Diagnosis and Management of Gestational Diabetes Mellitus

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Gestational diabetes occurs in 5 to 9 percent of pregnancies in the United States and is growing in prevalence. It is a controversial entity, with conflicting guidelines and treatment protocols. Recent studies show that diagnosis and management of this disorder have beneficial effects on maternal and neonatal outcomes, including reduced rates of shoulder dystocia, fractures, nerve palsies, and neonatal hypoglycemia. Diagnosis is made using a sequential model of universal screening with a 50-g one-hour glucose challenge test, followed by a diagnostic 100-g three-hour oral glucose tolerance test for women with a positive screening test. Treatment consists of glucose monitoring, dietary modification, exercise, and, when necessary, pharmacotherapy to maintain euglycemia. Insulin therapy is the mainstay of treatment, although glyburide and metformin may become more widely used. In women receiving pharmacotherapy, antenatal testing with nonstress tests and amniotic fluid indices beginning in the third trimester is generally used to monitor fetal well-being. The method and timing of delivery are controversial. Women with gestational diabetes are at high risk of subsequent development of type 2 diabetes. Lifestyle modification should therefore be encouraged, along with regular screening for diabetes. (*Am Fam Physician.* 2009;80(1):57-62. Copyright © 2009 American Academy of Family Physicians.)

▶ **Patient information:** A handout on gestational diabetes, written by the authors of this article, is available at http://www.aafp.org/afp/20090701/57-s1.html.

Evidence for screening, diagnosing, and managing gestational diabetes mellitus has continued to accrue over the past several years. In 2003, the U.S. Preventive Services Task Force[1] (USPSTF) and the Cochrane Collaboration[2] found insufficient evidence to recommend for or against screening for or treating gestational diabetes. However, a subsequent randomized controlled trial (RCT) found that screening and intervention for gestational diabetes were beneficial.[3] Nonetheless, in 2008, the USPSTF again concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for gestational diabetes, and therefore made no recommendation.[4] A recent observational study confirmed the association between increased maternal blood glucose and increased birth weight.[5] Further studies are needed to unequivocally support the benefit of universal screening, although most obstetric practices employ this strategy.[6]

Gestational diabetes is defined as carbohydrate intolerance that begins or is first recognized during pregnancy. In the United States, universal screening has been adopted by more than 90 percent of practices, according to the American College of Obstetricians and Gynecologists (ACOG).[6] Data suggest that a small percentage of women may be safely excluded from testing.[7] However, implementation of such modified screening criteria has proven difficult, and universal screening appears to offer better outcomes.[8] Risk factors for gestational diabetes include current glycosuria, diabetes in a first-degree relative, history of glucose intolerance (including previous gestational diabetes), marked obesity, and a previous infant with macrosomia.[9]

Screening

Expert consensus has put forth a sequential model of testing using a 50-g nonfasting one-hour glucose challenge test between 24 and 28 weeks' gestation. In contrast, women at high risk of gestational diabetes should be screened using the 50-g glucose challenge test at their first antepartum visit.[10] Screening cutoffs are 130 mg per dL (7.20 mmol per L; 90 percent sensitivity) or 140 mg per dL (7.75 mmol per L; 80 percent sensitivity).[9] The

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Universal screening for gestational diabetes is recommended by some experts, but the U.S. Preventive Services Task Force found the evidence insufficient to recommend universal screening.	C	3-5
In patients diagnosed with gestational diabetes, glucose monitoring should be undertaken using fasting and two-hour postprandial glucose levels to guide treatment.	C	10
Treatment with diet control or pharmacotherapy should be directed based on blood glucose levels.	C	10, 21
Antenatal testing (including ultrasonography, nonstress testing, and amniotic fluid indices) should be performed to monitor fetal status.	C	10
Women with gestational diabetes are at an increased risk of type 2 diabetes and should be screened postpartum at routine intervals.	C	34

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 1. Diagnostic Glucose Values for Gestational Diabetes in the United States

Diagnostic test	*Fasting (mg per dL [mmol per L])*	*One hour (mg per dL [mmol per L])*	*Two hours (mg per dL [mmol per L])*	*Three hours (mg per dL [mmol per L])*
100-g OGTT Carpenter and Coustan[15] (two or more abnormal)	95 (5.25)	180 (10.00)	155 (8.60)	140 (7.75)
75-g OGTT World Health Organization[16] (one or more abnormal)	126 (7.00)	—	140 (7.75)	—
75-g OGTT American Diabetes Association[17] (two or more abnormal)	95 (5.25)	180 (10.00)	155 (8.60)	—

OGTT = oral glucose tolerance test.

Information from references 14 through 17.

most recent American Diabetes Association (ADA)[11] and ACOG[6] guidelines recommend either cutoff. Random or fasting glucose measurement is not recommended for screening because of poor specificity.[12]

For women with a positive screening test, the 100-g three-hour oral glucose tolerance test is used to diagnose gestational diabetes. Although most organizations recommend a high-carbohydrate diet for up to three days before the test, a recent study showed that test results are not affected by modest variations in carbohydrate intake.[13] Gestational diabetes is diagnosed if two or more plasma glucose measurements meet or exceed the following thresholds: fasting level of 95 mg per dL (5.25 mmol per L), one-hour level of 180 mg per dL (10.00 mmol per L), two-hour level of 155 mg per dL (8.60 mmol per L), or three-hour level of 140 mg per dL *(Table 1*[14-17]*)*.[11] Other screening criteria are often used outside the United States. The World Health Organization recommends simultaneous screening and diagnosis using a 75-g oral glucose tolerance test. Although this approach almost doubles the number of patients diagnosed with gestational diabetes, there is no current evidence of additional clinical benefit.[18]

Antenatal Management

EVIDENCE FOR TREATMENT

Whereas some authorities question the clinical value of treating gestational diabetes,[14] recent data provide strong

evidence that treatment reduces adverse outcomes. The Australian Carbohydrate Intolerance Study in Pregnant Women randomized women to receive routine care or treatment for gestational diabetes.[3] Primary fetal outcomes included death, shoulder dystocia, bone fracture, and nerve palsy. Primary maternal outcomes were induction of labor and cesarean delivery. Infants of women in the treatment group had significantly fewer perinatal complications (relative risk [RR] = 0.33; 95% confidence interval [CI], 0.14 to 0.75). There were more labor inductions in the treatment group (RR = 1.36; 95% CI, 1.15 to 1.62), but the number of cesarean deliveries was similar in both groups. The results of this trial offer strong evidence that treatment of gestational diabetes improves fetal outcomes.

Further evidence of possible adverse effects associated with even mild maternal hyperglycemia comes from the Hyperglycemia and Adverse Pregnancy Outcomes trial.[5] In this study, investigators followed a group of 23,316 pregnant women at 24 to 32 weeks' gestation with fasting glucose levels of up to 105 mg per dL (5.85 mmol per L), and with levels of up to 200 mg per dL (11.10 mmol per L) after a 75-g glucose load. This cohort included women with glucose levels at the upper end of the normal range, as well as women with mild gestational diabetes. The investigators found a linear correlation between increasing maternal glucose levels and increasing birth weight, first-time cesarean delivery, fetal C peptide levels, and neonatal hypoglycemia.

TREATMENT STRATEGIES

It is difficult to provide definitive, evidence-based recommendations for postprandial glucose level goals.[13] However, two recent observational studies provided insight into glucose levels in pregnant women without gestational diabetes.[19,20] Average fasting maternal glucose levels in these studies were between 69 and 75 mg per dL (3.80 and 4.15 mmol per L), with one-hour postprandial glucose levels between 105 and 108 mg per dL (5.85 and 6.00 mmol per L). Current treatment goals are substantially higher than these levels and differ among expert organizations. These differences reflect the lack of head-to-head trials comparing treatment strategies.

Although there is no consensus regarding specific glucose targets *(Table 2[10])*, the timing of glucose testing is less controversial. Most authorities recommend measurement of fasting glucose combined with postprandial testing (one- or two-hour), in contrast with preprandial glucose monitoring, which has been associated with higher A1C levels, larger infants, and more cesarean deliveries.[21]

Table 2. Treatment Targets for Women with Gestational Diabetes

Test	*Glucose levels (mg per dL [mmol per L])*
Fasting	< 96 (5.35)
One-hour postprandial	< 140 (7.75)
Two-hours postprandial	< 120 to 127 (6.65 to 7.05)

Information from reference 10.

First-line therapy for women with gestational diabetes is dietary modification, often referred to as medical nutritional therapy. This is best done in consultation with an experienced nutritionist, and should take cultural preferences into account. Most programs involve carbohydrate counting, with meal- and snack-specific recommendations. Modifications in nutritional therapy are made based on patient preferences, amount (or lack) of weight gain, and glucose monitoring. Moderate exercise also may help in the management of gestational diabetes. Although medical nutritional therapy and exercise are safe, practical, and inexpensive interventions, their impact on patient outcomes has not been conclusively demonstrated in large RCTs.

Pharmacotherapy is indicated when medical nutritional therapy results in inadequate glucose control, lack of expected weight gain (as a result of calorie restriction), or when patients are consistently hungry. Pharmacotherapy is also indicated in the setting of elevated fasting glucose levels, because dietary modification has little effect on these levels. ACOG recommends insulin therapy for women receiving medical nutritional therapy whose fasting glucose level exceeds 95 mg per dL, whose one-hour postprandial glucose level exceeds 130 to 140 mg per dL, or whose two-hour postprandial glucose level exceeds 120 mg per dL (6.65 mmol per L).[6] The ADA describes upper boundary targets of 90 to 99 mg per dL (5.00 to 5.50 mmol per L) in the fasting state, less than 140 mg per dL one hour after eating, and less than 120 to 127 mg per dL (6.65 to 7.05 mmol per L) two hours after eating.[10]

Insulin is the first-line pharmacologic therapy for gestational diabetes. Most insulin regimens include intermediate-acting insulins, such as isophane (NPH), and short-acting insulins, such as regular recombinant (Humulin R) and the insulin analogues aspart (Novolog) and lispro (Humalog).

Although regular insulin is the most time-tested form of short-acting insulin, evidence supports the use of

short-acting insulin analogues in gestational diabetes.[22] The U.S. Food and Drug Administration categorizes lispro and aspart as class B drugs in pregnancy. However, ACOG and the ADA have yet to officially recommend their use. In contrast with lispro and aspart, there are little data on the use of the long-acting insulin analogues glargine (Lantus) and detemir (Levemir) in pregnancy. Thus, NPH is the intermediate-acting insulin of choice for women with gestational diabetes who require pharmacologic therapy.

Expert opinion guides insulin therapy because data from RCTs are lacking. Insulin is typically started at a dosage of 0.7 units per kg per day (based on prepregnancy weight), given in divided doses. A commonly used dosing strategy calls for two thirds of the total insulin dose to be given in the morning, with the remainder given before dinner. The morning dose should be two thirds NPH and one third short-acting insulin, and the pre-dinner dose should be equal parts NPH and short-acting insulin. However, this approach requires modification based on the patient's body mass index, glucose levels, and lifestyle.

Most patients who require insulin are euglycemic in labor and do not require active management of glucose levels.

A safe and effective oral agent for the treatment of gestational diabetes is highly desired. The sulfonylurea glyburide (formerly Micronase) is close to meeting these goals, with prospective[23] and retrospective[24] studies demonstrating its effectiveness and probable safety. Despite the available data, the absolute safety of glyburide is difficult to prove because of the relatively small number of patients in these studies.[25] Also, there is disagreement as to whether glyburide crosses the placenta.[26,27] Nevertheless, glyburide therapy is a viable alternative for women who are unable or unwilling to take insulin, and it is used in many practices as first-line therapy.

Metformin (Glucophage) may be another option for women with gestational diabetes. The Metformin in Gestational Diabetes (MiG) trial randomized 751 women with gestational diabetes to open treatment with metformin (plus insulin, if needed) or insulin alone.[28] The trial was designed as a noninferiority study; its purpose was to show that, compared with insulin, metformin is not associated with an increase in perinatal complications. A composite of several neonatal complications was a primary outcome. Although the results of this long-awaited study are encouraging, 46 percent of the women receiving metformin also required insulin therapy. It should also be noted that metformin crosses the placenta and that the MiG trial was not designed to identify the more effective drug. Despite these concerns, metformin appears to be poised for a new role in the treatment of gestational diabetes.

Fetal Surveillance

Fetal surveillance can be divided into screening for congenital anomalies, monitoring for fetal well-being, and ultrasound assessment for estimated fetal weight and macrosomia. The ADA recommends screening for congenital anomalies in women with gestational diabetes who present with evidence of preexisting hyperglycemia, such as an A1C level greater than 7 percent, a fasting glucose level greater than 120 mg per dL, or a diagnosis of gestational diabetes in the first trimester.[10] Women with these findings are more likely to have unrecognized pregestational diabetes and are therefore at higher risk of fetal malformation from exposure to hyperglycemia during organogenesis.

Monitoring for fetal well-being is generally based on local practice. The frequency of antenatal monitoring should reflect the patient's degree of metabolic control, the type of therapy she is receiving, and the presence of other risk factors (e.g., hypertension). ACOG recommends that women with gestational diabetes who are on insulin or who have poor glucose control have the same antenatal monitoring as women with pregestational diabetes.[6] This typically consists of twice-weekly nonstress testing, with amniotic fluid determinations beginning early in the third trimester.[29]

Intrapartum Management

Patients with diet-controlled gestational diabetes typically do not require active glucose management in labor; however, it is advisable to measure blood glucose levels on admission. In contrast, women who are taking medication for gestational diabetes require more frequent glucose monitoring, typically with hourly evaluations. Historically, these patients were treated with adjustable intravenous insulin infusions with dextrose-containing solutions.[30] However, most patients who require insulin are euglycemic in labor and do not require active management of glucose levels.[10]

DELIVERY

Preferred method and timing of delivery in women with gestational diabetes are determined by expert opinion because of the lack of definitive data. In the setting of gestational diabetes, macrosomia (i.e., estimated fetal weight greater than 4,500 g) serves as a surrogate marker

of adverse maternal and neonatal outcomes. One RCT compared patient outcomes with elective delivery (induction at 38 weeks' gestation) or elective cesarean delivery with expectant management to 42 weeks.[31] Although earlier delivery reduced the risk of macrosomia, it did not reduce rates of brachial plexus injuries, hypoglycemia, or clavicle fractures. However, given the limited statistical power of this study, additional data are needed to determine whether elective delivery improves outcomes in patients with gestational diabetes. A financial-based decision analysis argues against facilitated delivery; an estimated 443 elective cesarean deliveries need to be performed to prevent one case of brachial plexus injury, at a cost of $930,000 (in 1996).[32]

Based on the limited data, as well as the medicolegal climate, many physicians still opt to facilitate delivery before 39 weeks' gestation. If this option is chosen in the absence of maternal or fetal compromise, amniocentesis should be strongly considered to assess for fetal lung maturity.[6]

Postpartum Maternal Management

Most women with gestational diabetes do not require insulin therapy following delivery, although it is prudent to check glucose levels before discharge. Approximately 50 percent of women with gestational diabetes will develop type 2 diabetes within five to 10 years.[33] These women are also at risk of earlier gestational diabetes in subsequent pregnancies. Thus, regular screening for type 2 diabetes should be strongly encouraged. An oral glucose tolerance test at three-year intervals has been shown to be a cost-effective strategy for screening.[34] Because women with a history of gestational diabetes are at risk of type 2 diabetes, it also seems reasonable that the lifestyle recommendations of the Diabetes Prevention Program would be applicable.[35] Recommendations to promote postpartum weight loss and decrease the incidence of type 2 diabetes include breastfeeding, exercising at a moderate intensity for at least 150 minutes per week, and modifying the diet for specific weight-loss goals.[35]

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