

# Gestational Diabetes Mellitus

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## ABSTRACT

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Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. Available evidence suggests that beta cell defects in GDM result from the same spectrum of causes that underlie hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance; the concept of risk based screening is explained. The maternal and fetal morbidity is discussed. The surveillance and monitoring during pregnancy is explained. Management and post-partum followup is discussed.

**Keywords:** Gestational diabetes, Risk stratified screening, Maternal morbidity, Fetal morbidity, Surveillance, Management, Post partum followup.

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## DEFINITION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. Available evidence suggests that beta cell defects in GDM result from the same spectrum of causes that underlie hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance.<sup>1</sup>

### American Diabetes Association Classification

#### 3 Forms of Glucose Intolerance<sup>5</sup>

1. Type I diabetes: Immunologic destruction of the pancreas
2. Type II diabetes: Exhaustion or resistance of the pancreatic cells
3. Gestational: A glucose intolerance that had not previously been present prior to Pregnancy

## PATHOPHYSIOLOGY

Pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in type 2 diabetes. The insulin resistance of pregnancy may result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormones made by the placenta. Rapid abatement of insulin resistance after delivery suggests a major contribution from placental

hormones.<sup>1</sup> The placenta produces human chorionic somatomammotropin (HCS, formerly called human placental lactogen), bound and free cortisol, estrogen, and progesterone. GDM results from an endogenous insulin supply that is inadequate to meet tissue insulin demands.

Beta cell dysfunction in women diagnosed with GDM may fall into one of three major categories: 1) autoimmune, 2) monogenic, or 3) occurring on a background of insulin resistance (as is most common). The loss of the first-phase insulin response leads to post-prandial hyperglycemia, whereas impaired suppression of hepatic glucose production is responsible for fasting hyperglycemia. Because insulin does not cross the placenta, the fetus is exposed to the maternal hyperglycemia. At the 11<sup>th</sup> or 12<sup>th</sup> week of gestation, the fetal pancreas is capable of responding to this hyperglycemia. The fetus thus becomes hyperinsulinemic, which in turn promotes growth and subsequent macrosomia. Autoimmune or monogenic forms of diabetes should be considered in lean patients, who can rapidly develop overt diabetes after pregnancy. These monogenic forms of GDM account for < 10% of GDM cases.<sup>2</sup>

## SCREENING

The clinical detection of GDM is accomplished in different ways in different countries. In general, the approaches apply one or more of the following procedures: 1) clinical risk assessment, 2) glucose

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tolerance screening, and 3) formal glucose tolerance testing.<sup>1</sup> Currently, and after extensive deliberation, universal screening of all pregnant women is recommended by some groups; however, the American Diabetes Association (ADA) recommends screening of only moderate- and high- risk pregnancies.<sup>2</sup>

### Risk Category and Clinical Characteristics

#### High risk

- Marked obesity
- Diabetes in first-degree relative
- Current glycosuria
- Previous history of GDM or glucose intolerance
- Previous infant with macrosomia

#### Average risk

- Neither high or low risk

#### Low risk

- Age < 25 years
- No previous poor obstetrical outcomes
- Belongs to a low-risk ethnic group
- No diabetes in first-degree relatives
- Normal prepregnancy weight and weight gain during pregnancy
- No history of abnormal glucose tolerance

When the universal screening approach is employed, patients with no known risk factors should undergo a 1-hour glucose test (glucose challenge test) at 24 to 28 weeks of gestation.<sup>5</sup> For normal-risk patients, it is widely recommended to screen with a nonfasting, 1-hour, 50-g OGTT at 24–28 weeks' gestation. For higher-risk patients, screening is warranted earlier in pregnancy. If this initial screen is normal, then the test is repeated at the beginning of the third trimester (24 weeks). Patients with symptoms of overt severe hyperglycemia, such as polyuria and polydipsia, may be diagnosed with a random blood glucose test result  $\geq 200$  mg/dl. 1-hour 50-g OGTT value  $\geq 140$  mg/dl would have an  $\sim 80\%$  sensitivity, a cut off value  $\geq 130$  mg/dl increases sensitivity to  $\sim 90\%$ . A positive test requires further diagnostic testing. Women with either the 75- or the 100-g OGTT. Both tests are administered after an overnight fast of at least 8 hours and after at least 3 days of unrestricted diet including  $> 150$  g of carbohydrate per day.

If using the 100-g OGTT, the cutoff values are as follows.

### Diagnosis of GDM

Time of measurement	Glucose concentration (mg/dl)
After overnight fast	$> 95$
1 hour postchallenge	$> 180$
2 hour postchallenge	$> 155$
3 hour postchallenge	$> 140$

Two or more abnormal values must be measured for the test to be considered a positive diagnostic test. When using the 2-hr 75-g OGTT, the cutoffs are the same at 1 and 2 hrs

### CLINICAL SIGNIFICANCE OF GDM

Patients with GDM are at higher risk for excessive weight gain, preeclampsia, and cesarean sections. Infants born to mothers with GDM are at higher risk for macrosomia, birth trauma, and shoulder dystocia. After delivery, these infants have a higher risk of developing hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia, and subsequent obesity and type 2 diabetes. In addition, having a history of GDM puts the mother at risk for development of type 2 diabetes or recurrent GDM in the future. Recent data suggest an increased risk of cardiovascular disease also. Infants exposed to maternal diabetes in utero have an increased risk of diabetes and obesity in childhood and adulthood. Infants of mothers with GDM are at increased risk of serious birth injury and neonatal intensive care unit admissions. The magnitude of fetal-neonatal risks is proportional to the severity of maternal hyperglycemia.<sup>2</sup>

### MONITORING

Identification and intensive management of GDM are associated with a decrease in mortality and morbidity in infants. With appropriate therapy, the likelihood of intrauterine fetal death is not detectably higher than in the general population. The recommendation of the Fourth International Workshop-Conference on GDM is to maintain maternal capillary glucose concentrations at  $< 96$  mg/dl (5.3 mmol/l) in the fasting state,  $< 140$  mg/dl (7.8 mmol/l) at 1 h, and  $< 120$  mg/dl (6.7 mmol/l) 2 h after starting the meal. Daily SMBG, using meters (preferably with memory capability) appears to be superior to less frequent monitoring in the clinic. Assessing the fetal response to maternal GDM by ultrasound measurement of fetal abdominal circumference starting in the second and early third trimesters and repeated every 2– 4 weeks can provide useful

information (in combination with maternal SMBG levels) to guide management decisions. Measurement of blood pressure and urinary protein is recommended at each prenatal visit to detect the development of preeclampsia.

The effectiveness of ketone monitoring (urine or blood) in improving fetal outcome has not been tested. Insufficient data are available to determine whether measurement of glycosylated hemoglobin or other circulating proteins is of value in the routine management of GDM. Psychosocial assessment of women with GDM is encouraged to detect issues such as depression, eating disorders, stress, and anxiety that can block effective response to prescribed treatment.<sup>4</sup>

## FETAL SURVEILLANCE

- All women with GDM should monitor fetal movements during the last 8–10 weeks of pregnancy and report immediately any reduction in the perception of fetal movements.
- Non-stress testing should be “considered” after 32 weeks’ gestation in women on insulin and “at or near” term in women requiring only dietary management.
- Biophysical profile testing and Doppler velocimetry to assess umbilical blood flow “may be considered” in cases of excessive or poor fetal growth, or when there are comorbid conditions, such as preeclampsia.
- Ultrasound should be used to detect fetal anomalies in women with GDM diagnosed in the first trimester or with fasting glucose levels  $\geq 120$  mg/dl.
- Amniocentesis to determine fetal lung maturity in preparation for delivery is not necessary in well-dated pregnancies after 38 weeks’ gestation.<sup>3</sup>

Data are insufficient to determine whether surveillance beyond self-monitoring of fetal movements is indicated in women with GDM who continue to meet the targets of glycemic control with MNT/physical activity regimens alone and in whom fetal growth is appropriate for gestational age.<sup>4</sup>

## TREATMENT

### Diet and exercise

MNT is the cornerstone of treatment for GDM. The Institute of Medicine report recommended a relatively small gain during pregnancy of  $<7$ kg for patients

who are obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and a proportionally greater weight gain (up to 18 kg) for patients who are underweight (BMI  $\leq 18.5$  kg/m<sup>2</sup>) at the onset of pregnancy. Excess gestational weight gain can be associated with fetal macrosomia and unhealthy maternal postpartum weight retention.<sup>4</sup> Caloric allotment is based on ideal body weight. Recommendations are 30 kcal/kg for women with a BMI of 22 to 25, 24 kcal/kg for women with a BMI of 26 to 29, and 12 to 15 kcal/kg for women with a BMI above 30. The recommended overall dietary ratio is 33% to 40% complex carbohydrates, 35% to 40% fat, and 20% protein. This calorie distribution will help 75% to 80% of GDM women become normoglycemic.<sup>5</sup>

Planned physical activity of 30 min/day is recommended for all individuals capable of participating. Advising GDM patients to walk briskly or do arm exercises while seated in a chair for at least 10 min after each meal accomplishes this goal. Pharmacological treatment. Although the majority of women will achieve adequate glycemic control with diet and exercise alone, 30–40% require pharmacological treatment.

### Insulin

Two approaches are to initiate insulin when the fasting blood glucose concentration is greater than 90 mg/dL on 2 or more occasions during a 2-week period, or when the 1-hour postprandial blood glucose concentration is greater than 120 mg/dL.<sup>5</sup> Human insulin is the least immunogenic of commercially available preparations, but the rapid-acting insulin analogs, lispro and aspart, develop antibodies at rates and titers that are comparable to human regular insulin. No reports of glulisine use in pregnancy are available. Using insulin preparations of low antigenicity minimizes the transplacental transport of insulin antibodies. Of the three rapid-acting insulin analogs, lispro and aspart have been investigated in pregnancy, demonstrating clinical effectiveness, minimal transfer across the placenta, and no evidence of teratogenesis.<sup>4</sup> Using analogs has the advantage of dosing 5–10 minutes before meals, versus 30–45 minutes before meals with regular insulin. Because these analogs are rapid acting and have a short duration of action, they better control postprandial glycemia and are associated with less postprandial hypoglycemia than regular insulin. Randomized controlled trials have not been carried out using long-acting insulin analogs of any type in diabetic pregnant women (insulin glargine, insulin detemir). Thus, human NPH insulin as part of a multiple injection regimen should be used for intermediate acting insulin effect in GDM.

If the fasting blood glucose is > 90 mg/dl, then NPH at a dose of 0.2 units/kg per day should be initiated at bedtime. Next, if both fasting and preprandial levels are elevated, a rapid-acting analog should be added with meals.<sup>2</sup>

### **Glyburide (Glibenclamide)**

In the United States, use of oral hypoglycemic agents is controversial and not approved by the US Food and Drug Administration. That said, many practices have successfully used glyburide to manage GDM when diet alone was insufficient, although a significant number of these patients go on to require insulin in order to maintain optimal glycemic control. Glyburide does not significantly cross the placenta. A disadvantage to taking glyburide is that it sometimes takes > 1 week to observe the effect of titration.<sup>2,5</sup>

### **Metformin**

Preliminary studies have shown that in women with PCOS, metformin may be safe and may reduce risk of miscarriage and development of GDM when used for the entire pregnancy. Metformin may also have a role in therapy for GDM.<sup>2</sup>

Acarbose, an alpha-glucosidase inhibitor, is poorly absorbed from the gastrointestinal tract, and two preliminary studies have suggested efficacy in reducing postprandial glucose excursions in GDM, but with the expected high frequency of abdominal cramping. A small proportion of this drug may be absorbed systemically, and safety and potential transplacental passage have not been fully evaluated. Use of thiazolidinediones, glinides, and glucagon-like peptide 1 agonists during pregnancy is considered experimental.<sup>4</sup>

### **Obstetric management**

There is continuing debate about whether induction of labor or expectant labor is more efficacious, and it is not clear which is better with regard to the outcomes of cesarean delivery incidence, birth injury, or neonatal morbidity and mortality. There are no contraindications for epidural analgesia, spinal anesthesia, or, if indicated, general anesthesia. Insulin is rarely needed during delivery. Typically, a normal saline infusion is all that is required for the patient to remain normoglycemic. The ideal target glucose concentration during labor has not been established. Some evidence indicates that delivery past 38 weeks can lead to an increase in the rate of large-for-gestational-age infants without reducing the rate of cesarean deliveries.<sup>4,5</sup>

### **Postpartum follow-up**

Blood glucose should be monitored the day after delivery to ascertain that the mother is no longer hyperglycemic according to the criteria for non-pregnant 95% will return to a completely normal glucose status postpartum. In the postpartum period, glucose tolerance screening should be performed at 2 to 4 months after delivery to help detect the 3% to 5% of women who remain diabetic and require further treatment. For this screening, the 75-g 2-hour glucose challenge test mentioned earlier is recommended.<sup>5</sup>

Patients should attempt to minimize insulin resistance through exercise, maintenance of normal weight, and avoidance of drugs that induce insulin resistance. The ADA has recommended 1) an annual fasting blood glucose test, 2) a 6-week postpartum 75-g 2-hour OGTT, and 3) contraception to ensure that patients will not conceive in the face of marked hyperglycemia, which could lead to increased congenital malformations and dysorganogenesis.<sup>2</sup>

### **Main Points**

Risk factors for GDM include a history of macrosomia, presence of polycystic ovarian syndrome, obesity, age older than 25, and persistent glucosuria.

There is debate regarding the preferred screening protocol for GDM. Some experts recommend universal screening, whereas others exempt women who are at low risk.

Data show that increasing levels of plasma glucose are associated with birth weight above the 90th percentile, cord blood serum C-peptide level above the 90th percentile, and, to a lesser degree, primary cesarean deliveries and neonatal hypoglycemia.

The cornerstone of management is glycemic control. Quality nutritional intake is essential. Patients with GDM who cannot control their glucose levels with diet alone will require insulin.

It is generally recommended that pregnancies complicated by GDM do not go beyond term.

### **END NOTE**

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**Conflict of Interest:** None declared

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