Gestational Diabetes

Abnormal maternal glucose regulation occurs in 3-10% of pregnancies, and gestational diabetes mellitus (GDM), which is defined as glucose intolerance of variable degree with onset or first recognition during pregnancy, accounts for 90% of cases of diabetes mellitus (DM) in pregnancy. However, the rising prevalence of diabetes mellitus—21 million people (7% of the population) have some form of diagnosed diabetes[1] ; another 6 million people may be undiagnosed[2] —particularly type 2 among women of childbearing age in the United States, has resulted in increasing numbers of pregnant women with preexisting diabetes. Currently, type 2 diabetes mellitus accounts for 8% of cases of diabetes mellitus in pregnancy, and preexisting diabetes mellitus now affects 1% of all pregnancies.

A study by Stuebe et al found that gestational diabetes mellitus and impaired glucose tolerance during pregnancy are associated with persistent metabolic dysfunction at 3 years after delivery, separate from other clinical risk factors.[3] A study by O’Reilly et al concluded that gestational insulin use, non-European ethnicity, a family history of type 2 diabetes mellitus, and an elevated body mass index (BMI) were factors associated with persistent dysglycemia in women who have had gestational diabetes mellitus. The study also concluded that breastfeeding may provide beneficial metabolic effects in women with gestational diabetes mellitus and should be recommended.[4]

In addition, medical interventions during pregnancy may increase the likelihood of developing gestational diabetes. A study reported in 2007 demonstrated an increased incidence of gestational diabetes mellitus in women receiving prophylactic 17 alpha-hydroxyprogesterone caproate for the prevention of recurrent preterm delivery (from 4.9% in controls to 12.9% in treated patients).[5]

Gestational diabetes in minority populations

The prevalence of gestational diabetes is strongly related to the patient's race and culture. Prevalence rates are higher in black, Hispanic, Native American, and Asian women than in white women. For example, typically, only 1.5-2% of white women develop gestational diabetes mellitus, whereas Native Americans from the southwestern United States may have rates as high as 15%. In Hispanic, black, and Asian populations, the incidence is 5-8%.

In these high-risk populations, the recurrence risk with future pregnancies has been reported to be as high as 68%.[6] In addition, approximately one-third will develop overt diabetes mellitus within 5 years of delivery, with higher-risk ethnicities having risks nearing 50%.[7]

Race also influences many complications of diabetes mellitus in pregnancy. For instance, black women have been shown to have lower rates of macrosomia, despite similar levels of glycemic control. Conversely, Hispanic women...
have higher rates of macrosomia and birth injury than women of other ethnicities, even with aggressive management.\textsuperscript{[8, 9]}

**Infants of mothers with maternal hyperglycemia**

Infants of mothers with preexisting diabetes experience double the risk of serious injury at birth, triple the likelihood of cesarean delivery, and quadruple the incidence of newborn intensive care unit (NICU) admission. Studies indicate that the risk of these morbidities is directly proportional to the degree of maternal hyperglycemia.

In gestational diabetes mellitus, OGTT gut glucose absorption is markedly lowered. Thus hyperglycemia of pregnancy does not result from too rapid or increased glucose absorption.\textsuperscript{[10]}

The excessive fetal and neonatal morbidity attributable to diabetes in pregnancy should be considered preventable with early diagnosis and effective treatment therapies. Guidelines have been established for the screening of pregnant women (see Screening for Diabetes Mellitus during Pregnancy) and for tailoring treatment to the unique needs of pregnancy.

**Maternal education on gestational diabetes**

Education is the cornerstone of effective metabolic management of the patient with diabetes during pregnancy. The American Diabetes Association (ADA) offers educational curricula specific to each type of diabetes encountered during pregnancy (type 1, type 2, gestational), specifically organized around each phase of pregnancy. This information can be transmitted to the patient by office staff and labor/delivery nurses. However, specially trained and certified nurses and dietitians (ie, certified diabetes educators) are the most effective in this regard.

For more information, see Diabetes Type 1 and Diabetes Type 2.

**Maternal-Fetal Metabolism in Normal Pregnancy**

In the pregnant woman, each meal sets in motion a complex series of hormonal actions, including a rise in blood glucose and the secondary secretion of pancreatic insulin, glucagon, somatomedins, and adrenal catecholamines. These adjustments ensure that an ample, but not excessive, supply of glucose is available to the mother and fetus.

Compared with nonpregnant subjects, pregnant women tend to develop hypoglycemia (plasma glucose mean = 65-75 mg/dL) between meals and during sleep. This occurs because the fetus continues to draw glucose across the placenta from the maternal bloodstream, even during periods of fasting. Interprandial hypoglycemia becomes increasingly marked as pregnancy progresses and the glucose demand of the fetus increases.

Levels of placental steroid and peptide hormones (eg, estrogens, progesterone, and chorionic somatomammotropin) rise linearly throughout the second and third trimesters. Because these hormones confer increasing tissue insulin resistance as their levels rise, the demand for increased insulin secretion with feeding escalates progressively during pregnancy. By the third trimester, 24-hour mean insulin levels are 50% higher than in the nonpregnant state.

**Maternal-Fetal Metabolism in Diabetes**

If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results. This typically manifests as recurrent postprandial hyperglycemic episodes. These postprandial episodes are the most significant source of the accelerated growth exhibited by the fetus.

Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia. Fetal hyperinsulinemia promotes excess nutrient storage, resulting in macrosomia. The energy expenditure associated with the conversion of excess glucose into fat causes depletion in fetal oxygen levels.

These episodes of fetal hypoxia are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red cell hyperplasia, and increased hematocrit. Polycythemia (hematocrit >65%) occurs in 5-10% of newborns of diabetic mothers. This finding appears to be related to the level of glycemic control and is mediated by decreased fetal oxygen tension. High hematocrit values in the neonate lead to vascular sludging, poor circulation, and postnatal hyperbilirubinemia.

During a healthy pregnancy, mean fasting blood sugar levels decline progressively to a remarkably low value of 74 ±
Meticulous replication of the normal glycemic profile during pregnancy has been demonstrated to reduce the macrosomia rate. Specifically, when 2-hour postprandial glucose levels are maintained below 120 mg/dL, approximately 20% of fetuses demonstrate macrosomia. If postprandial levels range up to 160 mg/dL, macrosomia rates rise to 35%.

Maternal Morbidity

Diabetic retinopathy

Diabetic retinopathy is the leading cause of blindness in women aged 24-64 years. Some form of retinopathy is present in virtually 100% of women who have had type 1 diabetes for 25 years or more; of these women, approximately 1 in 5 is legally blind. A prospective study showed that although half the patients with preexisting retinopathy experienced deterioration during pregnancy, all the patients had partial regression following delivery and returned to their prepregnant state by 6 months postpartum.

Other studies have suggested that rapid induction of glycemic control in early pregnancy stimulates retinal vascular proliferation. However, when the total effect of pregnancy on ophthalmologic status was considered, progression of retinopathy was slower in pregnant than in nonpregnant women, probably because the modest deterioration in retinal status during rapid improvement in control is offset by the excellent control during the remainder of the pregnancy.

Consider an ophthalmologic evaluation in the first trimester.

Renal disease

In general, patients with underlying nephropathy can expect varying degrees of deterioration of renal function during a pregnancy. As renal blood flow and glomerular filtration rate increase 30-50% during pregnancy, the degree of proteinuria will also increase.

The most recent studies indicate that pregnancy does not measurably alter the time course of diabetic renal disease, nor does it increase the likelihood of progression to end-stage renal disease. Regardless of pregnancy, the progression to renal disease in diabetic patients appears to be related to duration of diabetes and degree of glycemic control. A randomized study in 36 patients with insulin-dependent diabetes who had microalbuminuria found that after 2 years, none of the patients who had strict metabolic control with a subcutaneous insulin pump progressed to clinical nephropathy. Among study patients receiving conventional treatment, which was associated with higher mean glucose levels, 5 patients progressed to clinical nephropathy.

Perinatal complications are greatly increased in patients with diabetic nephropathy. Preterm birth, intrauterine growth restriction, and preeclampsia are all significantly more common.

A systematic review and meta-analysis by Deshpande et al found that although pregnancy is feasible in women after kidney transplantation, complications are relatively high and should be considered in both patient education and clinical decision making.

Elevated blood pressure

Chronic hypertension complicates approximately 1 in 10 diabetic pregnancies overall. Women with gestational diabetes are at a significantly higher risk of developing hypertension after the index pregnancy. Patients with underlying renal or retinal vascular disease are at a substantially higher risk, with 40% having chronic hypertension. Patients with chronic hypertension and diabetes are at increased risk of intrauterine growth restriction, superimposed preeclampsia, abruptio placenta, and maternal stroke.

Preeclampsia consists of abrupt elevation in blood pressure, significant proteinuria, and plasma uric acid levels greater than 6 mg/dL or evidence of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Preeclampsia is more frequent among women with diabetes (approximately 12%) versus the nondiabetic population (8%). The risk of preeclampsia also increases with maternal age and the duration of preexisting diabetes. In patients who have chronic hypertension coexisting with diabetes, preeclampsia may be difficult to distinguish from near-term blood pressure elevations.
The rate of preeclampsia has been found to correlate with the level of glycemic control: In one study, when the fasting plasma glucose (FPG) was < 105 mg/dL, the rate of preeclampsia was 7.8%; with an FPG >105 mg/dL, the rate of preeclampsia was 13.8%. In this same study, pregravid body mass index (BMI) was also significantly related to the development of preeclampsia.

Fetal Morbidity

Miscarriage

In all women with preexisting diabetes mellitus, there is a 9-14% rate of miscarriage. Current data suggest a strong association between the degree of glycemic control before pregnancy and the miscarriage rate. Suboptimal glycemic control has been shown to double the miscarriage rate in women with diabetes. A correlation also exists between more advanced diabetes and miscarriage rates. Patients with long-standing (>10 y) and poorly controlled diabetes (glycohemoglobin exceeding 11%) have been shown to have a miscarriage rate of up to 44%. Conversely, excellent glycemic control normalizes the miscarriage rate.

Birth defects

Among the general population, major birth defects occur in 1-2% of the population. In women with overt diabetes and suboptimal glycemic control before conception, the likelihood of a structural anomaly is increased 4- to 8-fold.

Although initial reports demonstrated anomaly rates as high as 18% in women with preexisting diabetes mellitus,[16] more recent studies, in patients who received more aggressive preconception and first trimester management, report anomaly rates between 5.1 and 9.8%.[17, 18]

Two-thirds of birth anomalies involve the cardiovascular and central nervous systems. Neural tube defects occur 13-20 times more frequently in diabetic pregnancies, and genitourinary, gastrointestinal, and skeletal anomalies are also more common.

It is notable that no increase in birth defects occurs among the offspring of fathers who have diabetes or the offspring of women who develop gestational diabetes after the first trimester. This suggests that periconceptional glycemic control is the main determinant of abnormal fetal development in diabetic women.

When the frequency of congenital anomalies in patients with normal or high first-trimester maternal glycohemoglobin values was compared to the frequency in healthy patients, the rate of anomalies was only 3.4% with glycosylated hemoglobin values (HbA1C) of less than 8.5%, versus 22.4% with poorer glycemic control in the periconceptional period (HbA1C >8.5%). An overall malformation rate of 13.3% was reported in 105 patients with diabetes, but the risk of delivering a malformed infant was comparable to a normal population when the HbA1C was less than 7%. More recently, in a review of 7 cohort studies, researchers found that patients with a normal glycohemoglobin (0 SD above normal), the absolute risk of an anomaly was 2%. At 2 SD above normal, this risk was 3%, with an odds ratio of 1.2 (1.1- 1.4). As the glycohemoglobin increased so did the risk for malformation, in a direct relationship.[20]

Clinical trials of intensive metabolic care have demonstrated that malformation rates similar to those in the nondiabetic population can be achieved with meticulous preconceptional glycemic control.[18] Subsequent trials comparing a preconceptional intensive metabolic program to standard treatment have demonstrated lowered rates of perinatal mortality (0% vs 7%) and congenital anomalies (2% vs 14%). In addition, when the preconceptional counseling program was discontinued, the congenital anomaly rate increased by over 50%.[21]

Growth restriction

Although most fetuses of diabetic mothers exhibit growth acceleration, growth restriction occurs with significant frequency in pregnancies in women with preexisting type 1 diabetes. The most important predictor of fetal growth restriction is underlying maternal vascular disease. Specifically, pregnant patients with diabetes-associated retinal or renal vasculopathies and/or chronic hypertension are most at risk for growth restriction.

Obesity

Excessive body fat stores, stimulated by excessive glucose delivery during diabetic pregnancy, often extends into childhood and adult life. Maternal obesity, common in type 2 diabetes, appears to significantly accelerate the risk of
infants being LGA. Approximately 30% of fetuses of women with diabetes mellitus in pregnancy are large for gestational age (LGA). In preexisting diabetes mellitus, this incidence appears to be slightly higher (38%).[8]

In women with gestational diabetes, weight gain during pregnancy that exceeds Institute of Medicine (IOM) weight-gain guidelines increases the risk of preterm delivery, of having a newborn who is LGA, and of requiring a cesarean delivery.[22] The chance that a newborn would be small for gestational age (SGA) was greater among women with gestational diabetes whose weight gain was below the IOM guidelines.

Plotting of serial ultrasonographic examination findings from diabetic fetuses shows that the growth velocity of the abdominal circumference is often well above the growth percentiles seen in nondiabetic fetuses, and it is higher than the fetal head and femur percentiles. The growth of the abdominal circumference begins to rise significantly above normal after 24 weeks.

**Macrosomia**

Macrosomia is typically defined as a birth weight above the 90th percentile for gestational age or greater than 4000 g. Macrosomia occurs in 15-45% of babies born to diabetic women, a 3-fold increase from normoglycemic controls.

Maternal obesity has a strong and independent effect on fetal macrosomia. Birth weight is largely determined by maternal factors other than hyperglycemia, with the most significant influences being gestational age at delivery, maternal prepregnancy body mass index (BMI), maternal height, pregnancy weight gain, the presence of hypertension, and cigarette smoking.

When women who are very obese (weight >300 lb) were compared with women of normal weight, the newborns of obese women had more than double the risk of macrosomia compared to those of women of normal weight.[23] This may explain the failure of glycemic control to completely prevent fetal macrosomia in several series.

Excess nutrient delivery to the fetus causes macrosomia and truncal fat deposition, but whether fasting or peak glucose values are more correlated with fetal overgrowth is less clear. Data from the Diabetes in Early Pregnancy project indicate that fetal birth weight correlates best with second- and third-trimester postprandial blood sugar levels and not with fasting or mean glucose levels.[24] When postprandial glucose values average 120 mg/dL or less, approximately 20% of infants can be expected to be macrosomic. When postprandial levels range as high as 160 mg/dL, macrosomia rates can reach 35%.

Macrosomia is associated with excessive rates of neonatal morbidity, as illustrated by a study by Hunter et al in 1993, in which the infants of diabetic mothers had 5-fold higher rates of severe hypoglycemia, a 4-fold increase in macrosomia, and a doubled increase in neonatal jaundice relative to infants of mothers without diabetes.[25]

The macrosomic fetus in diabetic pregnancy develops a unique pattern of overgrowth, involving central deposition of subcutaneous fat in the abdominal and interscapular areas.[26] Skeletal growth is largely unaffected.

Neonates of diabetic mothers have a larger shoulder and extremity circumference, a decreased head-to-shoulder ratio, significantly higher body fat, and thicker upper extremity skin folds compared with nondiabetic control infants of similar weights. Because fetal head size is not increased during poorly controlled diabetic pregnancy, but shoulder and abdominal girth can be markedly augmented, the risk of injury to the fetus after delivery of the head (eg, Erb palsy) is significantly increased. Thus, birth injury, including shoulder dystocia and brachial plexus trauma, are more common among infants of diabetic mothers, and macrosomic fetuses are at the highest risk.

More recent data from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial demonstrated a positive relationship between severity of maternal fasting hyperglycemia and risk of shoulder dystocia, with a 1 mmol increase in fasting glucose leading to a 2.09 relative risk for shoulder dystocia.[27]

In addition, there appears to be a role for excessive fetal insulin levels in mediating accelerated fetal growth. In the study by Simmons et al which compared umbilical cord sera in infants of diabetic mothers and controls, the heavier, fatter babies from diabetic pregnancies were also hyperinsulinemic.[28]

**Metabolic syndrome**

The adverse downstream effects of abnormal maternal metabolism on the offspring have been documented well into puberty. Glucose intolerance and higher serum insulin levels are more frequent in children of diabetic mothers than
in normal controls. By age 10-16 years, offspring of diabetic pregnancy have a 19.3% rate of impaired glucose intolerance.[29]

A study by Patel et al found that maternal pregnancy glycosuria, gestational diabetes, and existing diabetes demonstrate some association with higher offspring fasting glucose and insulin; however, little evidence suggests an association between maternal diabetes or glycosuria with offspring lipids, blood pressure, and C-reactive protein.[30]

The childhood metabolic syndrome includes childhood obesity, hypertension, dyslipidemia, and glucose intolerance. A growing body of literature supports a relationship between intrauterine exposure to maternal diabetes and risk of a metabolic syndrome later in life.[31, 32] Fetuses of diabetic women that are born large for gestational age appear to be at the greatest risk.[32]

**Cardiovascular risk factors**

An associational study examined the effect on maternal diabetes in utero and cardiovascular risk factors in offspring.[33] Offspring born to mothers with diabetes exhibited higher levels of biomarkers for endothelial damage and inflammation, as well as higher leptin levels, BMI, waist circumference, and systolic blood pressure and decreased adiponectin levels. The association remained significant when controlling for maternal prepregnancy BMI.

**Neurocognitive development**

In a study of 212 preschool children, Nomura et al found that maternal GDM and low socioeconomic status were associated with an increased risk for attention-deficit/hyperactivity disorder (ADHD) at age 6 and that children exposed to both GDM and low socioeconomic status were at even greater risk for ADHD and also at increased risk for compromised neurobehavioral functioning. {Ref88}

**Perinatal Mortality, Morbidity, and Birth Injury**

**Perinatal mortality**

In diabetic pregnancy, perinatal mortality has decreased 30-fold since the discovery of insulin in 1922 and the introduction of intensive obstetrical and infant care in the 1970s. Nevertheless, the current perinatal mortality rates among women who are diabetic remain approximately twice those observed in the nondiabetic population.

Congenital malformations, respiratory distress syndrome (RDS), and extreme prematurity account for most perinatal deaths in contemporary diabetic pregnancies (see the table below).

Table 1. Perinatal Morbidity in Diabetic Pregnancy (Open Table in a new window)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Gestational Diabetes</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperbilirubinemia</td>
<td>29%</td>
<td>55%</td>
<td>44%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>9%</td>
<td>29%</td>
<td>24%</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>3%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Transient tachypnea</td>
<td>2%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Adapted from California Department of Health Services, 1991.

**Birth injury**

Injuries of birth, including shoulder dystocia and brachial plexus trauma, are more common among infants of diabetic mothers, and macrosomic fetuses are at the highest risk.

Most of the birth injuries occurring to infants of diabetic mothers are associated with difficult vaginal delivery and shoulder dystocia. Although shoulder dystocia occurs in 0.3-0.5% of vaginal deliveries among healthy pregnant
women, the incidence is 2- to 4-fold higher in women with diabetes. Common birth injuries associated with diabetes are brachial plexus injury, facial nerve injury, and cephalohematoma. With strict glycemic control, the birth injury rate has been shown to be only slightly higher than controls (3.2 vs 2.5%).

Currently, clinical ability to predict shoulder dystocia is poor. Warning signs during labor (labor protraction, suspected fetal macrosomia, need for operative vaginal delivery) successfully predict only 30% of these events.

**Polycythemia**

A central venous hemoglobin concentration greater than 20 g/dL or a hematocrit value greater than 65% (polycythemia) is not uncommon in infants of diabetic mothers and is related to glycemic control. Hyperglycemia is a powerful stimulus to fetal erythropoietin production, mediated by decreased fetal oxygen tension. Untreated neonatal polycythemia may promote vascular sludging, ischemia, and infarction of vital tissues, including the kidneys and central nervous system.

**Hypoglycemia**

Approximately 15-25% of neonates delivered from women with diabetes during gestation develop hypoglycemia during the immediate newborn period.[34] Neonatal hypoglycemia is less frequent when tight glycemic control is maintained during pregnancy[35] and in labor. Unrecognized postnatal hypoglycemia may lead to neonatal seizures, coma, and brain damage.

**Neonatal Hypocalcemia**

Up to 50% of infants of diabetic mothers have low levels of serum calcium (< 7 mg/100 mL). These changes in calcium appear to be attributable to a functional hypoparathyroidism, though the exact pathophysiology is not well understood. With improved management of diabetes in pregnancy, the rate of neonatal hypocalcemia has been reduced to 5% or less.

**Postnatal hyperbilirubinemia**

Hyperbilirubinemia occurs in approximately 25% of infants of diabetic mothers, a rate approximately twice that in a healthy population. The causes of hyperbilirubinemia in infants of diabetic mothers are multiple, but prematurity and polycythemia are the primary contributing factors. Increased destruction of red blood cells contributes to the risk of jaundice and kernicterus. Treatment of this complication is usually with phototherapy, but exchange transfusions may be necessary if bilirubin levels are markedly elevated.

**Respiratory problems**

The nondiabetic fetus achieves pulmonary maturity at a mean gestational age of 34-35 weeks. By 37 weeks' gestation, more than 99% of healthy newborn infants have mature lung profiles as assessed by phospholipid assays. However, in a diabetic pregnancy, the risk of respiratory distress may not pass until after 38.5 gestational weeks.

Until recently, neonatal respiratory distress syndrome was the most common and serious morbidity in infants of diabetic mothers. In the 1970s, improved prenatal maternal management for diabetes and new techniques in obstetrics for timing and mode of delivery resulted in a dramatic decline in its incidence, from 31% to 3%. [36] Nevertheless, respiratory distress syndrome continues to be a relatively preventable complication.

The majority of the literature indicates a significant biochemical and physiologic delay in infants of diabetic mothers. Tyden et al[37] and Landon and colleagues[38] reported that fetal lung maturity occurred later in pregnancies with poor maternal glycemic control, regardless of class of diabetes.

**Screening for Diabetes Mellitus During Pregnancy**

**Risk factors**

In 1995, Moses et al assessed the prevalence of gestational diabetes mellitus in patients with various risk factors and recommended universal testing.[39] Gestational diabetes mellitus was diagnosed in 6.7% of the women overall, in 8.5% of the women aged 30 years or older, in 12.3% of the women with a preconception body mass index of 30
kg/m² or greater, and in 11.6% of women with a family history of diabetes in a first-degree relative. A combination of one or all of these risk factors predicted gestational diabetes mellitus in 61% of cases. Gestational diabetes mellitus was present in 4.8% of the women without risk factors.[39]

A nested case-control study indicated that another risk factor for the development of gestational diabetes is the presence of hypertension before pregnancy or during early pregnancy.[40] The report, which looked at 381 women with hypertension or prehypertension (the latter being defined in the study as 120-139/80-89 mmHg), as well as at 942 control subjects, found that prehypertension before or during early pregnancy was associated with a slightly increased risk of gestational diabetes, but hypertension was associated with a twofold increase in risk.

High cholesterol and egg intake prior to and during pregnancy increase the risk of gestational diabetes.[41]

**American Diabetes Association recommendations**

The current recommendations from the American Diabetes Association "Standards of Medical Care in Diabetes--2010"[42] are to conduct a risk assessment for all pregnant women at the first prenatal visit. Women who are at very high risk should undergo testing as soon as possible, in order to identify those with occult type 2 diabetes, using the standard diagnostic approach to diabetes (see Preexisting Diabetes Diagnosis, below). Criteria for very high risk are as follows:

- Severe obesity
- Gestational diabetes mellitus during a previous pregnancy or delivery of an LGA infant
- Presence of glycosuria
- Diagnosis of polycystic ovarian syndrome
- Strong family history of type 2 diabetes

All pregnant women should be screened for gestational diabetes at 24-28 weeks' gestation—including those with negative test results in the first trimester—unless they are at low risk. To be considered at low risk, a woman must meet all of the following criteria:

- Age < 25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

**Screening tests**

The best method for screening for gestational diabetes continues to be controversial. The 2-step system is currently recommended in the United States. A 50-g, 1-hour glucose challenge test (GCT) is followed by a 100-g, 3-hour oral glucose tolerance test (OGTT) for those with an abnormal screening result. Alternatively, for high-risk women, or in areas in which the prevalence of insulin resistance is 5% or higher (eg, the southwestern and southeastern United States), a 1-step approach can be used by proceeding directly to the 100-g, 3-hour OGTT.

The sensitivity of gestational diabetes mellitus testing depends on the threshold value used for the 50-g glucose challenge. Current recommendations from the American Diabetes Association "Standards of Medical Care in Diabetes--2010"[40] and the American College of Obstetricians and Gynecologists (ACOG)[43] note that a threshold value of 140 mg/dL results in approximately 80% detection of gestational diabetes, whereas a threshold of 130 mg/dL results in 90% detection. A potential disadvantage of using the lower value of 130 mg/dL is an approximate doubling in the number of OGTTs performed.

Meltzer et al found that 2-step screening with a 1-hour, 50-g glucose screen, followed by (if necessary) an OGTT, was superior to 1-step screening with a 75-g OGTT. In a prospective, randomized, controlled trial, the total cost per woman screened was lower with the 2-step approach, because many patients with gestational diabetes were diagnosed on the basis of a glucose screen result of 10.3 mmol/L (185.4 mg/dL) or greater, thus obviating the additional blood draws and time required for the OGTT.[44]

Other tests (eg, maternal HbA1C, random postprandial or fasting blood sugar level, or fructosamine level) are not recommended because of low sensitivity.
Patients undergoing oral glucose tolerance testing for gestational diabetes should undertake carbohydrate loading for 3 days preceding the test (>150 g carbohydrates) and an overnight fast of 8–14 hours the night before. The patient should remain seated during the test, and should not smoke. Two or more glucose values, as listed in the table below, must be met or exceeded for the diagnosis of gestational diabetes.

Table 2. Plasma Glucose Criteria for Gestational Diabetes (Open Table in a new window)

<table>
<thead>
<tr>
<th>Time</th>
<th>100 g Glucose Load, mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>95 (5.3)</td>
</tr>
<tr>
<td>1 hour</td>
<td>180 (10.0)</td>
</tr>
<tr>
<td>2 hours</td>
<td>155 (8.6)</td>
</tr>
<tr>
<td>3 hours</td>
<td>140 (7.8)</td>
</tr>
</tbody>
</table>

Patients with a single abnormal value on a 3-hour OGTT are likely to exhibit some degree of glucose intolerance. Left untreated, these patients are at higher risk for fetal macrosomia and neonatal morbidity. Consequently, patients with a single abnormal value should receive dietary and physical activity counseling. If the abnormal value on the OGTT was obtained before 26 weeks' gestation, a repeat OGTT should be performed approximately 4 weeks later. Whether administered at 12 or 26 weeks' gestation, the GCT can be performed without regard to recent food intake (ie, nonfasting state). Indeed, results from tests performed in fasting subjects are more likely to be falsely elevated than results from tests conducted between meals. [45]

**Type 1 Diabetes**

Patients with type 1 diabetes are typically diagnosed during an episode of hyperglycemia, ketosis, and dehydration; this occurs most commonly in childhood or adolescence, before pregnancy. Type 1 diabetes is rarely diagnosed during pregnancy; in these cases, patients most often present with unexpected coma, because early pregnancy may provoke diet and glycemic control instability in patients with occult diabetes. A pregnancy test should be ordered in all reproductive-aged women admitted to the hospital for blood sugar management.

**Type 2 Diabetes**

It can be difficult to distinguish gestational diabetes mellitus from type 2 diabetes that preceded pregnancy but was unrecognized, or whose onset occurred during pregnancy. Traditionally, the distinction has been based on whether the diabetes persisted after delivery. However, the International Association of Diabetes and Pregnancy Study Groups now recommends that high-risk women who are found to have diabetes at their initial prenatal visit, according to standard diagnostic criteria, receive a diagnosis of overt diabetes rather than gestational diabetes.

According to the American Diabetes Association "Standards of Medical Care in Diabetes--2010," [36] the presence of any one of the following criteria supports the diagnosis of diabetes mellitus:

- HbA1C = 6.5%
- Fasting plasma glucose greater than 126 mg/dL (7.0 mmol/L); fasting is defined as no caloric intake for at least 8 hours
- A 2-hour plasma glucose level = 200 mg/dL (11.1 mmol/L) during a 75-g OGTT
- A random plasma glucose level = 200 mg/dL (11.1 mmol/l) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

In the absence of unequivocal hyperglycemia, a diagnosis based on any of the first 3 of the above criteria should be confirmed by repeat testing on a different day.

Despite advanced age, multiparity, obesity, and social disadvantage, patients with type 2 diabetes were found to
have better glycemic control, fewer large for gestational age infants, fewer preterm deliveries, and fewer neonatal care admissions compared with patients with type 1 diabetes. This suggests that better tools are needed to improve glycemic control in patients with type 1 diabetes.\[46\]

**Prediabetes**

Prediabetes is a term used to distinguish people who are at increased risk of developing diabetes. People with prediabetes have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Some people may have both impaired fasting glucose and impaired glucose tolerance.

Impaired fasting glucose is a condition in which the fasting blood sugar level is elevated (100-125 mg/dL) after an overnight fast but is not high enough to be classified as diabetes. Impaired glucose tolerance is a condition in which the blood sugar level is elevated (140-199 mg/dL after a 2-h OGTT) but is not high enough to be classified as diabetes.

Women with prediabetes identified before pregnancy should be considered at extremely high risk of developing gestational diabetes mellitus during pregnancy. As such, they should receive early (first-trimester) diabetic screening. Prediabetes, impaired fasting glucose, and impaired glucose tolerance are not meaningful terms in prenatal management, unless patients exceed the plasma glucose limits for diagnosing gestational diabetes mellitus.

**Differential Diagnosis**

- Acute Renal Failure
- Acute Respiratory Distress Syndrome
- Acute Tubular Necrosis
- Appendicitis
- Autoimmune Thyroid Disease and Pregnancy
- Cholecystitis
- Cholelithiasis
- Chronic Renal Failure
- Diabetes Mellitus, Type 1
- Diabetes Mellitus, Type 2
- Diabetic Foot Infections
- Diabetic Ketoacidosis
- Diabetic Nephropathy
- Diabetic Ulcers
- Early Pregnancy Loss
- Fetal Growth Restriction
- Hypertension
- Hypoglycemia
- Pulmonary Edema, Cardiogenic

**First-Trimester Laboratory Testing**

Once the diagnosis of diabetes is established in a pregnant woman, continued testing for glycemic control and
Diabetic complications is indicated for the remainder of the pregnancy. To some extent, this involves the more intensive use of studies that are part of normal prenatal care (eg, ultrasonography).

During the first trimester of pregnancy, women with diabetes should undergo testing (in addition to normal prenatal laboratory tests) for HbA1C, blood urea nitrogen, serum creatinine, thyroid-stimulating hormone, and free thyroxine levels, as well as spot urine protein-to-creatinine ratio and capillary blood sugar levels 4-7 times daily.

**Second-Trimester Laboratory Testing**

Second-trimester testing for women with diabetes includes a repeat spot urine protein-to-creatinine study in women with elevated value in first trimester, a repeat HbA1C, and capillary blood sugar levels 4-7 times daily.

If preeclampsia is suggested, order the following tests:

- 24-hour urine collection
- Blood urea nitrogen and serum creatinine
- Liver function tests
- Uric acid
- Complete blood cell count
- Assessment of fetal well-being with nonstress test, amniotic fluid index, fetal growth and Doppler ultrasonographic examination of the umbilical cord and middle cerebral artery

**Ultrasonography**

In the first trimester, patients should have an ultrasonogram assessment (including measurement of crown-rump length) for pregnancy dating and viability. Consider nuchal translucency if the fetus is at high risk for cardiac defects (eg, because of high maternal glycohemoglobin)

In the second trimester, perform a detailed anatomy ultrasonogram at 18-20 weeks, and a fetal echocardiogram if the maternal glycohemoglobin value was elevated in the first trimester.

In the third trimester, perform a growth ultrasonogram to assess fetal size every 4-6 weeks from 26 to 36 weeks in women with overt preexisting diabetes. Perform a growth ultrasonogram for fetal size at least once at 36-37 weeks for women with gestational diabetes mellitus. Consider performing this study more frequently if macrosomia is suggested.

**Electrocardiography**

If maternal diabetes is longstanding or associated with known microvascular disease, obtain a baseline maternal electrocardiogram (ECG) and echocardiogram.

**Amniocentesis**

Consider an amniocentesis for the fetal lung profile if delivery is contemplated before 39 weeks' gestation.

**Prepregnancy Management of Women With Preexisting Diabetes**

In patients with preexisting diabetes, nutritional and metabolic intervention must be initiated well before pregnancy begins, because birth defects occur during the critical 3-6 weeks after conception.

Insulin remains the standard medication for treatment of diabetes during pregnancy, but the oral agents glyburide and metformin are increasingly used.

A study by Goh et al found that, in routine practice, metformin use in gestational diabetes was associated with fewer adverse outcomes compared with insulin.¹⁴⁷

Proper management can minimize the risks posed by glucose intolerance during pregnancy, but vigilance and meticulous monitoring is necessary. Therapeutic goals are best achieved through a team approach.

To reduce diabetes-associated neonatal morbidity, counsel the patient before conception and perform a medical risk
assessments in all women with overt diabetes and those with a history of gestational diabetes mellitus during a previous pregnancy.

Key features of an effective diabetes management program include performing a thorough assessment of cardiovascular, renal, and ophthalmologic status; and instituting a regimen of frequent and regular monitoring of both preprandial and postprandial capillary glucose levels.

Controversy exists as to whether the target glucose levels to be maintained during diabetic pregnancy should be designed to limit macrosomia or to closely mimic nondiabetic pregnancy profiles. The Fifth International Workshop Conference on Gestational Diabetes recommends the following:

- Fasting plasma glucose 90-99 mg/dL (5.0–5.5 mmol/L)
- One-hour postprandial plasma glucose less than 140 mg/dL (7.8 mmol/L)
- Two-hour postprandial plasma glucose less than 120-127 mg/dL (6.7–7.1 mmol/L)

The insulin regimen should result in a smooth glucose profile throughout the day, with no hypoglycemic reactions between meals or at night. Initiate the regimen early enough before pregnancy so that the glycohemoglobin level is lowered into the reference range for at least 3 months before conception.

Patients should take a prenatal vitamin containing at least 1.0 mg of folic acid daily for at least 3 months before conception to minimize the risk of neural tube defects in the fetus.

The development of family, financial, and personal resources necessary to achieve successful pregnancy is important. Pay particular attention to support systems that permit extended bedrest in the third trimester if necessary.

Preemptive outreach is helpful. In many perinatal centers, diabetes-in-pregnancy programs focus on outreach to nonpregnant reproductive-aged women with diabetes in order to minimize the morbidity attendant to poor periconceptional control. Urge nonpregnant women to avoid pregnancy until their HbA1C value is within the reference range (< 6.5%).

Hone and Jovanovic have summarized a convenient and structured method of managing diet and insulin therapy to optimize glycemic control. These principles are outlined in the subsequent sections.

**Team Care**

Most large programs for treating women with diabetes during pregnancy have a staff that includes a registered nurse, a certified diabetes educator, a dietitian knowledgeable about pregnancy, and a social worker. Successful management of diabetic pregnancy is optimized when this type of team care is available.

The diabetes-in-pregnancy team is also able to help the patient during the puerperal period with the challenges of lactation, diet, sleep, and glycemic control. This team is most effective in providing a smooth return to nonpregnant metabolic management.

**Dietary Therapy**

The goal of dietary therapy is to avoid single large meals and foods with a large percentage of simple carbohydrates. A total of 6 feedings per day is preferred, with 3 major meals and 3 snacks to limit the amount of energy intake presented to the bloodstream at any interval. The diet should include foods with complex carbohydrates and cellulose, such as whole grain breads and legumes.

Carbohydrates should account for no more than 50% of the diet, with protein and fats equally accounting for the remainder. However, moderate restriction of carbohydrates to 35–40% has been shown to decrease maternal glucose levels and improve maternal and fetal outcomes.

Nutritional therapy should be supervised by a trained professional, ideally a registered dietitian, with formal dietary
assessment and counseling provided at several points. For obese women (BMI >30 kg/m²), a 30–33% calorie restriction (to 25 kcal/kg actual weight per day or less) has been shown to reduce hyperglycemia and plasma triglycerides with no increase in ketonuria.

**Insulin Therapy**

Patients with preexisting diabetes require modification of their pharmacologic regimen to meet the changing metabolic demands of pregnancy. In gestational diabetes, early intervention with insulin or an oral agent is key to achieving a good outcome when diet therapy fails to provide adequate glycemic control. Determine the choice of insulin and regimen based on the patient's individual glucose profile.

The goal of insulin therapy during pregnancy is to achieve glucose profiles similar to those of nondiabetic pregnant women. Given that healthy pregnant women maintain their postprandial blood sugar excursions within a relatively narrow range (70-120 mg/dL), reproducing this profile requires meticulous daily attention by both the patient and clinician.

Insulins lispro, aspart, regular, and neutral protamine hagedorn (NPH) are well-studied in pregnancy and regarded as safe and effective. Insulin glargine is less well-studied, and given its long pharmacologic effect, may exacerbate periods of maternal hypoglycemia. Insulin detemir is safe and comparable to NPH insulin in pregnancy.

As pregnancy progresses, the increasing fetal demand for glucose and the progressive lowering of maternal fasting and between-meal blood sugar levels increases the risk of symptomatic hypoglycemia. Upward adjustment of short-acting insulin doses to control postprandial glucose surges within the target band only exacerbates the tendency to interprandial hypoglycemia. Thus, any insulin regimen for pregnant women requires combinations and timing of insulin injections quite different from those that are effective in the nonpregnant state. Further, the regimens must be continuously modified as the pregnancy progresses from the first to the third trimester and insulin resistance rises. Strive to stay ahead of the rising need for insulin, and increase insulin dosages preemptively.

When more than 20% of postprandial blood glucose levels exceed 130 mg/dL, administer lispro insulin (4-8 U subcutaneously [SC] initially) before meals. If more than 10 U of regular insulin is needed before the noon meal, adding 8-12 U of NPH insulin before breakfast helps achieve control. When more than 10% of fasting glucose levels exceed 95 mg/dL, initiate 6-8 U NPH insulin at bedtime (hs). Titrate doses as needed according to blood glucose levels.

In women with type 1 diabetes, postprandial glucose control is significantly impaired in late gestation. It is largely accounted for by slower glucose disposal. Early prandial insulin should help accelerate glucose disposal and potentially improve or ameliorate postprandial hyperglycemia in late pregnancy.

**Dietary therapy**

The goal of dietary therapy is to avoid single large meals and foods with a large percentage of simple carbohydrates. A total of 6 feedings per day is preferred, with 3 major meals and 3 snacks to limit the amount of energy intake presented to the bloodstream at any interval. The diet should include foods with complex carbohydrates and cellulose, such as whole grain breads and legumes.

Carbohydrates should account for no more than 50% of the diet, with protein and fats equally accounting for the remainder. However, moderate restriction of carbohydrates to 35–40% has been shown to decrease maternal glucose levels and improve maternal and fetal outcomes.

Nutritional therapy should be supervised by a trained professional, ideally a registered dietitian, with formal dietary assessment and counseling provided at several points. For obese women (BMI >30 kg/m²), a 30–33% calorie restriction (to 25 kcal/kg actual weight per day or less) has been shown to reduce hyperglycemia and plasma triglycerides with no increase in ketonuria.

**Insulin pump**

In a select group of patients, use of an insulin pump may improve glycemic control while enhancing patient convenience. These devices can be programmed to infuse varying basal and bolus levels of insulin, which change smoothly even while the patient sleeps or is otherwise preoccupied.
The effectiveness of continuous subcutaneous insulin infusion in pregnancy is well established. Hieronimus et al. reported similar HbA1C levels, macrosomia rates, and cesarean rates in 33 pregnant women managed with insulin pump, compared with 23 receiving multiple insulin injections. Lapolla et al. found no differences in glycemic control or perinatal outcome between 25 women treated with insulin pump in pregnancy and 68 women who received conventional insulin treatment.

**Oral hypoglycemic therapy**

**Glyburide**

The efficacy and safety of insulin have made it the standard for treatment of diabetes during pregnancy. Nevertheless, the oral agents glyburide and metformin are gaining popularity. Trials have shown these agents to be effective and no evidence of harm to the fetus has been found, although the potential for long-term adverse effects remains a concern.

Glyburide is a second-generation sulfonylurea that is minimally transported across the human placenta. This is probably largely due to the high plasma protein binding coupled with a short half-life. In addition, a human placenta perfusion study demonstrated active glyburide transport from the fetus to the mother.

A 2000 randomized trial comparing glyburide to insulin in 404 pregnancies found no difference between the groups in mean maternal blood glucose levels, the percentage of infants who were LGA, birth weights, or neonatal complications. Only 4% of patients in the glyburide study arm required addition of insulin to achieve glucose control. Since this study, several prospective and retrospective studies involving more than 775 pregnancies have concluded glyburide is as safe and effective as insulin. All studies comparing glyburide to traditional insulin have demonstrated similar levels of glycemic control. Most studies show no differences in maternal or neonatal outcomes with glyburide.

Success rates for achieving glycemic control with glyburide vary from 79% to 86%. Studies evaluating predictors of failure with glyburide cite the following risk factors:

- Advanced maternal age
- Earlier gestational age at diagnosis
- Higher gravidity and parity
- Higher mean fasting glucose level

Glyburide should not be used in the first trimester, because its effects, if any, on the embryo are unknown. Research in this area, although needed, has been difficult given the known teratogenic effects of first-generation sulfonylurea, which readily crossed the placenta.

Glyburide has been shown to be safe in breastfeeding, with no transfer into human milk.

**Metformin**

Metformin is a biguanide, which functions mainly by decreasing hepatic glucose output. Metformin crosses the placenta, and umbilical cord levels have been shown to be even higher than maternal levels.

An initial retrospective study comparing glyburide, metformin, and insulin in pregnancy raised concern, because of increased rates of preeclampsia and perinatal mortality when metformin was used in the third trimester. It should be noted that in this study the patients on metformin had a higher body mass index and were older than the patients on glyburide or insulin. Since this initial study, however, several other prospective and retrospective studies involving over 300 pregnant patients have not confirmed the increased rates of preeclampsia or perinatal mortality. These subsequent studies have demonstrated similar efficacy, safety, and maternal and fetal outcomes with metformin.

Moore et al. compared the effect of metformin and glyburide in women with gestational diabetes who did not achieve glycemic control with diet. Between the 2 groups, patients who achieved glycemic control did not differ with regard to mean fasting and 2-hour postprandial blood glucose level. However, the percentage of women who did not achieve glycemic control and required insulin was 2.1 times higher with metformin (34.7%) than with glyburide (16.2%).
Prenatal obstetric management

Periodic fetal biophysical testing

The goals of management of third-trimester pregnancies in women with diabetes are to prevent stillbirth and asphyxia while minimizing maternal and fetal morbidity associated with delivery. Monitoring fetal growth is essential to select the proper timing and route of delivery. This is accomplished by frequent testing for fetal well-being and serial ultrasonographic examinations to follow fetal size.

Various fetal biophysical tests are available to the clinician to ensure that the fetus is well oxygenated, including fetal heart rate testing, fetal movement assessment, ultrasonographic biophysical scoring, and fetal umbilical Doppler ultrasonographic studies (see the table below). If applied properly, most of these tests can be used with confidence to provide assurance of fetal well-being while awaiting fetal maturity.

Table 3. Biophysical Tests of Fetal Well-Being for Diabetic Pregnancy (Open Table in a new window)

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
<th>Reassuring Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal movement counting</td>
<td>Every night from 28 weeks</td>
<td>10 movements in &lt; 60 min</td>
<td>Performed in all patients</td>
</tr>
<tr>
<td>Nonstress test (NST)</td>
<td>Twice weekly</td>
<td>2 heart rate accelerations in 20 min</td>
<td>Begin at 28-34 weeks with insulin-dependent diabetes, and begin at 36 weeks in diet-controlled GDM.</td>
</tr>
<tr>
<td>Contraction stress test</td>
<td>Weekly</td>
<td>No heart rate decelerations in response to 3 contractions in 10 min</td>
<td>Same as for NST</td>
</tr>
<tr>
<td>Ultrasonographic biophysical profile</td>
<td>Weekly</td>
<td>Score of 8 in 30 min</td>
<td>3 movements = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 flexion = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 s breathing = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 cm amniotic fluid = 2</td>
</tr>
</tbody>
</table>

Initiate testing early enough to avoid significant stillbirth but not so early that a high rate of false-positive test results is encountered. In patients with poor glycemic control, intrauterine growth restriction, or significant hypertension, begin formal biophysical testing as early as 28 weeks. In patients who are at lower risk, most centers begin formal fetal testing by 34 weeks. Fetal movement counting is performed in all pregnancies from 28 weeks onward.

There is no consensus regarding antenatal testing in patients with gestational diabetes that is well controlled with diet.

Assessing fetal growth

Monitoring fetal growth continues to be a challenging and imprecise process. Although currently available tools (serial plotting of fetal growth parameters based on ultrasonographic measurement) are superior to those used previously for clinical estimations, accuracy is still only within ±15%.[73]

In the obese fetus, the inaccuracies are further magnified. In 1992, Bernstein and Catalano reported that significant correlation exists between the degree of error in the ultrasonogram-based estimation of fetal weight and the percentage of body fat on the fetus.[74] Perhaps this is the reason no single formula has proven to be adequate in
identifying a macrosomic fetus with certainty.

Despite problems with accuracy, ultrasonogram-based estimations of fetal size have become the standard of care. Estimate fetal size once or twice at least 3 weeks apart in order to establish a trend. Time the last examination to be at 36-37 weeks' gestation or as close to the planned delivery date as possible.

**Timing and route of delivery**

Select the timing of delivery to minimize morbidity for the mother and fetus. Delaying delivery to as near as possible to the expected date of confinement helps maximize cervical maturity and improves the chances of spontaneous labor and vaginal delivery. However, the risks of advancing fetal macrosomia, birth injury, and in utero demise increase as the due date approaches.

Although delivery as early as 37 weeks might reduce the risk of shoulder dystocia, it increases the likelihood of failed labor induction and poor neonatal pulmonary status. Because fetal growth from 37 weeks onward may be 100-150 g/wk, the reduction in net fetal weight and the risk of shoulder dystocia by inducing labor 2 weeks early may theoretically improve outcome.

By comparing the outcomes associated with labor induction in patients with gestational diabetes at 38 weeks versus expectant management with fetal testing, Kjos et al compared found that expectant management increased the gestational age at delivery by 1 week, but it did not significantly reduce the cesarean delivery.[75] However, the prevalence of macrosomia was significantly greater among infants in the expectantly managed group (23%) than among those in the active induction group (10%). This suggests that routine induction of women with diabetes on or before 39 weeks' gestation does not increase the risk of cesarean delivery and may reduce the risk of macrosomia.[75]

If the fetus is not macrosomic and the results of biophysical testing are reassuring, the obstetrician can await spontaneous labor. In patients with gestational diabetes mellitus and superb glycemic control, continued fetal testing and expectant management can be considered until 41 weeks' gestation. In the fetus with an abdominal circumference significantly larger than the head circumference or an estimated fetal weight above 4000 g, consider induction. After 40 or more weeks, the benefits of continued conservative management are likely to be outweighed by the danger of fetal compromise. Induction of labor before 41 weeks' gestation in pregnant women with diabetes, regardless of the readiness of the cervix, is prudent.

An optimal time for delivery of most diabetic pregnancies is typically on or after the 39th week. Deliver a patient with diabetes before 39 weeks' gestation without documented fetal lung maturity only for compelling maternal or fetal indications. For elective induction before 38.5 weeks, fetal lung maturity should be verified via amniocentesis.

Because the risk of shoulder dystocia and fetal injury in labor is increased 3-fold in diabetic pregnancy, elective cesarean section should be considered if the fetus is suspected to be significantly obese. The American College of Obstetricians and Gynecologists recommends offering cesarean delivery to diabetic patients if the fetal weight is estimated to be 4500 g or more.

**Prevention of Shoulder Dystocia**

Although ultrasonographic measurements of the fetus have proven to be poor predictors of the risk of shoulder dystocia, this technique continues to be the mainstay for assessing risk in pregnancy for women with diabetes. The commonly used formulas derived from a multivariate regression multiply multiple coefficients together, with the resultant product (estimated fetal weight) typically having an accuracy that is seldom less than within 15%. Fetuses predicted to weigh 4000-4500 g based on ultrasonographic findings actually weigh that much only 50% of the time.

In a study involving more than 300 fetuses who weighed more than 4000 grams at birth, ultrasonography was found to have a sensitivity of only 65% in identifying macrosomia. However, a sensitivity of approximately 80% is typically associated with a specificity of 50-60%. This means a false-positive rate of 30-50% occurs even with the more predictive formula, possibly requiring an unnecessary cesarean delivery of more than 100 fetuses in order to prevent 1 from having permanent Erb palsy.

Thus, current data do not support a policy of early induction of labor in cases of possible fetal macrosomia. If one accepts that 8-20% of infants of diabetic mothers born weighing 4500 g or more will experience shoulder dystocia, 15-30% of these will have recognizable brachial plexus injury, and 5% of these injuries will result in permanent deficit, approximately 333-1667 cesarean deliveries would have to be performed for possible macrosomia to prevent...
Intrapartum glycemic management

Maintenance of intrapartum metabolic homeostasis optimizes postnatal infant transition by reducing neonatal hyperinsulinemia and subsequent hypoglycemia. The use of a combined insulin and glucose infusion during labor to maintain maternal blood sugars in a narrow range (80-110 mg/dL) is a common and clinically efficient practice. Typical infusion rates are 5% dextrose in Ringer lactate solution at 100 mL/h and regular insulin at 0.5-1.0 U/h. Capillary blood sugar levels are monitored hourly in these patients.

For patients with diet-controlled gestational diabetes mellitus or mild type 2 diabetes, avoiding dextrose in intravenous fluids normally maintains excellent blood glucose control. After 1-2 hours of monitoring, no further assessments of capillary blood sugar typically are necessary.

For patients with diet-controlled gestational diabetes, myoinositol improves insulin resistance and increased adiponectin levels.[76]

Management of the neonate

The most critical metabolic problem that affects infants of diabetic mothers is hypoglycemia. Unmonitored and uncorrected hypoglycemia can lead to neonatal seizures, brain damage, and death. The strongest predictor of neonatal hypoglycemia is maternal mean blood glucose level during labor. Infants of diabetic mothers also appear to have disorders of both catecholamine and glucagon metabolism and have a diminished capability to mount normal compensatory responses to hypoglycemia.

Thus, current recommendations specify frequent blood glucose checks and early oral feeding when possible (ideally from the breast), with infusion of intravenous glucose if oral measures prove insufficient. Most neonatologists maintain strict monitoring of the glucose levels of newborn infants of diabetic mothers for at least 4-6 hours (frequently 24 h), often necessitating admission to a newborn special care unit.

Current evidence indicates that with proper encouragement, sustained breastfeeding is possible for a significant proportion of patients with overt diabetes. In fact, evidence indicates that breast-fed infants have a much lower risk of developing diabetes than those exposed to cow's milk proteins.

Studies of breastfeeding women with diabetes indicate that lactation, even for a short duration, also has a beneficial effect on overall maternal glucose and lipid metabolism. For postpartum women who had gestational diabetes mellitus during their pregnancies, breastfeeding may offer a practical low-cost intervention that helps reduce or delay the risk of subsequent diabetes.

In a longitudinal study comparing breastfeeding habits among women with diabetes and without diabetes, Webster et al reported that diabetic women breastfed at least as commonly and for as long as women without diabetes. At discharge, 63% of diabetic mothers and 78% of mothers without diabetes were breastfeeding. At 8 weeks, the proportions of each were nearly identical (58% and 56%, respectively). At 3 months, 47% percent of mothers with diabetes and 33% mothers without diabetes continued to breastfeed. [77]

A study by Gunderson et al found that a higher intensity of lactation among exclusively or mostly breastfeeding (< 6 oz formula per 24 h) mothers improved insulin sensitivity and glucose metabolism. This may reduce the future diabetes risk after gestational diabetes.[78]

Prevention of gestational diabetes mellitus

Prevention of gestational diabetes is an attractive concept, but no progress has been made, despite attempts in small studies. Because body fat and diet contribute to the risk of gestational diabetes mellitus, patients who lose weight before pregnancy and follow an appropriate diet may lower their risk of gestational diabetes mellitus. However, the hormone levels in pregnancy impose such a high degree of insulin resistance that in very susceptible individuals, even marked weight loss and attention to diet are not likely to be successful.

Additionally, a large study by Stafne et al found that a 12-week standard exercise program during the second half of pregnancy had no benefit in preventing gestational diabetes in healthy women with normal BMI.[79]
Contributor Information and Disclosures

Author

Thomas R Moore, MD  Chairman, Professor, Department of Reproductive Medicine, University of California at San Diego School of Medicine

Disclosure: Nothing to disclose.

Specialty Editor Board

Robert K Zurawin, MD  Associate Professor, Director of Baylor College of Medicine Program for Minimally Invasive Gynecology, Director of Fellowship Program, Minimally Invasive Surgery, Department of Obstetrics and Gynecology, Baylor College of Medicine

Robert K Zurawin, MD is a member of the following medical societies: American Association of Gynecologic Laparoscopists, American College of Obstetricians and Gynecologists, American Society for Reproductive Medicine, Association of Professors of Gynecology and Obstetrics, Central Association of Obstetricians and Gynecologists, Harris County Medical Society, North American Society for Pediatric and Adolescent Gynecology, and Texas Medical Association

Disclosure: Johnson and Johnson Honoraria Speaking and teaching; Conceptus Honoraria Speaking and teaching; ConMed Consulting fee Consulting

Francisco Talavera, PharmD, PhD  Adjunct Assistant Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference

Disclosure: Medscape Salary Employment

Romesh Khardori, MD, PhD, FACP  Professor of Endocrinology, Director of Training Program, Division of Endocrinology, Diabetes and Metabolism, Strelitz Diabetes and Endocrine Disorders Institute, Department of Internal Medicine, Eastern Virginia Medical School

Romesh Khardori, MD, PhD, FACP is a member of the following medical societies: American Association of Clinical Endocrinologists, American College of Physicians, American Diabetes Association, and Endocrine Society

Disclosure: Nothing to disclose.

Chief Editor

Carl V Smith, MD  The Distinguished Chris J and Marie A Olson Chair of Obstetrics and Gynecology, Professor, Department of Obstetrics and Gynecology, Senior Associate Dean for Clinical Affairs, University of Nebraska Medical Center

Carl V Smith, MD is a member of the following medical societies: American College of Obstetricians and Gynecologists, American Institute of Ultrasound in Medicine, Association of Professors of Gynecology and Obstetrics, Central Association of Obstetricians and Gynecologists, Council of University Chairs of Obstetrics and Gynecology, Nebraska Medical Association, and Society for Maternal-Fetal Medicine

Disclosure: Nothing to disclose.

Additional Contributors

The authors and editors of eMedicine gratefully acknowledge the contributions of previous author Carri Warshak, MD, to the development and writing of the source article.

References


60. Ramos GA, Jacobson GF, Kirby RS, Ching JY, Field DR. Comparison of glyburide and insulin for the


