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Gestational Diabetes Mellitus

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This paper reviews what gestational diabetes mellitus is; it’s pathophysiology, epidemiology, risks, effects, clinical characteristics, screenings, diagnostics, treatment, and recommended follow up. Gestational diabetes mellitus rate has doubled during the last 20 years in the United States. There is currently only one FDA approved medication (insulin) for gestational diabetes mellitus; however there are a couple anti-hyperglycemic agents that are used off label for this disease. This paper looks at their efficacy and safety of such medications; metformin and glyburide. Current guidelines, clinical trials, retrospective studies, systematic reviews, and case reports were used to assess gestational diabetes and management. This is to help guide pharmacists to understand gestational diabetes mellitus, best practices to manage this disease state, and recommended follow up.

Key words: gestational diabetes mellitus, insulin, metformin, and glyburide
Definition

“Gestational diabetes mellitus is a condition in which carbohydrate intolerance develops during pregnancy” according to American College of Gynecologists. This condition only occurs during pregnancy. Per the American Diabetes Association guideline gestational diabetes mellitus (GDM) is defined as “diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes.”

Pathophysiology

The pathophysiology of GDM is that it is characterized by pancreatic \(\beta\)-cell dysfunction and peripheral insulin resistance.\(^1,2\) The sensitivity of insulin is thought to be mediated by tumor necrosis factor alpha (TNF\(\alpha\)), C-reactive protein, and glucose transporter 1 (GLUT1) receptor.\(^1,2\) These receptors mediate metabolism and once altered have been associated with gestational diabetes based on downstream effects shown through clinical presentation. It is also thought to be influenced by the hormones: human placental lactogen, progressterone, estrogen, cortisol and prolactin.\(^1,2\) These hormones influence the metabolic system in terms of storing and using energy sources and thus have been associated with GDM when dysfunctional.

Epidemiology

During the last twenty years in the United States rate of GDM has more than doubled.\(^3\) Approximately 9% of pregnancies are affected with GDM.\(^4\) If using two step diagnostics 5 to 6% of pregnancies are diagnosed with GDM.\(^5\) If using a less selective one step diagnostic test 15 to 20% of pregnancies are diagnosed with GDM.\(^5\) In most recent data from 2007 GDM cost the United States approximately $636 million annually.\(^6\) It costs $3,305 to manage GDM per each pregnancy.\(^6\)

Effects of GDM

Diabetes mellitus affects all aspects of nutrient development. For example, amino acid metabolism that used is for energy in early gestation and for protein in late gestation is effected by diabetes mellitus causing abnormalities in these pathways.\(^2\) It has been reported that there is an increase in triglycerides and decreased high density lipoprotein concentration in women with GDM.\(^2\) Lipid metabolism is affected, showing an association between large for gestational age infants to have increased protein, lipase and fat calls.\(^2\) Some factors associated with teratogenesis (causing malformation of the fetus) in pregnancy complicated by diabetes mellitus include hyperglycemia (high blood sugar), ketone body excess (toxic acidic chemicals), somatomedin (growth hormone) inhibition, arachidonic acid (essential nutrient) deficiency and free oxygen radical (cell damaging radicals) excess.\(^2\) It has been demonstrated that hyperglycemia induced alterations in neural tube closure that include disordered cells, decreased mitoses, and changes indicative of premature maturation.\(^2\)
The effects of nutrient development that GDM has can result in preeclampsia, cesarean section delivery, hypoglycemia, respiratory distress syndrome, shoulder dystocia, large for gestational age births, macrosomia, and small for gestational age births.\textsuperscript{2,4,5} “Preeclampsia is defined as an elevated blood pressure greater than 140/90 mm Hg that appears after 20 weeks’ gestation accompanied by new-onset proteinuria (greater than or equal to 300 mg/24 hours), can lead to life-threatening complications for both mother and fetus”.\textsuperscript{7} Women with GDM are at a 9.8 to 18% higher risk of preeclampsia.\textsuperscript{4} The risk rate of cesarean section deliveries with associated anesthetic and surgical morbidity are increased by 17 to 25% in pregnancies with poor glucose control.\textsuperscript{8} Hypoglycemia is seen most when the GDM is uncontrolled and can lead to infant mortality.\textsuperscript{4} The result from clamping the umbilical cord during birth causes a rapid drop in plasma glucose concentrations for the infant, it takes several days for the infant’s pancreas to adjust beta cell production of insulin.\textsuperscript{2} This is seen most commonly in macrosomic newborns. Insulin excess may interfere with the normal timing of glucocorticoid-induced pulmonary maturation in the fetus thus leading to respiratory distress syndrome.\textsuperscript{2} Specifically, cortisol acts on the pulmonary fibroblasts to induce synthesis of fibroblast-pneumocyte factor that acts on type II cells to stimulate phospholipid synthesis.\textsuperscript{2} Approximately 50% of pregnancies in women with GDM are complicated with fetal macrosomia.\textsuperscript{2} Macrosomia is defined as a birthweight greater than 4000 grams or 8.8 pounds and large for gestational age is the birthweight greater than 90\textsuperscript{th} percentile for the local population and specific growth curves.\textsuperscript{2} Shoulder dystocia occurs in 30\% of macrosomia infants.\textsuperscript{2} It is a specific type of obstructed labor when the anterior shoulder of the infant cannot pass the birthing canal being caught on the mother’s pubic symphysis and thus requires significant manipulation to pass. 4-16\% of such deliveries result in infant brachial plexus injuries.\textsuperscript{9} This is quite painful for the infant and can cause permanent damage. In fact, it was found that when delivering macrosomic infants to mothers with GDM by cesarean delivery it saves $880,000 health care dollars per case by avoiding brachial plexus injury.\textsuperscript{9}

Long Term Effects

After pregnancy the majority of women with GDM become normoglycemic.\textsuperscript{4,10} However, these women are 1.5 times more likely to develop type 2 diabetes later in life (roughly 22 to 28 years after pregnancy).\textsuperscript{4} It is of note that 60\% of Latin American women who had GDM in their pregnancies, will develop type 2 diabetes within 5 years post pregnancy.\textsuperscript{4}

Clinical Characteristics

Clinical characteristics associated with GDM include maternal obesity that is defined as body mass index greater than 30 kg/m\textsuperscript{2}. Weight gain in maternal pregnancy is greater than expected. Expected weight gain is determined by patient’s physician, though it is generally 25 to 35 pounds.\textsuperscript{9} Also there are ultrasound findings such as enlarged abdominal circumference, macrosomia, and polyhydramnios that could suggest GDM.\textsuperscript{11}
Screening

When screening for GDM it is important to distinguish between type 2 diabetes and gestational diabetes. A tool for distinguishing the difference to check for diabetes at the first prenatal visit using standard diagnostic criteria is available in appendix 1. It is especially important to test high risk patients as soon as possible. The most prominent criteria that categorizes a patient high risk is if they have a previous history of GDM, impaired glucose metabolism, or glucosuria (glucose in their urine). The patient has a strong family history of type 2 diabetes; this is defined as a first degree relative, and/or there is a history of cardiovascular disease. They are severely obese (body mass index greater than 40 kg/m$^2$), or body mass index greater than 25 if they are high risk ethnicity including; African American, Latina, Native American, Asian American, and Pacific Islander. See Appendix 2 for complete criteria. If the patient is found to have diabetes in the first visit, then they are diagnosed with type 2 diabetes rather than GDM.$^2,4$

Diagnosis

What is typically seen in pregnancy during the first trimester is a decrease in insulin concentration because of the increased insulin sensitivity.$^2$ Then, during the second and third trimesters there is a peak insulin concentration between weeks 28 to 32, and a decreased insulin sensitivity.$^2$ Thus, testing for gestational diabetes should be performed later in pregnancy because it may test as a false negative due to natural decrease in insulin in the first trimester.

All pregnant women at or beyond 24 weeks of gestation should be screened. This screening diagnosis GDM. The screening is typically done in weeks 24 to 28 of gestation. The tool that is used it the oral glucose tolerance test (OGTT) and this can be done as either a one step or two step. The one step is a 75 gram OGTT, this is done when the patient has fasted for 1, 2, or greater than 8 hours and plasma glucose measurement reading greater than or equal to 92 mg/dL, 180 mg/dL, or 153 mg/dL respectively constitutes diagnosis of GDM. This test is less selective than the 2 step test and thus is not recommended by the American Diabetes Association and American College of Gynecologists. The two step strategy is performed with the first step: the patients receives 50 grams OGTT non-fasting, if the plasma glucose level measured after 1 hour is greater than or equal to 140 mg/dL, then proceed to step 2. Step 2: patient is to take 100 grams OGTT when fasting 1, 2, 3, or greater than 8 hours, and if glucose measurement reading is greater than or equal to 180 mg/dL, 155 mg/dL, 140 mg/dL, or 95 mg/dL respectively, then patient is diagnosed with GDM.$^5$ See Appendix 3 for table.

Goals of therapy

The ultimate goals for women with pregnancies affected by GDM are to reduce pregnancy and newborn complications. These complications include: preeclampsia, cesarean section delivery, hypoglycemia, respiratory distress syndrome, shoulder dystocia, large for gestational age births, macrosomia, and small for gestational age births.
The goals for blood glucose are to be stable and within goal range. Specifically, fasting blood glucose should be less than 95 mg/dL, 1 hour post-prandial (after eating) less than 140 mg/dL and 2 hours post-prandial less than 120 mg/dL.\textsuperscript{4,5}

Monitoring

It is recommended to self-monitor blood glucose if diagnosed with GDM.\textsuperscript{4,5} It is most recommended to check blood glucose 4 times daily. This would be to check blood glucose when fasting, and 1 to 2 hours after each meal.\textsuperscript{4} Essentially one is self-monitoring their blood glucose in the morning before breakfast and then an hour to 2 hours after that meal and repeat with lunch and dinner as well. This can be cumbersome for patients that have not had to test there blood sugar in the past.

A recent study shows that self-monitoring blood glucose 4 times daily, every other day is equally efficacious in control compared to the recommended. In the study “Gestational Diabetes Mellitus and Frequency of Blood Glucose Monitoring A Randomized Controlled Trial” published in 2017, they found no statistically significant difference in birth age at delivery, preeclampsia, shoulder dystocia or neonatal intensive care unit admission.\textsuperscript{12} This study met power with 293 participants; majority ages 20 to 45 years of age and 91% were obese with body mass index greater than 30 kg/m\textsuperscript{2}. Compliance in self-monitoring blood glucose was significantly greater with every other day testing (92%) compared to every day testing (89%), p-value<0.01. Thus, this study suggests that women with GDM who are well controlled may be candidates for every other day self-monitoring blood glucose monitoring.

Non-pharmacologic therapy

The first line therapy for treatment of GDM is diet modification and exercise. Diet is a huge factor in managing GDM. It is recommended to have a personalized nutrition plan based on patient’s body mass index with a registered dietitian.\textsuperscript{4,5} In general the diet should be low-fat, high fiber, and carbohydrates are to be restricted to 35 to 40% of daily intake. Also sugar and concentrated sweets should be avoided. It is important to eat small and frequent meals for better blood glucose control.\textsuperscript{4}

Lifestyle is the other key component to keeping blood glucose within range. It is recommended to have regular moderate exercise.\textsuperscript{4} This can be accomplished in various ways. The American Diabetes Association recommends 30 minutes of moderate intensity aerobic exercise at least 5 days a week.\textsuperscript{5} Per American College of Gynecologists it is recommended to exercise at least 150 minutes per week, this can be as simple as walking for 10 to 15 minutes after each meal.\textsuperscript{4}

Pharmacologic Treatment
Pharmacologic treatment is appropriate when non-pharmacologic treatment fails or is not applicable. Sole non-pharmacologic treatment is considered a failure when blood glucose levels are consistently high for more than two weeks.\textsuperscript{4} Fasting blood glucose greater than 95 mg/dL, 1 hour post-prandial greater than 140 mg/dL, and 2 hours post-prandial greater than 120 mg/dL are considered high blood glucose levels.\textsuperscript{4,5}

Current pharmacologic treatments for gestational diabetes mellitus are insulin, metformin and glyburide. Insulin is the only FDA medication approved for gestational diabetes mellitus, while metformin and glyburide are used off-label.

Insulin therapy is the gold standard for treating GDM. Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs for insulin include the liver, skeletal muscle, and adipose tissue.\textsuperscript{1} It does not cross the placenta.\textsuperscript{1} There are various types of insulin including: long-acting insulin, fast-acting insulin, and regular insulin. Long-acting insulin is used to keep a steady state of insulin throughout the day to keep blood glucose levels more consistent, see appendix 4 for visual. Fast-acting glucose has roughly 1 to 15 minutes to onset of action and time to peak concentration, while regular insulin takes 30 to 60 minutes.\textsuperscript{1,4} See appendix 5 for action profile of commonly used insulin agents. It is recommended to use fast acting insulin over regular insulin because it is less likely to cause hypoglycemia. This rationale is because a patient is more likely to forget to eat 30 to 60 minutes after injecting a dose, instead of eating right after. Therapy is typically started at dose of 0.7 to 1.0 units/kg daily in divided doses.\textsuperscript{1,4} Though, it is recommended to use individualized therapy to reach therapeutic goals.\textsuperscript{4} An example of this would be a 180 pound patient taking 30 unites of long-acting insulin at night with 10 units of fast-acting insulin with each meal.

Insulin has drug-drug interactions with glyburide, hydorchorothizide and chlorthalidone. This is not a comprehensive list of drug-drug interactions; these medications are considered to be non-harmful in pregnancy and thus might be seen in pregnant women with other disease states. The interaction between insulin and glyburide can increase the risk of hypoglycemia, they should not be taken together, and if taken together it is important to monitor blood glucose closely.\textsuperscript{1} Hydrochorothiazide and chlorthalidone may diminish the therapeutic effect of insulin, thus therapies should be monitored and adjusted appropriately.\textsuperscript{1}

The most prominent side effect of insulin is hypoglycemia and thus should be monitored closely. Mild to moderate hypoglycemia is defined as blood glucose levels less than 70 mg/dL.\textsuperscript{13} Signs and symptoms of hypoglycemia include: confused thought, shakiness, cold sweats, and general “not feeling right”.\textsuperscript{5} The recommended treatment for hypoglycemia is to give 15 grams of rapidly absorbed glucose such as 4 to 6 ounces of fruit juice.\textsuperscript{13} Then, check blood glucose 15 minutes later and once stable to eat a small meal or snack that contains protein and carbohydrates.\textsuperscript{13} Severe hypoglycemia is defined as blood glucose levels less than 50 mg/dL.\textsuperscript{13} In this case it is recommended to administer a glucagon kit and to contact emergency medicine such as calling 911. A glucagon kit is an antidote kit given for hypoglycemia, this injection promotes hepatic glycogenolysis and gluconeogenisis, causing blood glucose levels to rise.\textsuperscript{1} If hypoglycemcic events occur, follow-up is recommended to raise glycemic targets and reduce insulin dose by 20 to 40%.\textsuperscript{13} Hypoglycemia can ultimately be fatal to the fetus because it is
unable to get any nutrients, as well as be fatal to the mother. In lesser extremes it can also cause infants to be underweight at birth and cause delayed growth of the fetus.²

Metformin is the second-line choice for patients with GDM that are unable to safely administer insulin according to American College of Gynecologists recommendations.⁴ Metformin decreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.¹ It is recommended to initiate therapy at 500 mg every evening for one week then to increase to 500 mg twice daily (once in the morning and once in the evening).¹ ⁵ The maximum daily dose allowed is 2,500-3,000 mg per day in divided doses such as twice daily or three times daily.¹ Metformin has 33.8% single agent failure rate to achieve therapy goals for GDM, and often insulin has to be added down the line.⁴

The most common side effect of metformin is abdominal pain and diarrhea. This side effect affects between 2.5 to 45.7% of patients.¹ It also causes decreased vitamin B₁₂ serum concentration.¹ So, it is recommended to take metformin with meals to decrease the chance of abdominal pain and to monitor B₁₂ serum concentration and supplement if needed.

Metformin is contraindicated in patients with reduced kidney function that have a creatinine clearance rate of less than 30 ml/min.¹ Metformin has noted drug-drug interactions with cephalexin, cimetidine, sertraline, and fluoxetine. This is not a comprehensive list of drug-drug interactions; these medications are considered to be non-harmful in pregnancy and thus might be seen in pregnant women with coexisting disease states. Cephalexin may increase the serum concentration of metformin, it is recommended to monitor for signs and symptoms of metformin toxicity that include reduced renal function and lactic acidosis.¹ Cimetidine may increase the serum concentration of metformin that could lead to lactic acidosis, and thus therapy should be modified.¹ Sertraline and fluoxetine may enhance the hypoglycemic effects of blood glucose lowering agents such as metformin and thus should be monitored, and metformin dose may need to be decreased.¹

Metformin is known to cross the placenta according to “Pharmacokinetics of Metformin during Pregnancy” published in 2010. This study consisted of 35 participants treated with metformin during pregnancy; 12 of these participants allowed maternal and umbilical cord blood samples to be collected.¹⁴ It was found that at the time of delivery, the fetus is exposed to metformin, with concentrations ranging from negligible to as high as maternal concentrations. This was related to time of the last dose given before delivery, it appears that if last dose given greater than 10 hours then concentrations would be negligible.¹⁴

“Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy” prospective study in 2004 found that metformin did not adversely affect birth length and weight, growth or motor-social development in the first 18 months of life.¹⁵ It was also found in “Neurodevelopmental outcome at 2 years in offspring of women randomized to metformin or insulin treatment for gestational diabetes” study, published in 2016 no significant differences between the two therapies.¹⁶
Glyburide is not a preferred agent for the treatment of GDM, though it is commonly used.\textsuperscript{4} Glyburide stimulates insulin release from the pancreatic beta cells, thus reduces glucose output from the liver and insulin sensitivity is increased at peripheral target sites.\textsuperscript{1} It is a clinically effective alternative to insulin therapy. The typical dose of glyburide for GDM is 2.5 to 20 mg daily into divided doses.\textsuperscript{1} Up to 30 mg/day have been used when necessary.

The most common side effects associated with glyburide are hypoglycemia, allergic reactions, and stomach upset.\textsuperscript{1} Glyburide is contraindicated in patients with a sulfa allergy since it is a sulfa containing medication. Glyburide has noted drug-drug interactions with insulin, and CYP2C9 inhibitors that include clopidogrel, metronidazole, and efavirenz.\textsuperscript{1} This is not a comprehensive list of drug-drug interactions; these medications are considered to be non-harmful in pregnancy and thus might be seen in pregnant women with coexisting disease states. The interaction between glyburide and insulin can increase the risk of hypoglycemia, they should not be taken together, and if they are taken together it is important to monitor blood glucose closely.\textsuperscript{1} Since glyburide is metabolized by the CYP2C9 enzyme in the liver, medications such as clopidogrel, metronidazole, and efavirenz inhibit this enzyme thus causing an increased effect of glyburide and could cause a hypoglycemic effect.\textsuperscript{1} It is recommended to monitor blood glucose when taking these medications together and modify therapy as needed.\textsuperscript{1}

“A Comparison of Glyburide and Insulin in Women with Gestational Diabetes Mellitus” was published in October of 2000. This seminal prospective randomized study was what made glyburide as popular as it is for the treatment of GDM. The use of glyburide for GDM increased from 8.5% in 2000 to 64.4% in 2011.\textsuperscript{3} It was performed in San Antonio, Texas with all participants being insured by Medicaid. 83% of the demographics were Mexican American women ages ranging from 22 years of age to 36 years of age with the average of 29 years of age.\textsuperscript{17} 201 participants received glyburide starting dose 2.5 mg every morning and increased each week as needed up to 20 mg.\textsuperscript{17} While, 203 participants received insulin starting dose 0.7 mg/kg three times daily and increased each week as needed.\textsuperscript{17} This study concluded; no statistically significant difference in blood glucose levels in fasting, pre-prandial, postprandial, glycosylated hemoglobin, and the week of gestation when blood glucose testing started. There was no statistically significant difference in birth defects at delivery which were measured for: large for gestational age or macrosomia, hypoglycemia, hypocalcemia, admissions to neonatal intensive care unit, and still births.\textsuperscript{17} It is also of note that study used detection limit of 10 ng/mL in cord serum of the infant to detect fetal transfer of glyburide.

There were a few factors in this study to weaken its external validity. For example, the sample size was small and thus would erroneously project on how well the medication works on the GDM population as a whole in the United States. This also is applied to the demographics as well, with 83% of participants being Mexican American this study should be narrowly applied to that specific population. Since the publication of this study, the detection level for fetal transfer of glyburide is 0.25 ng/mL\textsuperscript{18} A recent meta-analysis found that glyburide was in 70% fetal blood concentration compared to maternal blood concentration of 100% using the more stringent detection level.\textsuperscript{18} This finding probes the question if glyburide affects fetal development.

Retrospective studies have since been performed on this topic. In a more recent study “Association of Adverse Pregnancy Outcomes with Glyburide vs Women with Gestational Diabetes” published in March 2015 concluded that there is an association between glyburide and
elevated risk of Neonatal Intensive Care Unit (NICU) admissions of neonate who’s mothers took glyburide compared to insulin. This retrospective cohort collected data from 2000 through 2011, assessing pharmacy claims that included glyburide treatment used within 150 days of delivery and NICU admission within 30 days of birth and greater than 24 hours stay. The number needed to harm (NNH) was 36 for NICU admissions with 95% confidence interval (CI) between 225-60. This means that it would take at least 36 patients treated with glyburide to see one infant admitted to the NICU within 30 days of birth and greater than 24 hours stay. The study also found that NNH 71 for large-for-gestational-age (95% CI, 46-164) and NNH 96 for respiratory distress (95 CI, 61-233).

Follow Up

After delivery it is recommended for women with GDM to be tested for diabetes mellitus at 4 to 12 weeks postpartum. The testing tools include testing fasting plasma glucose or using a 2 hour OGTT. If results for fasting plasma glucose are greater than 125 mg/dL or 2 hour glucose is greater than 199 mg/dL the patient is diagnosed with diabetes mellitus and should be referred for diabetes management. If results for fasting plasma glucose is between 100 and 125 mg/dL or 2 hour glucose is between 140 and 199 mg/dL the patient has impaired fasting glucose and/or impaired glucose tolerance and thus should consider referral for management. If fasting plasma glucose is less than 100 mg/dL or 2 hour glucose is less than 140 mg/dL the patient is normal and glycemic status should be assessed every 1 to 3 years. See appendix 6 for diagram.

Conclusion

In conclusion, GDM is only diagnosed when diabetes is not clearly defined by type 1 or 2 diabetes mellitus. It is recommended to screen for GDM at weeks 24-28 of gestation using 2-step OGTT. Self-monitoring blood glucose is important to adhering to goal ranges. Eating small frequent meals low in sugars, and exercising at least 5 times per week is first line treatment for GDM. If these measures are not sufficient, it is recommended to use pharmacologic treatments that include the gold standard-insulin and metformin and glyburide if insulin is not a choice. Mothers with GDM are 1.5 times more likely to have type 2 diabetes later in life. It is important to screen for diabetes at least every 3 years post-partum for mothers with pregnancies complicated with GDM.
References


12. Hector Mendez-Figueroa, MD, Meike Schuster, DO, Lindsay Maggio, MD, MPH, Claudia Pedroza, PhD, Suneet P. Chauhan, MD, and Michael J. Paglia, MD, PhD. Gestational Diabetes Mellitus and Frequency of Blood Glucose Monitoring Randomized Controlled Trial (Obstet Gynecol 2017;130:163–70) DOI: 10.1097/AOG.0000000000002101


BOX 40-2 SCREENING STRATEGY FOR DETECTING GDM

GDM risk assessment should be ascertained at the first prenatal visit.

- Low risk: Blood glucose testing is not routinely required if all of the following characteristics are present:
  - Member of an ethnic group with a low prevalence of GDM
  - No known diabetes in first-degree relatives
  - Age <25 years
  - Weight normal before pregnancy
  - No history of abnormal glucose metabolism
  - No history of poor obstetric outcome

- Average risk: Perform blood glucose testing at 24 to 28 weeks by one of the following methods:
  - Two-step procedure: A 50-g GCT followed by a diagnostic oral GTT in those who meet the threshold value in the GCT
  - One-step procedure: Diagnostic oral GTT performed on all subjects

- High risk: Perform blood glucose testing as soon as feasible using the procedures described above if one or more of these are present:
  - Severe obesity
  - Strong family history of type 2 diabetes
  - Previous history of GDM, impaired glucose metabolism, or glucosuria

If GDM is not diagnosed, blood glucose testing should be repeated at 24 to 28 weeks or anytime a patient has symptoms or signs suggestive of hyperglycemia.


GCT, glucose challenge test; GDM, gestational diabetes mellitus; GTT, glucose tolerance test.
Box 1. Screening Strategy for Detecting Pregestational Diabetes or Early Gestational Diabetes Mellitus

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

- Physical inactivity
- First-degree relative with diabetes
- High-risk race or ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Have previously given birth to an infant weighing 4,000g (approximately 9 lb) or more
- Previous gestational diabetes mellitus
- Hypertension (140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein cholesterol level less than 35 mg/dL (0.90 mmol/L), a triglyceride level greater than 250 mg/dL (2.82 mmol/L)
- Women with polycystic ovarian syndrome
- $\text{HbA}_1\text{C}$ greater than or equal to 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (e.g., prepregnancy body mass index greater than 40 kg/m², acanthosis nigricans)
- History of cardiovascular disease

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

### Table 2.5—Screening for and diagnosis of GDM

#### One-step strategy
Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:
- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

#### Two-step strategy

**Step 1:** Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 h after the load is \( \geq 140 \text{ mg/dL}^* \) (7.8 mmol/L), proceed to a 100-g OGTT.

**Step 2:** The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

<table>
<thead>
<tr>
<th></th>
<th>Carpenter/Coustan (55)</th>
<th>or</th>
<th>NDDG (56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>95 mg/dL (5.3 mmol/L)</td>
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<td>105 mg/dL (5.8 mmol/L)</td>
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<tr>
<td>1 h</td>
<td>180 mg/dL (10.0 mmol/L)</td>
<td></td>
<td>190 mg/dL (10.6 mmol/L)</td>
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<tr>
<td>2 h</td>
<td>155 mg/dL (8.6 mmol/L)</td>
<td></td>
<td>165 mg/dL (9.2 mmol/L)</td>
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<tr>
<td>3 h</td>
<td>140 mg/dL (7.8 mmol/L)</td>
<td></td>
<td>145 mg/dL (8.0 mmol/L)</td>
</tr>
</tbody>
</table>

NDDG, National Diabetes Data Group. *The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).
Figure 1. Representative time action profiles of selected exogenous insulins. Source: References 25, 26.
Table 2. Action Profile of Commonly Used Insulin Agents

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

Appendix 6

Figure 1. Management of postpartum screening results. Abbreviations: FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.