Gestational Diabetes Mellitus

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Gestational diabetes mellitus (GDM) affects between 2% and 5% of pregnant women. Data show that increasing levels of plasma glucose are associated with birth weight above the 90th percentile, cord blood serum C-peptide level above the 90th percentile, and, to a lesser degree, primary cesarean deliveries and neonatal hypoglycemia. Risk factors for GDM include history of macrosomia, strong family history of diabetes, and obesity. Screening protocol for GDM is controversial; some recommend a universal approach, whereas others exempt low-risk patients. The cornerstone of management is glycemic control. Quality nutritional intake is essential. Patients with GDM who cannot control their glucose levels with diet alone will require insulin. There is no consensus as to when to initiate insulin therapy, but more conservative guidelines are in place to help minimize macrosomia and its associated risks to the infant. It is generally recommended that pregnancies complicated by GDM do not go beyond term.

[Rev Obstet Gynecol. *2008;1(3):129-134*]

Key words: Gestational diabetes mellitus • Plasma glucose • Hyperglycemia • Glycemic control • Insulin

Pregnancy confers a state of insulin resistance and hyperinsulinemia that may predispose some women to develop diabetes. Gestational diabetes mellitus (GDM) occurs when a woman's pancreatic function is not sufficient to overcome the diabetogenic environment of pregnancy. GDM is defined as glucose intolerance that was not present or recognized prior to pregnancy.[1] In the United States, prevalence rates for GDM are higher for African American, Hispanic, American Indian, and Asian women than for white women. The prevalence of

Table 1
White Classification

A: Abnormal glucose tolerance test at any age or of any duration treated only by diet therapy

B: Onset at age 20 years or older and duration of less than 10 years

C: Onset at age 10 to 19 years or duration of 10 to 19 years

D: Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia)
- D1: Onset before age 10 years
- D2: Duration over 20 years
- D3: Calcification of vessels of the leg (macrovascular disease)
- D4: Benign retinopathy (microvascular disease)
- D4: Hypertension (not preeclampsia)

R: Proliferative retinopathy or vitreous hemorrhage

F: Renal nephropathy with over 500 mg/d proteinuria

RF: Criteria for both classes R and F

G: Many pregnancy failures

H: Evidence of arteriosclerotic heart disease

T: Prior renal transplant

Gestational diabetes
- A1: Controlled by diet and exercise
- A2: Requires insulin

Data from White P.[3]

GDM in the United States varies from 1.4% to 14%. Most commonly, GDM affects between 2% and 5% of pregnant women. The amount of GDM varies in direct proportion to the prevalence of type II diabetes.[2]

There are 2 different methods of classifying diabetes in pregnancy. The first is the White classification (Table 1),[3] and the second is the American Diabetes Association (ADA) classification (Table 2).[4]

Pathophysiology

Insulin resistance during pregnancy stems from a variety of factors, including alterations in growth hormone and cortisol secretion (insulin antagonists), human placental lactogen secretion (which is produced by the placenta and affects fatty acids and glucose metabolism, promotes lipolysis, and decreases glucose uptake), and insulinase secretion (which is produced by the placenta and facilitates metabolism of insulin). In addition, estrogen and progesterone also contribute to a disruption of the glucose insulin balance. Increased maternal adipose deposition, decreased exercise, and increased caloric intake also contribute to this state of relative glucose intolerance.

Risk Factors for GDM

Several risk factors are associated with the development of GDM. The most common risk factors include a history of macrosomia (birth weight $>$ 4000 g), being a member of an ethnic group with a higher rate of type II diabetes (as mentioned above), polycystic ovarian syndrome, essential hypertension or pregnancy-related hypertension, history of spontaneous abortions and unexplained stillbirths, strong family history of diabetes (especially in first-degree relatives), obesity (pregnancy weight $>$ 110% of ideal body weight or body mass index [BMI] $>$ 30), age older than 25 years, persistent glucosuria, and a history of GDM in a previous pregnancy.[5,6] No known risk factors are identified in 50% of patients with GDM.[5,6]

Screening and Diagnosis of GDM

There is debate regarding the preferred screening protocol for GDM. Some experts recommend universal screening because not all women who develop GDM have risk factors. The ADA policy states that screening may be omitted in low-risk women. A woman is considered low risk if all of the following factors are present: age younger than 25 years; BMI less than 25 before pregnancy; not of Hispanic,

Table 2
American Diabetes Association Classification

3 Forms of Glucose Intolerance
- Type I diabetes: Immunologic destruction of the pancreas
- Type II diabetes: Exhaustion or resistance of the pancreatic cells
- Gestational: A glucose intolerance that had not previously been present prior to pregnancy

Data from the American Diabetes Association.[4]

African American, American Indian, South or East Asian, or Pacific Islander descent; no first-degree relative with DM; no history of abnormal glucose tolerance; and no history of poor obstetric outcome. The American College of Obstetricians and Gynecologists (ACOG) practice bulletin states that universal screening is the most sensitive and more practical approach, but it notes that low-risk women may be excluded from screening per the ADA recommendation.[2] The United States Preventive Services Task Force on Preventive Health Care concluded that there is not enough evidence to support or deny universal screening for GDM.[7]

Screening

When the universal screening approach is employed, patients with no known risk factors should undergo a 1-hour glucose test (glucose challenge test) at 24 to 28 weeks of gestation. Patients with known risk factors that indicate the possibility of glucose intolerance may be tested at the onset of prenatal care. If this initial screen is normal, then the test is repeated at the beginning of the third trimester (24 weeks).

For the glucose challenge test, the patient receives 50 g of glucose. One hour later, blood is drawn for a plasma glucose determination. A glucose value above 130 to 140 mg/dL is considered abnormal and necessitates a second test, the 3-hour glucose tolerance test. Our center uses 140 mg/dL as the cutoff point. Abnormal results for the 1-hour screening test will occur in 15% of patients. Of those patients who go on to have the 3-hour screening test, 15% will be diagnosed with GDM.

To perform glucose tolerance testing (GTT), clinicians first draw a fasting glucose sample and then administer 100 g of glucose. Blood for glucose values is drawn at 1 hour, 2 hours, and 3 hours. Although some centers perform a 75-g 2-hour GTT as both a screening test and a diagnostic test, most centers in the United States rely on the 2-step method described above.

Diagnosis

In the Carpenter/Coustan conversion method, diagnosis of GDM is based on the presence of 2 or more of the following factors[8,9]:

- Fasting serum glucose concentration exceeding 95 mg/dL
- 1-hour serum glucose concentration exceeding 180 mg/dL
- 2-hour serum glucose concentration exceeding 155 mg/dL
- 3-hour serum glucose concentration exceeding 140 mg/dL

Alternatively, some centers employ the National Diabetes Data Group (NDDG) criteria, which are slightly more liberal.[10] The abnormal values are as follows:

- Fasting serum glucose concentration exceeding 105 mg/dL
- 1-hour serum glucose concentration exceeding 190 mg/dL
- 2-hour serum glucose concentration exceeding 165 mg/dL
- 3-hour serum glucose concentration exceeding 145 mg/dL

The Hyperglycemic and Adverse Pregnancy Outcomes (HAPO) study showed that increasing levels of plasma glucose are associated with birth weight above the 90th percentile, cord blood serum C-peptide level above the 90th percentile, and, to a lesser degree, primary cesarean deliveries and neonatal hypoglycemia.[11] There were also associations between increased maternal plasma glucose levels and premature delivery, shoulder dystocia, preeclampsia, and hyperbilirubinemia. The results of the HAPO and Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)[12] studies indicate that maternal hyperglycemia that does not meet diagnostic criteria for overt diabetes still has a correlation with perinatal disorders and problems. This association suggests a need to reevaluate the standards and criteria for diagnosing and treating hyperglycemia in pregnancy.

Management/Treatment of GDM

The cornerstone of management is glycemic control.[13] Blood glucose levels should be monitored up to 4 times a day: upon awakening (for a fasting level), and 1-hour after the first bite of each meal. The morning fasting glucose level goal is 70 to 90 mg/dL. The postprandial goal is ideally below 120 mg/dL; the upper limit of acceptable is 135 to 140 mg/dL. These values are more stringent for pregnant women than they are for nonpregnant patients with diabetes.

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Quality nutritional intake is essential.[14] Caloric allotment is based on ideal body weight. Recommendations are 30 kcal/kg for women with a BMI of 22 to 25, 24 kcal/kg for women with a BMI of 26 to 29, and 12 to 15 kcal/kg for women with a BMI above 30. The recommended overall dietary ratio is 33% to 40% complex carbohydrates, 35% to 40% fat, and 20% protein. This calorie distribution will help 75% to 80% of GDM women become normoglycemic.[13]

Patients with GDM who cannot control their glucose levels with diet

alone will require insulin.[12] There is no consensus as to when to initiate insulin therapy, but more conservative guidelines are in place to help minimize macrosomia and its associated risks to the infant.[15,16] Two approaches are to initiate insulin when the fasting blood glucose concentration is greater than 90 mg/dL on 2 or more occasions during a 2-week period, or when the 1-hour postprandial blood glucose concentration is greater than 120 mg/dL. The insulin types most commonly used in GDM are neutral protamine Hagedorn (NPH) and regular insulin. NPH is an intermediate-acting insulin. It is typically used when the fasting glucose is high. The onset of action is 2 to 4 hours, the peak effect is at 6 to 12 hours, and the duration of action is 10 to 16 hours. Regular insulin has an onset of action within 30 to 60 minutes, a peak effect at 2 to 3 hours, and a duration of 3 to 6 hours. Among women with GDM, 15% will require insulin. Human insulin is the least immunogenic.

In the United States, use of oral hypoglycemic agents is controversial and not approved by the US Food and Drug Administration. That said, many practices have successfully used glyburide to manage GDM when diet alone was insufficient, although a significant number of these patients go on to require insulin in order to maintain optimal glycemic control. Another oral hypoglycemic agent that is being considered as a substitute to insulin is metformin. Rowan and colleagues[17] compared the use of metformin and insulin in women diagnosed with GDM. Of note, neonatal complications did not vary between the 2 subject groups. There was less severe hypoglycemia in the infants of mothers on metformin. Preterm birth was more common in the metformin group, but there was no increase in other complications. Women who used metformin were more likely to say they would use metformin in a subsequent pregnancy (76%) than were women on insulin (27.2%). Among the women on metformin, 46.3% had to be on supplemental insulin as well. The overall conclusion of this study was that metformin was a safe option for GDM, and it was more agreeable to the patient. There have not been any trials comparing glyburide and metformin.

Exercise has been shown to improve glycemic control. The mechanism of this improvement is mostly secondary to increasing tissue sensitivity to insulin. It is not clear exactly how much exercise is enough to help control glucose levels. However, exercising 3 or more times a week for at least 15 to 30 minutes duration is the typical recommendation. Exercising both prior to and during pregnancy has the greatest correlation with protection against developing GDM.[18]

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Patients are usually scheduled for follow-up visits every 1 to 2 weeks throughout pregnancy, depending on severity and any other complications that arise. A 24-hour urine collection analysis may be performed to establish a baseline level of proteinuria and creatinine clearance due to the higher likelihood that preeclampsia will develop in the setting of GDM.[19]

There are no data from randomized trials on which to base recommendations regarding initiation of fetal monitoring in women whose pregnancies are complicated by GDM. For pregestational diabetic pregnancies, ACOG recommends antepartum monitoring beginning at 32 to 34 weeks of gestation. ACOG states that fetal monitoring is warranted in patients who do not have well-controlled GDM, who require insulin, or who have other complications of pregnancy.[2] The most commonly used test is the nonstress test. It is typically performed once or twice per week. (Twice per week is thought to be more efficacious because it offers confidence that the fetus is doing well for a 72-hour period and provides a sensitivity that is equivalent to a weekly contraction stress test or a weekly biophysical profile.) A reactive nonstress test is required if the fetal heart rate increases 15 beats or more per minute for at least 15 seconds twice within a 20-minute period. The fetal biophysical profile should include assessment of tone, amniotic fluid level, gross and fine motor movement, heart rate, and breathing. Fetal movement counting can be used in conjunction with the nonstress test and/or biophysical profile. The contraction stress test is another option, although it is used infrequently.

If blood glucose levels are close to normal during pregnancy, and there are no other complications, it is ideal for the mother to deliver at term. It is generally recommended that pregnancies complicated by GDM do not go beyond term. There is continuing debate about whether induction of labor or expectant labor is more efficacious, and it is not clear which is better with regard to the outcomes of cesarean delivery incidence, birth injury, or neonatal morbidity and mortality.

There are no contraindications for epidural analgesia, spinal anesthesia, or, if indicated, general anesthesia. Insulin is rarely needed during delivery. Typically, a normal saline infusion is all that is required for the patient to remain normoglycemic. Blood glucose should be monitored the day after delivery to ascertain that the mother is no longer hyperglycemic according to the criteria for nonpregnant

individuals. In general, no further insulin is required postpartum for patients with GDM. Among women with GDM, 95% will return to a completely normal glucose status postpartum.

In the postpartum period, glucose tolerance screening should be performed at 2 to 4 months after delivery to help detect the 3% to 5% of women who remain diabetic and require further treatment. For this screening, the 75-g 2-hour glucose challenge test mentioned earlier is recommended.

Complications

Women with GDM experience twice the number of urinary tract infections than women who do not have GDM. This increased infection incidence is thought to be due to the increased amount of glucose in the urine beyond the normal glucosuria that is present in pregnancy. There is also an increased risk of pyelonephritis, asymptomatic bacteriuria, and preeclampsia. There is a 10% risk of polyhydramnios that may increase the risk of abruption placentae and preterm labor as well as of postpartum uterine atony. Congenital anomalies do not occur at an increased rate in patients with GDM. There is reportedly an increased incidence of stillbirth when glucose control is poor. There is also a 10% per year risk of developing type II diabetes after the pregnancy in which GDM occurred, with the greatest risk within the first 5 years following the index pregnancy.

Macrosomia, if it occurs, typically becomes evident at 26 to 28 weeks gestation. Complications associated with macrosomia include fetopelvic disproportion leading to operative delivery, shoulder dystocia, and neonatal hypoglycemia.[20] There is an increased incidence of hyperbilirubinemia, hypocalcemia, respiratory distress syndrome, and polycythemia in the neonate. Long-term complications can include obesity, diabetes during childhood, impaired motor function, and higher rates of inattention and hyperactivity.[1,11]

Summary

GDM is a problem that affects a significant number of women during pregnancy. GDM can have lasting health impacts on both the mother and the fetus. In order to circumscribe and minimize potential complications to both mother and child, screening, diagnosis, and management of hyperglycemia are critical. There is still work to be done to gain a better sense of what screening protocols are most efficacious and cost effective, and when they should be administered. Future studies will provide guidance as to what the optimal management choices are. Insulin in addition to oral hypoglycemic therapy appears to be the focus of research in the near future. ■

References

1. Beckmann CRB, Ling FW, Smith RP, et al, eds. *Obstetrics and Gynecology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
2. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 30, September 2001 (replaces Technical Bulletin Number 200, December 1994). Gestational diabetes. *Obstet Gynecol*. 2001;98:525-538.
3. White P. Pregnancy complicating diabetes. *Am J Med*. 1949;7:609-616.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2006;29:S43-S48.
5. Proceedings of the 4th International Workshop-Conference on Gestational Diabetes Mellitus. Chicago, Illinois, USA. 14-16 March 1997. *Diabetes Care*. 1998;21(suppl 2):B1-B167.
6. Marion DW. Screening and diagnosis of gestational diabetes mellitus. UpToDate Web site. http://www.uptodate.com. Accessed August 29, 2008.
7. US Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;148:759-765.
8. National Institutes of Health, US Department of Health and Human Services. *Diabetes in America*. 2nd ed. Bethesda, MD: National Diabetes Data Group of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995. NIH publication 95-1468.

Main Points

- In the United States, prevalence rates for gestational diabetes mellitus (GDM) are higher for African American, Hispanic, American Indian, and Asian women than for white women.
- Risk factors for GDM include a history of macrosomia, presence of polycystic ovarian syndrome, obesity, age older than 25, and persistent glucosuria.
- There is debate regarding the preferred screening protocol for GDM. Some experts recommend universal screening, whereas others exempt women who are at low risk.
- Data show that increasing levels of plasma glucose are associated with birth weight above the 90th percentile, cord blood serum C-peptide level above the 90th percentile, and, to a lesser degree, primary cesarean deliveries and neonatal hypoglycemia.
- The cornerstone of management is glycemic control. Quality nutritional intake is essential. Patients with GDM who cannot control their glucose levels with diet alone will require insulin.
- It is generally recommended that pregnancies complicated by GDM do not go beyond term.

9. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144:768-773.
10. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance: National Diabetes Data Group. *Diabetes*. 1979;28:1039-1057.
11. Metzger BE, Lowe LP, Dyer AR, et al; for HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991-2002.
12. Crowther CA, Hiller JE, Moss JR, et al; for Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med*. 2005;352:2477-2486.
13. Marion DW. Treatment and course of gestational diabetes mellitus. UpToDate Web site. http://www.uptodate.com. Accessed August 29, 2008.
14. Jovanovic-Peterson L, Peterson CM. Nutritional management of the obese gestational diabetic pregnant woman. *J Am Coll Nutr*. 1992;11:246-250.
15. Marion DW. Obstetrical management of pregnancy complicated by diabetes mellitus. UpToDate Web site. http://www.uptodate.com. Accessed August 29, 2008.
16. Aronovitz A, Metzger BE. IV gestational diabetes mellitus. *ACP Medicine*. 2006;29:5-7.
17. Rowan JA, Hague WM, Gao W, et al. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358:2003-2015.
18. Gavard JA, Artal R. Effect of exercise on pregnancy outcome. *Clin Obstet Gynecol*. 2008;51:467-480.
19. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol*. 2003;102:857-868.
20. Acker DB, Sachs BP, Friedman EA. Risk factors for shoulder dystocia. *Obstet Gynecol*. 1985;66:762-768.