia, hypertension, thyroid disease, and depression must be tailored to the requirements of lactation.

Exercise during lactation is safe for most women when precautions are taken to avoid maternal hypoglycemia. Alcohol consumption while breastfeeding should be discouraged, since it may have adverse effects on the infant’s feeding and behavior as well as on the mother’s glycemic control.
Beginning in early adolescence, all women with preexisting diabetes should receive preconception counseling that emphasizes the importance of a planned pregnancy. During the prepregnancy assessment, the diabetes health care team needs to assess the woman's fitness for pregnancy, paying special attention to the presence and severity of ischemic heart disease, hypertension, nephropathy, retinopathy, and other diabetes complications. To optimize outcomes, the woman's A1C should be normal or near normal before conception and she should have solid skills in diabetes self-management, including nutrition, monitoring, and insulin dose adjustment.

During pregnancy, women need to maintain a healthy lifestyle, consuming an adequate, well-balanced diet and engaging in daily physical activity (unless contraindicated). Basal-bolus insulin therapy or insulin pump therapy is the most effective means of maximizing glycemic control. Safe, effective control of BP and serum lipids is also important.

Consistent glycemic control and monitoring during pregnancy, labor, and delivery can minimize the risk of complications for the mother and child.

Women should receive appropriate postpartum follow-up. Important components are maternal support and education and close monitoring of BG control to determine ongoing insulin requirements.
The correct statement is: __________.

a. active proliferative retinopathy is a permanent contraindication to pregnancy
b. a woman who manages her preexisting type 2 diabetes with an oral agent should continue this regimen during pregnancy
c. the A1C goal during pregnancy is less than 6%
d. ACE inhibitors are safe during pregnancy, but ARBs must be discontinued
Answer to Checkpoint 3

The correct answer is c.

The A1C goal during pregnancy is less than 6%.

The correct answer is c.

The A1C goal during pregnancy is less than 6%.
Summary

- Diabetes increases the risk for pregnancy complications in the mother and congenital anomalies in the child.
- Advances in screening, monitoring, and care have greatly improved maternal and fetal outcomes.
- Meticulous glycemic control before, during, and after pregnancy reduces the risk for major complications.
- Results of the HAPO Study have led to new diagnostic criteria for GDM that will increase its incidence but will also improve maternal and fetal outcomes.
- Mothers with a history of GDM and their children should receive ongoing monitoring after delivery.

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