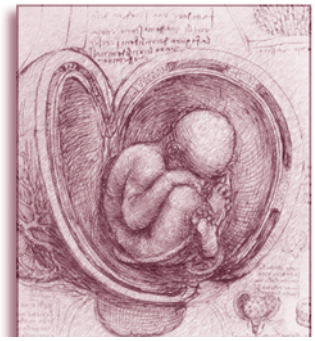

# *Diabetes in pregnancy*

JOSEPH N. BOTTALICO, DO

**Diabetes mellitus is one of the most common medical complications of pregnancy. Two percent to 5% of pregnancies are complicated by diabetes, of which 90% are classified as gestational diabetes mellitus. Prevention of the fetal and maternal complications of diabetes presents unique challenges to all providers of healthcare to reproductive-aged diabetic women. The management of diabetes before, during, and after pregnancy can serve as a model of preventive healthcare. Preconception counseling and metabolic control before pregnancy reduce the rate of congenital malformations and the burden of suffering in offspring.**

**(Key words: diabetes, pregnancy, preconception counseling, congenital malformations)**

Diabetes is one of the most common problems encountered by primary care physicians. Because it is inevitable that some diabetic patients under their care will become pregnant, physicians may be faced with issues of initial counseling and management until appropriate specialist referrals can be arranged.

Proper screening for gestational diabetes during pregnancy allows early recognition of women who often have a genetic predisposition to type 2 diabetes mellitus. This early identification should alert us to the need to provide preventive counseling on the importance of postpartum reclassification and long-term lifestyle modification strategies to reduce or delay the onset or complications of diabetes mellitus. Gestational diabetes can be thought of as early-onset type 2 diabetes in many women, especially those with a positive family history and an increased body mass with relative insulin resistance.[1] Planning for pregnancy, management during pregnancy, postpartum screening for type 2 diabetes, and lifelong lifestyle modifications form a continuum, providing an opportunity to prevent disease burden in women and their offspring.

Dr Bottalico is an associate professor of obstetrics and gynecology, University of Medicine and Dentistry of New Jersey–School of Osteopathic Medicine, Stratford, NJ.

Correspondence to Joseph N. Bottalico, DO, FACOOG, Specialty Care Center, Suite 2500, 42 E Laurel Rd, Stratford, NJ 08084-1504.

E-mail: *bottaljn@umdnj.edu*

## Gestational diabetes

*Gestational diabetes mellitus* (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of the need for insulin treatment or medical nutritional therapy alone. The definition also applies if glucose intolerance persists after pregnancy and includes the possibility that carbohydrate intolerance may have preceded pregnancy.[2] Six weeks or more after delivery, women should be reclassified according to the current American Diabetes Association criteria for the diagnosis of diabetes in nonpregnant adults. Although this reclassification can be done with measurement of fasting plasma glucose alone, the use of 75-g, 2-hour glucose tolerance testing confers a higher sensitivity. Until July 1997, the American Diabetes Association and the National Diabetes Data Group endorsed universal screening for GDM, but recent modifications recommend selective screening, because there are certain characteristics that confer a lower risk of development of glucose intolerance during pregnancy, leading to a lack of cost-effectiveness to screen such patients. The low-risk group comprises women who are younger than 25 years, who are of normal body weight, and who have no family history of diabetes in a first-degree relative and are not members of an ethnic or racial group with a high prevalence of diabetes. High prevalence groups include Hispanic, Native American, Asian, and African American women. Pregnant women who fulfill all these criteria need not be screened for GDM. In some centers, 10% or less of the pregnant population meet the low-risk criteria, and universal screening is still practiced, because the confusion and effort associated with deciding whom not to screen is inefficient. Other risk factors that are associated with an increased risk of gestational diabetes mellitus or undetected type 2 diabetes include the prior birth of a baby weighing 9 pounds or more, prior unexplained fetal anomalies, maternal obesity, and a positive family history in a first-degree relative. Symptoms of diabetes should certainly prompt diagnostic testing, regardless of risk factors.

Clinical recognition of GDM is generally accepted as important in the United States because therapy, including medical nutritional therapy, insulin when necessary, and antepartum fetal surveillance, can reduce GDM-associated perinatal morbidity and mortality. This view,[3] though endorsed by the American Diabetes Association, is by no means universal. Critics of GDM screening argue that solid, level 1 evidence demonstrating that screening leads to improved perinatal outcomes is lacking.

Pregnant women who are candidates for screening and have not had diabetes diagnosed before the 24th week should have a screening glucose load between 24 and 28 weeks, consisting of 50 g of oral glucose given without regard to the time of the last meal or time of day. Venous plasma or serum glucose is measured 1 hour later. A value of greater than or equal to 140 mg/dL is recommended as a threshold to indicate the need for a full diagnostic 3-hour, 100-g oral glucose tolerance test. The 140 mg/dL cutoff has 80% sensitivity and 90% specificity for the diagnosis of GDM. Using a cutoff of 130 mg/dL for the 1-hour screen increases the sensitivity to 90%, but leads to the need for 3-hour testing of 23% of patients screened, as opposed to 14%, with a subsequent increase in the false-positive rate. A positive 3-hour test requires two or more abnormal values using diagnostic criteria derived from the National Diabetes Data Group, modified by Carpenter and Coustan and endorsed by the American Diabetes Association (*Table 1*).[4]

## Treatment

In the past, the need for insulin in patients with gestational diabetes was an indication for hospitalization. Such is no longer necessary because many of these patients can be managed on an outpatient basis, especially when an aggressive team can be assembled. Hospitalization is reserved for those who are inappropriate candidates for outpatient therapy because of psychosocial barriers, recurrent hypoglycemia, or other medical or obstetric complications.

Treatment decisions are made initially based on the fasting component of the 3-hour oral glucose tolerance test, which, if elevated above 95 mg/dL, usually indicates the need for insulin, as opposed to a trial of medical nutritional therapy to control blood sugar levels. If the fasting plasma glucose level is below 95 mg/dL, then medical nutrition therapy is recommended, and ideally, the patient should be counseled by a dietitian or certified diabetes educator. The general caloric prescription is based on the woman's body weight as well as cultural and lifestyle factors. Women who weigh 80% to 120% of their ideal body weight can be given 30 kilocalories per kilogram of body weight per day, with reduced caloric intake for obese women. Calories are then divided into three meals or meals plus snacks, composed of:

- 45% carbohydrates, with attention to fiber content,
- 20% protein, and
- 35% to 40% fat.

Calories are distributed to provide 10% with breakfast, 20% to 30% percent with lunch, 30% to 40% with dinner, and 20% to 30% with snacks. The effectiveness of medical nutritional therapy should be assessed over at least 2 weeks before determining the possible need for insulin. Effectiveness is determined by self-monitoring of blood glucose levels, ideally using plasma-referenced meters with values checked four times a day, that is, fasting, and 1 or 2 hours after each meal. Glycemic thresholds are:

- fasting blood sugar levels, 60 mg/dL to 95 mg/dL,
- 2-hour postprandial blood sugar levels less than 120 mg/dL, and
- 1-hour postprandial blood sugar levels less than 130 mg/dL to 140 mg/dL (*Table 2*).

If adequate control is not achieved with diet alone, then insulin therapy should be started. All women started on insulin therapy for the first time should be given human insulin as it is less immunogenic than animal insulin. Insulin dosage formulas vary, depending on whether the patient has type 1 or type 2 preexisting diabetes, or whether the patient has GDM. Women with GDM requiring insulin tend to have significant insulin resistance, especially if obese. Although 0.7 U/kg to 1.0 U/kg, depending on stage of pregnancy, is frequently recommended for GDM, individual needs vary considerably and the risks of hypoglycemia are real, so it is recommended to start slowly. Women who have only fasting hyperglycemia may need just one dose of intermediate-acting insulin (isophane insulin [neutral protein Hagedorn; NPH]) at bedtime, using a formula of 0.2 U/kg (for example, a woman weighing 70 kg would be given 14 units of NPH at roughly 10 PM in an attempt to control fasting blood sugar levels). Women with fasting and postprandial hyperglycemia will generally need multiple doses, with two thirds of the daily dose given in the morning and one third in the evening. The morning dose is further split with two thirds given as prebreakfast intermediate-acting, NPH insulin, and one third as prebreakfast regular insulin. The evening dose can be split between 50% predinner regular insulin and 50% intermediate-acting, NPH insulin at bedtime. The use of the insulin analog lispro has been studied in gestational diabetes and has been found to be safe.[5] Premeal administration of insulin lispro has the advantage of a more rapid onset of action and greater control of postprandial hyperglycemia and shares immunogenicity characteristics with human regular insulin. Individual needs vary, and further dosing manipulations are often necessary, especially as pregnancy advances and insulin resistance increases as the result of high levels of circulating human placental lactogen. Treatment goals for GDM include a reduction in the risk of fetal macrosomia, with attendant decreased risk of birth trauma and neonatal hypoglycemia. Suboptimal metabolic control during pregnancy, even with GDM, has also been associated with childhood obesity, increased blood pressures, and impaired glucose tolerance, and it may even have long-term neurodevelopmental consequences.

The incidence of fetal demise in well-controlled class A, or diet-controlled gestational diabetes, is sufficiently low that weekly fetal surveillance tests such as nonstress tests, need not be started until 40 weeks. If there is any uncertainty about the degree of metabolic control, or if ultrasound reveals polyhydramnios or fetal macrosomia, non-stress tests are recommended because fetal hyperglycemia may not always be detected by monitoring maternal blood sugar levels alone. Fetal

**Table 1**
**American Diabetes Association–Endorsed Diagnostic Criteria for Gestational Diabetes Mellitus, Venous Plasma Concentrations After a 100-Gram Oral Glucose Load*[4]**

| Interval | Plasma glucose concentration | |
|---|---|---|
| | mg/dL | mmol/dL |
| Fasting | 95 | 5.3 |
| 1 Hour post oral glucose load | 180 | 10.0 |
| 2 Hours post oral glucose load | 155 | 8.6 |
| 3 Hours post oral glucose load | 140 | 7.8 |

*Two or more venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 hours and after at least 3 days of unrestricted diet (at least 150 g of carbohydrate per day) and unlimited physical activity. The patients should remain sitting and should not smoke during the test.

**Table 2**
**Glycemic Goals in Pregnancy—Gestational Diabetes Mellitus**

| Interval | Blood sugar level, mg/dL |
|---|---|
| Fasting | 60 to 95 |
| 2 Hours postprandial | 70 to 120 |
| 1 Hour postprandial | <130 to 140 |

hyperglycemia causes impaired red blood cell oxygen release and increases the risk of intrauterine fetal demise.

Alternative modes of therapy for gestational diabetes include exercise,[6] with some small studies demonstrating elimination of the need for insulin in women who underwent non–weight-bearing, nonimpact, regular exercise three times a week using devices such as a recumbent bicycle or arm ergometer. Not all studies examining exercise in gestational diabetes have revealed a substantial benefit, however.

Oral hypoglycemic agents in pregnancy have long been contraindicated in the United States because agents such as first-generation sulfonylureas cross the placenta and have been associated with profound and prolonged neonatal hypoglycemia. An expanded selection of oral antidiabetic agents is available currently, and the mechanisms of actions of these agents may confer safety and efficacy in pregnancy. A recent study published in *The New England Journal of Medicine* in October 2000[7] involved 404 women with GDM that required treatment. They were randomly assigned between 11 and 33 weeks' gestation to receive glyburide or insulin. Glyburide is a second-generation sulfonylurea that does not cross the placenta. Both groups achieved good glycemic control, and there were no significant differences between the glyburide- and insulin-treated groups in the percentage of macrosomic infants, neonatal lung complications, neonatal hypoglycemia, or admission to a neonatal intensive care unit. Cord serum insulin concentrations were similar in the two groups, and glyburide was not detected in the cord serum of any infant whose mother received that drug. The American Diabetes Association's 2001 position statement on Gestational Diabetes Mellitus[2] contains the following statement:

> Glyburide is not FDA approved for the treatment of gestational diabetes and further studies are needed in a larger patient population to establish its safety.

## Preconception care

Prepregnancy diabetes can be a model for preventive care. The greatest opportunity to prevent congenital malformations in the offspring of women with pregestational diabetes is through the provision of preconception care. This care is best accomplished by a multidisciplinary team approach, which often includes:

- ☐ a diabetologist,
- ☐ internist or primary care physician,
- ☐ obstetrician or maternal-fetal medicine subspecialist,
- ☐ certified diabetes educators,
- ☐ dietitians, and
- ☐ nurses of various practice levels.

Other subspecialists often need to be involved in the care of these women, including nephrologists, ophthalmologists, and cardiologists, with the team approach before, during, and after pregnancy. Their involvement is necessitated by the complex and far-reaching ramifications of diabetes with issues that transcend any one specialty or discipline. Primary care physicians should carefully consider whether resources and experience for such specialized care exist in their own practice or community, or whether referral to an experienced program is the most appropriate decision. All healthcare providers have the opportunity, however, to at least discuss the principles of preconception care and to begin to empower the patient to play an active role—ultimately, the most important role—in the team approach to diabetes in pregnancy. Preconception care also needs to include an assessment of the patient for various vascular complications such as nephropathy, hypertension, retinopathy, cardiovascular disease, and, less commonly, neuropathies.[4]

Although the percentages are rising, some studies have shown that less than 20% of women with diabetes seek preconception counseling or diabetes control. Preconception control has been convincingly associated with a significant reduction in serious, life-threatening, and often debilitating congenital malformations. Delaying pregnancy until hemoglobin $A_{1c}$ levels are in a low-risk category and after women have had a full examination and treatment of vascular complications makes sense medically and economically. Hemoglobin $A_{1c}$ levels less than 7.9% of total hemoglobin have been associated with a decreased incidence of congenital anomalies.[8] In fact, hemoglobin $A_{1c}$ less than 6.0 SD above the mean in certain populations has been associated with a decreased anomaly rate. In nonpregnant women, hemoglobin $A_{1c}$ values of less than 6.0% of total hemoglobin are considered ideal, but aiming for such levels prior to pregnancy may lead to unacceptable risks from maternal hypoglycemia. I usually counsel patients to aim for a hemoglobin $A_{1c}$ level of less than 7.0%, as long as hypoglycemic episodes are not frequent or severe.

The etiology of diabetic embryopathy is multifactorial[8] and probably involves an interaction between genetic susceptibility factors and alterations in gene expression that are induced by some of the metabolic alterations of uncontrolled diabetes. Reece and Homko[8] demonstrated the importance of early yolk sac metabolism in the reduction of diabetes-related birth defects in animals. Oxidative stresses may also play a significant role, and, in animal studies, antioxidants have been found to reduce the rate of diabetes-related congenital malformations. Folic acid is well known as a preventive measure for neural tube defects, but further studies may lead to recommendations for antioxidants such as vitamin E to reduce congenital malformations in offspring of women with pregestational diabetes.

## Diabetic vascular complications and pregnancy

Preconception medical assessment should include a blood urea nitrogen level, creatinine level, and 24-hour urine collection to evaluate for microalbuminuria, total protein, and creatinine clearance. A dilated eye examination by an ophthalmologist or retinal specialist is also recommended in women with pregestational diabetes. Background retinopathy is not worrisome or progressive in pregnancy, but proliferative retinopathy, which is often transiently worsened by tight glycemic control in early pregnancy, is a risk factor for vision-threatening complications. Pregnancy per se is an independent risk factor for worsening of diabetic proliferative retinopathy, with the rate of progression accelerated by hypertension and hyperglycemia, thus the importance of controlling these two variables as much as possible. Significant neovascularization should be treated if present, preferably before pregnancy.

Women with diabetic nephropathy need to be managed carefully, because there are significant risks of worsening hypertension, superimposed preeclampsia, fetal growth restriction, and the need for preterm delivery based on fetal or maternal considerations.[9] Factors that are associated with an increased risk of perinatal death or birth weight less than 1100 g include proteinuria exceeding 3 g in 24 hours, an initial serum creatinine level greater than 1.5 mg/dL, anemia with a hematocrit of less than 25%, and hyper-

tension. Fortunately, the risk of pregnancy-induced progression to end-stage renal disease is low, around 6%, and many women experience only transient declines in renal function induced by pregnancy. Women with diabetic nephropathy need to have careful management of their hypertension. Although ACE inhibitors are contraindicated, calcium channel blockers represent an acceptable alternative, but these decisions need to be made in conjunction with the patient's nephrologist. Excess dietary protein loads are to be avoided as they may accelerate diabetic nephropathy.

Medical nutritional therapy needs to be reinforced during pregnancy, and consultation with dietitians or certified diabetes educators is recommended. The principles of carbohydrate counting are useful when determining insulin doses and distribution and allow for greater flexibility in insulin dosing and glycemic control when women have lifestyles that do not allow meals at "conventional" times.

Diabetic ketoacidosis (DKA) is a life-threatening complication for mother and fetus, and specific treatment protocols need to be readily available. Detailed DKA treatment guidelines are beyond the scope of this article. It should be kept in mind that pregnant type 1 diabetics can have DKA develop at much lower plasma glucose levels than nonpregnant control subjects. Diabetic ketoacidosis can occur with blood sugar levels in the mid to upper 200-mg/dL range in susceptible pregnant type 1 diabetics. Hyperosmolar nonketotic complications also require prompt recognition and intensive treatment.

## Antepartum fetal surveillance, labor, and delivery

Prepregnancy diabetes, especially that which is insulin-requiring, is associated with an increased perinatal mortality rate and is a strong indication for antepartum fetal surveillance testing. Serial evaluation of fetal growth in the third trimester as well as non-stress tests and biophysical profiles are used to prevent fetal death in utero and to identify the fetus that is adversely affected by maternal metabolic derangements. Earlier in gestation, targeted fetal sonography is necessary to identify major congenital anomalies, especially cardiac malformations.

Women who require high insulin doses, especially those with type 1 diabetes who are prone to ketosis, need to have careful glycemic control during labor and delivery. Morning NPH should be withheld if induction of labor is anticipated. The caloric requirements of labor require sufficient glucose availability. Glucose requirements are approximately 5 g/h to 10 g/h in active labor, or 2.0 mg/kg/min to 2.5 mg/kg/min. Ten percent glucose solutions may be necessary to provide adequate metabolic fuel together with an insulin drip to allow glucose utilization and to prevent DKA and neonatal hypoglycemia. An insulin drip should be started at 1 U/h and titrated according to fingerstick glucose values. Twenty-five units of regular insulin diluted in 250 mL of isotonic sodium chloride solution (1 U/10 mL) can be used, with titration based on fingerstick glucose values. Blood sugar levels should be maintained between 70 mg/dL and 140 mg/dL in labor. Postpartum, insulin requirements usually fall significantly, and somewhat looser glycemic control is acceptable in the immediate postpartum period.

## References


**1.** Langer O. Management of gestational diabetes. *Clin Obstet Gynecol* 2000;43(1):106-115.

**2.** Diabetes Care, Volume 24 Supplement 1 . American Diabetes Association: Clinical Practice Recommendations 2001: Position Statement: Gestational Diabetes. Accessed at *http://journal.diabetes.org/FullText/Supplements/DiabetesCare/Supplement101/S77.htm*

**3.** Coustan D. Making the diagnosis of gestational diabetes. *Clin Obstet Gynecol* 2000;43(1):99-105.

**4.** *Diabetes Care* Volume 24 Supplement 1 . American Diabetes Association: Clinical Practice Recommendations 2001. Position Statement: Preconception care of women with diabetes. Available at: http://journal.diabetes.org/FullText/Supplements/DiabetesCare/Supplement101/S66.htm. Accessed February 1, 2001.

**5.** Jovanovic L, Ilic S, Pettitt DJ, Hugo K, Guitierrez M, Bowsher RR, et al. Metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care* 1999;22:1422-1427.

**6.** Carpenter M. The role of excercise in pregnant women with diabetes mellitus. *Clin Obstet Gynecol* 2000;43(1):56-64.

**7.** Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343:1134-1138.

**8.** Reece A, Homko C. Why do diabetic women deliver malformed infants? *Clin Obstet Gynecol* 2000;43:32-45.

**9.** Miodovnik M, Rosenn BM, Khoury JC, Grigsby JL, Siddigi TA. Does pregnancy increase the risk for development and progression of diabetic nephropathy. *Am J Obstet Gynecol* 1996;174:1180-1189; discussion 1189-1191.