Gestational diabetes mellitus (GDM) represents a heterogeneous group of metabolic disorders, which result in varying degrees of maternal hyperglycemia and pregnancy-associated risk. The frequency of GDM is rising globally and may also increase further as less-stringent criteria for the diagnosis are potentially adopted. The additional burden placed on the health care system by increasing cases of GDM requires consideration of diagnostic approaches and currently used treatment strategies. Debate continues to surround both the diagnosis and treatment of GDM despite several recent large-scale studies addressing these controversial issues. As many now have come to reassess their approach to the management of GDM, we provide information in this review to help guide this process. The goal for each health care practitioner should continue to be to provide optimum care for women discovered to have carbohydrate intolerance during pregnancy.

The term gestational diabetes mellitus (GDM) describes women with carbohydrate intolerance of variable severity with onset or recognition during the present pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether the condition persists after pregnancy. Classically, the definition has not excluded the possibility that unrecognized glucose intolerance may have antedated or begun with pregnancy. The American Diabetes Association has thus defined GDM as diabetes diagnosed during pregnancy that is not clearly overt diabetes. The term GDM also fails to specify whether the patient requires dietary adjustment alone or treatment with diet and insulin or oral medications. Thus, GDM encompasses a heterogeneous group of women with a wide spectrum of metabolic abnormalities and varying degrees of pregnancy-associated risk.

Controversy has surrounded the diagnosis and treatment of GDM for nearly 50 years. Much of the debate has centered on the validity of currently used diagnostic criteria and whether identification and treatment of GDM actually improves maternal and perinatal outcomes. Contributing to the discussion has been the fact that the original diagnostic criteria for GDM were based on a woman’s risk of developing subsequent type 2 diabetes mellitus (DM) and were not related to specific pregnancy outcomes. Those who have challenged the clinical significance of GDM in the past have also pointed to the lack of well-designed treatment trials. Although several recently conducted studies have provided important information concerning these fundamental issues, controversy remains regarding the choice of screening methods, diagnostic criteria as well as both medical and obstetric management of GDM.

SCREENING AND DIAGNOSIS

It has been estimated that approximately 6–7% of pregnancies in the United States are complicated by DM and that approximately 85% of the cases represent women with GDM. An increased prevalence of GDM is found in women of ethnic groups that have high frequencies of type 2 DM, including women of Hispanic, African, Native American, Asian, Pacific Island ancestry, or all. Women with GDM clearly represent a group with significant risk for developing glucose intolerance later in life. O’Sullivan originally

From the Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, Ohio.

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Corresponding author: Mark B. Landon, MD, The Ohio State University College of Medicine, Department of Obstetrics and Gynecology, 395 W 12th Avenue, Suite 530, Columbus, OH 43210; e-mail: Mark.Landon@osumc.edu.

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projected that 50% of patients with GDM would develop diabetes in a follow-up study of 22–28 years. The progression to type 2 DM may be influenced by ethnicity and the profound increased incidence of obesity in the U.S. population in recent years. For example, 60% of Latina women with GDM will develop type 2 DM, and this level of risk may actually be manifest by 5 years after the GDM index pregnancy. The likelihood for subsequent diabetes increases when GDM is diagnosed in early pregnancy, and presumably many of these women with impaired β-cell function represent cases of unidentified pre-existing type 2 DM.

Gestational diabetes mellitus is a state restricted to pregnant women whose impaired glucose tolerance is discovered during pregnancy. Women with GDM are unable to compensate for the insulin resistance of pregnancy, which is produced by a combination of hormonal and inflammatory changes. Because, in most cases, patients with GDM have normal fasting glucose levels, some challenge of glucose tolerance must be undertaken. Traditionally, obstetricians relied on historical and clinical risk factors to select those patients most likely to develop GDM. This group included women with family histories of diabetes or those whose past pregnancies were marked by an unexplained stillbirth or the delivery of a large neonate. Obesity, hypertension, glycosuria, and maternal age older than 25 years were other indications for screening. One large population-based study, however, revealed that more than half of all women with GDM lack these risk factors.

In the summary and recommendations of the Second and Third International Workshop-Conference on GDM, screening was recommended for all pregnant women who have not been identified as having glucose intolerance before the 24th week. After the Fourth International Workshop-Conference in 1997, screening was recommended for women in ethnic groups with relatively high rates of carbohydrate intolerance during pregnancy and of diabetes later in life. It was recognized and reaffirmed at the Fifth International Workshop Conference in 2005 that certain features place women at low risk for GDM (Box 1), and it may not be cost-effective to screen this subgroup of women. Those at low risk include women who are not members of ethnic groups at increased risk for developing type 2 DM, who have no history of abnormal glucose tolerance or poor obstetric outcomes usually associated with GDM, and who have all of the following characteristics: age younger than 25 years, normal prepregnancy body weight, and no family history of diabetes in a first-degree relative. However, such low-risk women represent only 10% of most populations and identifying these cases may add complexity to the screening process. It follows that although selective screening may limit false-positive rates and perhaps cost, the potential for missing a significant proportion of cases makes this approach unattractive.

As previously noted, the longstanding criteria for the diagnosis of GDM are conceptually flawed in that they represent a dichotomous definition of normal and abnormal gestational glucose tolerance, when the risk of adverse maternal-fetal outcomes and later diabetes should be logically graded upward with

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**Box 1. Screening Strategy for Detecting Gestational Diabetes Mellitus**

Gestational diabetes mellitus (GDM) risk assessment: should be ascertained at the first prenatal visit.

- **Low risk:** blood glucose testing not routinely required if all of the following characteristics are present:
  - Member of an ethnic group with a low prevalence of GDM
  - No known diabetes in first-degree relatives
  - Aged younger than 25 years
  - Weight normal before pregnancy
  - No history of abnormal glucose metabolism
  - No history of poor obstetric outcome

- **Average risk:** perform blood glucose testing at 24–28 weeks using either:
  - Two-step procedure: 50-g glucose tolerance test followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the glucose tolerance test
  - One-step procedure: diagnostic oral glucose tolerance test performed on all participants

- **High risk:** perform blood glucose testing as soon as feasible using the procedures described previously if one or more of these are present:
  - Severe obesity
  - Strong family history of type 2 diabetes
  - History of GDM, impaired glucose metabolism, or glycosuria

If GDM is not diagnosed, blood glucose testing should be repeated at 24–28 weeks or at any time a patient has symptoms or signs that are suggestive of hyperglycemia.

higher values on the oral glucose tolerance test (OGTT) and with the degree of fasting hyperglycemia. With this in mind, the Hyperglycemia and Adverse Pregnancy Outcome study was designed to aid in the development of internationally agreed on diagnostic criteria for GDM based on their predictive value for adverse pregnancy outcomes. This landmark multicenter international study (15 centers in nine countries) allowed for analysis of blinded 75-g 2-hour OGTT data in 25,862 nondiabetic gravidae. A total of 25,505 women underwent screening and 23,316 underwent final analysis. Approximately 2.9% of women were unblinded as a result of prespecified hyperglycemia exceeding entry criteria. Glycemia was evaluated in relation to various perinatal and maternal outcomes such as primary cesarean delivery, birth weight greater than the 90th percentile, clinical neonatal hypoglycemia, and fetal hyperinsulinemia (cord blood C-peptide greater than the 90th percentile). Secondary end points included preterm delivery, shoulder dystocia or birth trauma, need for neonatal intensive care, hyperbilirubinemia, and pre-eclampsia. Increases in each of the three values on the 75-g, 2-hour OGTT were associated with graded increases in the likelihood of the following outcomes, among others: large for gestational age (LGA), primary cesarean delivery, fetal insulin levels, and neonatal adiposity (Fig. 1).

Importantly, results were adjusted for several variables, including age, body mass index (BMI, calculated as weight (kg)/[height (m)]²), tobacco use, gestational age at glucose load, admission before delivery, neonatal sex, parity, and maternal hypertension. It is noteworthy that the birth weight centiles including LGA (90th percentile) in the Hyperglycemia and Adverse Pregnancy Outcome analysis was

![Fig. 1](image-url)
derived from the study population. This population of “low-risk” women excluded women with significant hyperglycemia, which if included would have increased cutoff levels and likely deceased rates of LGA to nonsignificant in lower glucose categories.

The Hyperglycemia and Adverse Pregnancy Outcome study investigators did not offer specific recommendations for the diagnostic criteria of GDM. Because there was a continuous association between glucose values and perinatal outcome, it was apparent that any new recommended diagnostic criteria would need to be arrived at by consensus. To meet this challenge, the International Association of Diabetes and Pregnancy Study Group convened a workshop conference in 2008.13 An odds ratio (OR) of 1.75 times the mean was selected for the outcomes of increased neonatal body fat, LGA, and cord serum C-peptide greater than the 90th centile, which yielded the recommended diagnostic criteria for GDM.

Importantly, the International Association of Diabetes and Pregnancy Study Group task force recommended universal 2-hour 75-g OGTT be performed during pregnancy and that the diagnosis of GDM be made when any single value on the 2-hour 75-g OGTT was met or exceeded.13 Using the fasting cutoff alone in the Hyperglycemia and Adverse Pregnancy Outcome population identified 8.3% of women as having GDM (Table 1). The addition of the 1-hour value identified an additional 5.7%, whereas adding the 2-hour value resulted in another 2.1% of women as having GDM. Overall, using the proposed criteria, 17.8% of the Hyperglycemia and Adverse Pregnancy Outcome study population would be identified as having GDM. Recently, the American Diabetes Association endorsed the International Association of Diabetes and Pregnancy Study Group criteria while acknowledging that adopting these new cutoffs will significantly increase the prevalence of GDM. The American Diabetes Association noted that the numerical glucose values defining GDM under the new International Association of Diabetes and Pregnancy Study Group criteria differ little from those of the prior endorsed criteria, albeit the latter were based on a 100-g 3-hour OGTT. The American Diabetes Association also noted that there are in fact few data from randomized clinical trials regarding therapeutic interventions in the additional women who would be diagnosed as having GDM.3 To underscore this fact, Horvath and colleagues have commented that the transferability of the benefits of recent randomized clinical trials for mild GDM to populations identified using the proposed International Association of Diabetes and Pregnancy Study Group criteria cannot be taken for granted.14

The resulting dramatic increase in the frequency of GDM and its consequences now must be considered by professional organizations such as the American College of Obstetricians and Gynecologists (the College), which are charged with evaluating whether to endorse the proposed International Association of Diabetes and Pregnancy Study Group criteria. Overdiagnosis of GDM will likely increase cost because women with GDM may undergo more interventions such as induction and cesarean delivery. Principal among the considerations is the substantial effect on workload and resources necessary to provide care for the increased number of GDM cases identified.15 It has been suggested that stratification of risk may allow for different care algorithms among the GDM population.15 In practice, one might provide for self blood glucose monitoring for a brief period of time, and, if satisfactory levels are achieved, these women may receive little additional care beyond continued diet modification. However, these approaches will need to be studied and validated in various populations to provide clear guidelines for practitioners.

Ryan16 has suggested a careful re-evaluation of the proposed International Association of Diabetes and Pregnancy Study Group criteria and recommended that an OR cutoff of 2.0 be applied to the

Table 1. Proposed International Association of Diabetes and Pregnancy Study Group13 Definition of Gestational Diabetes Mellitus (Universal 75-Gram 2-Hour Oral Glucose Tolerance Test)

<table>
<thead>
<tr>
<th>Glucose Measure</th>
<th>Glucose Concentrations Threshold (mg/dL)</th>
<th>Frequency of GDM* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>92</td>
<td>8.3</td>
</tr>
<tr>
<td>1-h</td>
<td>180</td>
<td>5.7</td>
</tr>
<tr>
<td>2-h</td>
<td>153</td>
<td>2.1*</td>
</tr>
</tbody>
</table>

GDM, gestational diabetes mellitus.
* The third column lists the frequency of GDM according to each cutoff value. The cumulative frequency of GDM is 16.1% (if any one of these cutoff values is met).
* A total of 1.7% of the Hyperglycemia and Adverse Pregnancy Outcome study population was unblinded because of fasting glucose levels of at least 105 mg/dL, 2-hour levels of at least 200 mg/dL, or both. As a result, the frequency of GDM in this population would be 17.8%.

Hyperglycemia and Adverse Pregnancy Outcome data instead of a cutoff of 1.75. This approach would result in a frequency of GDM of 8.8%. Ryan notes in his analysis (which assumes a treatment benefit similar to the two recent randomized controlled trials) that by using the less stringent 2.0 multiples of mean cutoff to the Hyperglycemia and Adverse Pregnancy Outcome population, 2,448 cases of GDM are identified compared with 4,150 at 1.75 multiples of mean and that by treating an extra 1,702 cases, one might expect to avoid 140 cases of LGA neonates, 21 cases of shoulder dystocia, and 16 cases of birth injury.16 The question posed is whether diagnosing this many extra women with GDM is worth the benefit. To aid in answering this question, a National Institutes of Health consensus conference is planned next year to specifically address the issue of screening and diagnosis for GDM. The information provided at this conference should help inform health care practitioners and the College as they pursue the optimal strategy for identifying cases of GDM.17

The diagnosis of GDM is based on OGTT criteria. In much of the world, a one-step approach using a 2-hour 75-g OGTT is used with measurement of fasting and 2-hour venous glucose. The two-step approach, commonly used in the United States, is based on administration of 50 g of glucose followed by a 1-hour venous glucose determination. A screening threshold is selected, and those meeting or exceeding this threshold then undergo a 3-hour 100-g diagnostic OGTT (Table 2). There have been few comparisons of these two approaches, yet a prospective randomized study comparing the two approaches resulted in an equivalent prevalence of GDM and demonstrated the one-step approach to be the most expensive.18 At the present time, most practitioners in the United States continue to perform a 50-g glucose challenge screening followed by a diagnostic 100-g oral OGTT. The 50-g glucose challenge may be performed in the fasting or fed state, although sensitivity is improved if the test is performed in the fasting state.19 A plasma value between 130 and 140 mg/dL is commonly used as a threshold for performing a 3-hour OGTT. Approximately 10% of women with GDM have screening test values between 130 and 139 mg/dL.20 The sensitivity of screening may be increased from 90% to nearly 100% if universal screening is used using a threshold of 130 mg/dL. Coustan and colleagues demonstrated that the prevalence of positive screening tests requiring further diagnostic testing increased in their population from 14% (140 mg/dL) to 23% (130 mg/dL), which was accompanied by an approximately 12% increase in the overall cost to diagnose each case of GDM.8 With these considerations, a screening cutoff value of 135 mg/dL is commonly used.20

Whereas most women can be screened for GDM at approximately 24–28 weeks of gestation, it is advisable to screen earlier in pregnancy those with strong risk factors such as morbid obesity, a strong family history, previous GDM, prior macrosomic stillbirth, or a neonate weighing more than 4,500 g.21 Many cases identified in early pregnancy will represent previously undetected overt diabetes. The recent International Association of Diabetes and Pregnancy Study Group consensus report considered the detection of overt diabetes during pregnancy and suggested that the assessment should be made during the initial visit for prenatal care. However, the panel could not agree on whether universal screening should be used compared with screening only high-risk women classified as such according to locally defined criteria. The panel favored the use of any available certified measure of glucose (fasting plasma glucose, random plasma glucose, or hemoglobin A1C). Consensus thresholds for the various measures for the diagnosis of overt diabetes are presented in Table 3. If initial screening is negative, repeat testing using the one- or two-step approach is recommended at 24–28 weeks. Using the plasma cutoff of 130–140 mg/dL for the 1-hour 50-g screen, one can expect approximately 15–20% of patients with an abnormal screening value to have an abnormal 3-hour OGTT. Patients whose 1-hour screening value exceeds 190 mg/dL (10.5 mmol/L) will exhibit an abnormal OGTT in 90% of cases.20 In women with a screening value between 190 and 215 mg/dL, we recommend obtaining a fasting blood glucose level before administering a 100-g carbohydrate load.22 If the fasting glucose is greater than 95 mg/dL, the patient is treated for GDM.

Table 2. Threshold Values to Diagnose Gestational Diabetes Mellitus*

<table>
<thead>
<tr>
<th>OGGT</th>
<th>NDDG20</th>
<th>Carpenter20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>105</td>
<td>95</td>
</tr>
<tr>
<td>1-h</td>
<td>190</td>
<td>180</td>
</tr>
<tr>
<td>2-h</td>
<td>165</td>
<td>155</td>
</tr>
<tr>
<td>3-h</td>
<td>145</td>
<td>140</td>
</tr>
</tbody>
</table>

OGGT, oral glucose tolerance test; NDDG, National Diabetes Data Group.
Diagnosis of gestational diabetes is made when any two values are met or exceeded.

* Screening test: 50 g, 1-hour; plasma (mg/dL): 130–140.
concerning treatment of GDM.25 Of the 1,418 women
Cochrane Review
livery, and shoulder dystocia. The 2009 update to the
mediate outcomes such as macrosomia, cesarean de-
knowledged that their review failed to consider inter-

1384
Landon and Gabbe

in Pregnant Women.26 In fact, the Australian Carbo-
the 2005 Australian Carbohydrate Intolerance Study
enrolled in these studies, 1,000 were represented by
annually.23 Because the frequency of GDM is rising
mated maternal and newborn costs of $636 million
GDM assuming a 4.5% incidence translates to esti-

The current U.S. economic burden of treatment for
GDM.14 This review included the second large-scale
randomized controlled trial that included a large untreated
control group because the remainder of the studies
described were trials comparing various treatment
modalities for GDM. The review concluded that
women with GDM should only be considered for
specific treatment in addition to routine obstetric care.
Most recently, a systematic review and meta-analysis
evaluated the effects of treatment in women with
GDM.14 This review included the second large-scale
randomized controlled trial for mild GDM performed
by the Eunice Kennedy Shriver National Institute of
Child Health and Human Development Maternal-
Fetal Medicine Units (NICHD MFMU) Network.
The authors concluded that compared with routine
care, treatment of GDM is associated with a reduction
in the incidence of shoulder dystocia and macrosomia.
This conclusion came with the caveat that al-
though these benefits might seem to justify screening
for and treatment of GDM, the evidence of the

treatment effect has been derived from two large-scale
randomized controlled trials, which used a two-step
strategy for identifying cases.

**IS THERE A BENEFIT TO THE TREATMENT OF
GESTATIONAL DIABETES MELLITUS?**

The decision to perform blood testing for evaluation of glycemia
on all pregnant women or only on women with characteristics
indicating a high risk for diabetes is to be made on the basis of
the background frequency of abnormal glucose metabolism in
the population and on local circumstances.

The 2008 guidelines of the U.S. Prevention Ser-
tice Task Force concluded that there is insufficient
evidence to assess the benefits and harms of screening
and treatment of GDM.24 This group, however, ac-
nowledged that their review failed to consider inter-
mediate outcomes such as macrosomia, cesarean de-

The 2009 update to the
Cochrane Review
identified eight randomized trials
concerning treatment of GDM.25 Of the 1,418 women
enrolled in these studies, 1,000 were represented by
the 2005 Australian Carbohydrate Intolerance Study
in Pregnant Women.26 In fact, the Australian Carbo-
hydrate Intolerance Study in Pregnant Women was
the only treatment trial that included a large untreated
control group because the remainder of the studies
described were trials comparing various treatment
modalities for GDM. The review concluded that
women with GDM should only be considered for
specific treatment in addition to routine obstetric care.
Most recently, a systematic review and meta-analysis
evaluated the effects of treatment in women with
GDM.14 This review included the second large-scale
randomized controlled trial for mild GDM performed

**Randomized Treatment Trials for
Gestational Diabetes Mellitus**

More than 40 years passed from O’Sullivan’s work
before the findings of the long-awaited Australian
Carbohydrate Intolerance Study in Pregnant Women
randomized controlled trial were reported.26 The Aus-
tralian Carbohydrate Intolerance Study in Pregnant
Women was a multicenter, 10-year, randomized treatment
trial of 1,000 women conducted at 14 sites in
Australia. The study was designed to determine
whether treatment of mild GDM would reduce the
rate of perinatal complications. Treatment was asso-
ciated with a significant reduction in the rate of the
primary outcome, a composite of serious perinatal
complications (perinatal death, shoulder dystocia,
birth trauma including fracture, or nerve palsy; ad-
justed relative risk 0.33; 95% confidence interval
0.14–0.75).

Among secondary neonatal outcomes, there were
no significant differences in the rates of neonatal
hypoglycemia requiring intravenous therapy, jaun-
dice requiring phototherapy, or respiratory disease
requiring supplemental oxygen. Importantly, treat-
ment did reduce the frequency of LGA neonates from
22% to 13% and birth weight greater than 4,000 g
from 21% to 10%. Among maternal outcomes, pre-
eclampsia was significantly reduced with treatment
(12% compared with 18%).

At the same time as the Australian Carbohydrate
Intolerance Study in Pregnant Women was being
planned, the NICHD MFMU Network designed a
randomized controlled trial of mild GDM to deter-
mine whether intervention reduces perinatal mortal-
ity and obstetric complications.26 Among the 958
women randomized, no significant difference in the
frequency of the primary composite perinatal out-
come (perinatal death, neonatal hypoglycemia, ele-

teved cord C-peptide level or birth trauma) was found
in the treatment group (32.4%) compared with the
usual care group (37.0%; P=.14). Several key differ-

Table 3. Diagnosis of Overt Diabetes in
Pregnancy*

<table>
<thead>
<tr>
<th>Measure of Glycemia</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>At least 7.0 mmol/L (126 mg/dL)</td>
</tr>
<tr>
<td>A1C</td>
<td>At least 6.5%</td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>At least 11.1 mmol/L (200 mg/dL) plus confirmation</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose.

* Apply to women without known diabetes antedating pregnancy.

Modified from International Association of Diabetes and Pregnancy
Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson
B, Buchanan TA, Catalano PA, et al. International association of
diabetes and pregnancy study groups recommendations on the
diagnosis and classification of hyperglycemia in pregnancy.
Diabetes Care 2010;33:676–82.
ences in secondary outcomes were, however, observed with treatment including a lower frequency of LGA neonates, birth weight exceeding 4,000 g, and decreased neonatal fat mass.

Among maternal outcomes, rates of labor induction were similar between groups; however, cesarean delivery was less often performed in treated women (26.9% compared with 33.8%). A lower rate of shoulder dystocia (1.5% compared with 4.0%) and preeclampsia or gestational hypertension (8.6% compared with 13.6%) was also found in the treatment group.

In summary, the NICHD MFMU Network trial demonstrated that although treatment of mild GDM did not reduce the frequency of several neonatal morbidities characteristic of diabetic pregnancy, it did lower the risk for fetal overgrowth, neonatal fat mass, shoulder dystocia, cesarean delivery, and hypertensive disorders of pregnancy. Importantly, these findings along with those reported in the Australian Carbohydrate Intolerance Study in Pregnant Women confirmed perinatal and maternal benefits from treatment of even mild carbohydrate intolerance of pregnancy.27 (Table 4). As previously mentioned, whether the benefits described in the two randomized controlled trials for treatment of GDM might be extended to additional women who might be identified by the proposed International Association of Diabetes and Pregnancy Study Group criteria remains unknown. Another significant gap in our knowledge concerns whether long-term benefits to women and their offspring result from the treatment of GDM irrespective of the criteria used for the diagnosis.29

**TREATMENT OF THE WOMAN WITH GESTATIONAL DIABETES MELLITUS**

The mainstay of treatment of GDM remains nutritional counseling and dietary intervention. The optimal diet should provide caloric and nutrient needs to sustain pregnancy without resulting in significant postprandial hyperglycemia.30 Women with GDM in most cases can receive dietary instruction and self blood glucose management teaching in an outpatient setting. Once the diagnosis is established, women are begun on a dietary program of 2,000–2,500 kcal daily.30 This represents approximately 35 kcal/kg of present pregnancy weight. A diet composed of 50–60% carbohydrates will often result in excessive weight gain and postprandial hyperglycemia. For this reason, it has been suggested that carbohydrate intake be limited to 33–40% of calories.31 Complex carbohydrates are preferred to simple carbohydrates because they are less likely to produce significant postprandial hyperglycemia. However, adequately powered randomized trials are lacking to determine the benefit of low glycemic index carbohydrate diets in GDM. In practice, three meals and two to three snacks are recommended to distribute glucose intake and to minimize postprandial glucose excursions.

In light of the 2009 Institute of Medicine (IOM) recommendations concerning weight gain during pregnancy, the question arises as to whether caloric restriction, limited weight gain, or both may be advisable in obese women with GDM. The IOM now recommends a weight gain of 11–20 pounds compared with the previous recommendation of at least 15 pounds for obese women (BMI 30 or higher).32 A specified carbohydrate limited diet in obese women with GDM improves glycemic control and reduces weight gain. Both the Australian Carbohydrate Intolerance Study in Pregnant Women and the NICHD MFMU Network trial demonstrated that treated women with GDM experience less weight gain compared with women in a control group.26,27

There appears to be an independent effect of maternal obesity, weight gain, and diabetes on birth weight.33,34 Cheng and associates reported that women diagnosed with GDM who had gestational weight gain exceeding 15 pounds had a higher risk of preterm delivery, macrosomia, and cesarean delivery. Langer found that women with diet-controlled GDM who were obese had an increased risk for fetal macrosomia compared with women of normal weight with GDM.34 In well-controlled insulin-treated women with GDM, he observed no increased risk of macrosomia with increasing maternal BMI. Given that the IOM guideline only provides a recommendation for the general category of obese women, some have called for recommendations in which gestational weight gain is more individualized especially for different categories of obese women.35 In a study of nearly 300,000 nondiabetic women, limited gestational weight gain of less than 6 kg was associated with improved pregnancy outcomes for obese women.36

### Table 4. Results of Randomized Controlled Trials for Treatment of Gestational Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Landon et al27</th>
<th>Crowther et al26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Weight gain</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Neonatal fat mass</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>↓</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, nonsignificant. — indicates not assessed by Crowther study.
morbidty, including macrosomia, birth trauma, shoulder dystocia, hypoglycemia, and jaundice, was found to increase with increasing maternal BMI categories including a subset of morbidly obese women (BMI greater than 40). However, weight gain was not considered as an independent variable. Nonetheless, an individualized approach to weight gain recommendations seems reasonable for obese women with GDM. It must be recognized that there are few studies examining caloric restriction in GDM, and most include a small sample size. Caloric restriction less than 1,500 kcal/d is associated with ketonuria. Although the adverse fetal effects of maternal ketonuria long have been debated, caloric restriction (less than 1,500 kcal/d) is not recommended in treating GDM.

Regular physical activity improves insulin sensitivity and may therefore be a useful adjunct in the treatment of GDM. Although one randomized trial of 19 women demonstrated improved fasting and postprandial glucose levels in the exercise group (20 minutes per day three times weekly) compared with the control group, other studies of exercise in GDM have shown mixed results. Although these studies lack statistical power to assess benefits specific to women with GDM, it is accepted that regular exercise promotes a healthy lifestyle and it is recommended for GDM women.

Once the woman with GDM is placed on an appropriate diet, surveillance of blood glucose levels is necessary to be certain that glycemic control has been established. Daily self blood glucose monitoring has been associated with a decline in macrosomia, although nearly half of all women using self blood glucose monitoring in one study required insulin therapy. A practical approach may be to initially provide women with GDM with a reflectance meter. If after a few weeks both fasting and postprandial measurements are within the normal range, the frequency of testing can be reduced and tailored accordingly. In women using self blood glucose monitoring, there is considerable variation regarding the frequency and timing of recommended testing. Both randomized controlled trials for the treatment of GDM used four times per day testing consisting of a fasting determination followed by three postprandial tests. Some individuals prefer 1-hour postprandial assessment as opposed to 2-hour testing after meals because the 1-hour postprandial value often represents peak glucose excursion.

Target thresholds of a fasting glucose less than 95 mg/dL and 1-hour postprandial glucose less than 140 mg/dL as well as 2-hour postprandial glucose less than 120 mg/dL have been suggested by the Fifth International Workshop Conference on GDM. Emerging data in pregnant women using the technology of continuous blood glucose monitoring suggest that normoglycemia in pregnancy may be considerably lower than the cited recommended targets for management of GDM. The use of the mentioned cutoffs for initiating medical management are based on data regarding increased perinatal morbidity when such values are exceeded in women with pre-existing diabetes. These therapeutic targets were thus chosen to alleviate the risk for fetal macrosomia; however, they have never been prospectively tested in comparison with lower targets. Until data are available from controlled trials to identify ideal glycemic targets for prevention of fetal risk for women with GDM, the recommended target thresholds (Table 5) are suggested for clinical use.

Insulin has been the preferred medication for women with GDM who fail to achieve satisfactory glucose control with dietary intervention. These women demonstrate elevated glucose levels in the majority of tests at a particular time of the day. In our experience, approximately 25% of women with GDM require medical management. Some women are managed with a single dose of bedtime neutral protamine Hagedorn insulin (usual starting dose 0.2 units/kg body weight) in response to elevated fasting glucose levels, whereas other women may require only injections of short-acting insulin to cover postprandial hyperglycemia. In cases in which both fasting and postmeal hyperglycemia are evident, a regimen of multiple injections combining intermediate-acting and short-acting insulin is administered. The starting total dose is generally 0.7–1.0 units/kg daily. Approximately 50% of total daily insulin is administered as neutral protamine Hagedorn (given at breakfast and bedtime) with the remainder consisting of either insulin lispro or aspart, both rapid-acting insulin analogs before meals as necessary. The short-acting analogs are safe and are superior to regular insulin in reducing postprandial glucose excursions. Long-acting insulin analogs (insulin glargine and detemir) have been designed to more accurately mimic basal insulin secretion, yet neither has been extensively

Table 5. Target Plasma Glucose Levels in Pregnancy

<table>
<thead>
<tr>
<th>Time</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before breakfast</td>
<td>60–90</td>
</tr>
<tr>
<td>Before lunch, supper, bedtime snack</td>
<td>60–105</td>
</tr>
<tr>
<td>2 h after meals</td>
<td>At or below 120</td>
</tr>
<tr>
<td>2 AM to 6 AM</td>
<td>Above 60</td>
</tr>
</tbody>
</table>
studied in women with GDM. For this reason, we continue to use neutral protamine Hagedorn insulin when indicated.

Some authors have suggested that estimation of glycemia alone may not be sufficient to optimally prescribe insulin therapy in GDM. Several randomized trials have evaluated the use of fetal ultrasonographic measurements to guide insulin therapy in women with GDM. In diet-treated patients with GDM, ultrasonography performed at 29–33 weeks has been used to identify pregnancies with fetuses having a large abdominal circumference (greater than 75th percentile). In several studies, these women have been randomized to diet compared with diet and insulin treatment. The insulin-treated groups have demonstrated a reduced frequency of LGA neonates compared with those in control groups. Less intensified management has thus been suggested when normal fetal growth is apparent (fetal abdominal circumference less than 75th percentile for gestational age), although self blood glucose monitoring is still recommended.

Over the past decade, oral antidiabetic therapy has emerged as an alternative to insulin treatment in women with GDM. Concerns with first-generation sulfonylurea agents included potential teratogenesis and increased neonatal hypoglycemia as a result of fetal β-cell stimulation. A systematic review of the evidence from randomized trials and observational studies concluded that glycemia was equivalent in women receiving oral hypoglycemic agents compared with those receiving insulin. Moreover, there was no evidence of increased adverse neonatal outcomes with oral hypoglycemic agent use. However, studies to date have been inadequately powered to detect differences in relevant neonatal outcomes.

Glyburide, a second-generation sulfonylurea that binds to pancreatic β-cell receptors to increase insulin secretion as well as increasing peripheral insulin sensitivity is the most commonly used oral agent used in the treatment of GDM. Many women with GDM prefer the use of oral agents to insulin and convenience, cost, and compliance have all been considered as relative advantages to insulin therapy. Seminal work from Langer and colleagues, a randomized trial of 404 women receiving insulin compared with glyburide, noted similar improvement in glycemia with both regimens. The frequency of macrosomia and neonatal hypoglycemia was similar in the two study groups. Only 4% of women failed glyburide therapy, requiring a change to insulin. In contrast to Langer’s findings as well as those of two other randomized controlled trials, a recent small-scale randomized controlled trial demonstrated higher mean fasting glucose levels in women treated with glyburide compared with insulin (95.6±13.4 mg/dL compared with 89±13.2 mg/dL). With regard to neonatal outcomes, Nicholson and colleagues, in their meta-analysis, conclude that insulin may be associated with a neonatal birth weight lower by an average of 95 g compared with glyburide, but this difference was not statistically significant. A similar conclusion was reached by Moretti in a 2008 meta-analysis, which revealed that the risk of macrosomia with glyburide was not increased over insulin (OR 1.07, 95% confidence interval 0.78–1.47).

Lain and colleagues recently reported results of a randomized trial of 99 women with GDM, comparing glyburide and insulin treatment. These authors reported no increase in neonatal fat mass, BMI, ponderal index, or anthropometric measures in the offspring of glyburide-treated patients, although a significantly greater rate of neonates larger than 4,000 g was observed in the glyburide-treated group (22% compared with 2.4%). Similar to insulin therapy, glyburide action must be carefully balanced with meals and snacks to prevent maternal hyperglycemia. Observational data suggest that glyburide may be less successful in obese women or those with marked hyperglycemia discovered early in gestation. The usual dose of glyburide is 2.5–20 mg daily in divided doses, although pharmacokinetic studies during pregnancy indicate daily doses as great as 30 mg may be necessary to achieve adequate control. In our experience, most women with a fasting glucose 115 mg/dL or greater will not be adequately controlled with glyburide and require insulin. Thus, insulin is prescribed from the outset in such cases.

Metformin has also been used for treatment of GDM. Metformin is a biguanide that acts to inhibit hepatic gluconeogenesis as well as to stimulate glucose uptake in peripheral tissues. Although metformin clearly crosses the placenta, it does not appear to be teratogenic. Rowan and colleagues randomized 761 women with GDM at 20–33 weeks to metformin (and insulin as needed) compared with insulin therapy. Maternal glycemia was similar in both arms of the study. There were also no differences in perinatal outcomes as reflected in a composite of perinatal morbidity (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, and prematurity), which was observed in approximately one-third of women in each group. Metformin use was well tolerated. However, 46% of women receiving metformin required supplemental insulin to achieve glycemic control.
It appears that glyburide may be superior to metformin in achieving satisfactory control in women with GDM. A randomized trial of 149 women compared metformin with glyburide for the treatment of GDM. Thirty-five percent of women randomized to metformin compared with 16% receiving glyburide required insulin to achieve adequate control. In our practice, most women entering pregnancy on metformin are switched to insulin therapy.

The safety of the use of oral agents in pregnancy continues to be challenged. In Langer's randomized controlled trial, cord blood analysis revealed no detectable glyburide in exposed pregnancies. More recently, Hebert and colleagues have reported that glyburide does cross the placenta in significant amounts. Although clinical studies have failed to reveal increased rates of neonatal hypoglycemia with glyburide use in GDM, it is, however, unknown whether glyburide can affect progression to type 2 DM in treated women or whether glucose homeostasis is altered later in life in their offspring. Prospective studies assessing the newborns and children of women treated with both glyburide and other oral agents such as metformin are thus desperately needed to provide information regarding long-term safety. In the meantime, clinicians must inform women with GDM that although relative short-term risks of currently used oral agents appear to be minimal if any compared with insulin, theoretical concerns do exist about long-term safety. This disclosure must be considered before a decision is reached concerning their use.

FETAL SURVEILLANCE

Women with GDM who are well controlled are at low risk for an intrauterine death. For this reason, we do not advocate routine antepartum fetal heart rate testing in uncomplicated diet-controlled GDM. Women with hypertension, a history of a prior stillbirth, or suspected macrosomia are monitored with nonstress testing. Women in these categories as well as those who require insulin or oral agents for treatment undergo twice-weekly heart rate testing at approximately 32 weeks of gestation. Using such a protocol, we have observed only five intrauterine deaths in more than 2,800 women with uncomplicated GDM over the past 20 years. Thus, it appears that the third-trimester stillbirth rate in uncomplicated GDM may be no higher than that of the general obstetric population. At present, without prospective studies comparing outcomes in monitored and nonmonitored women with GDM without other risk factors, it is not possible to determine if any benefits exist to antepartum fetal heart rate testing in this population. Many practitioners choose to evaluate fetal growth with serial ultrasonographic measurements after the established diagnosis of GDM. Our approach is to assess fetal growth shortly after diagnosis and again at 36–39 weeks to assist in planning for delivery.

TIMING AND MODE OF DELIVERY

Because many obstetricians have extrapolated the increased risk for stillbirth in women with type 1 and type 2 DM to those with GDM, a remarkable number of such pregnancies are subject to scheduled delivery at term. If glycemic control is suboptimal, or maternal hypertension or a previous stillbirth exists, such an approach seems reasonable. The use of amniocentesis to document fetal lung maturity in such cases should be based on clinical circumstances. It is debatable as to whether scheduled induction should be the standard approach for pregnancies complicated by GDM. Available observational and retrospective data do not permit an evidence-based recommendation. A retrospective analysis of 124 women with GDM delivered beyond 40 weeks of gestation compared with the same number of women with GDM delivered before their expected date of confinement revealed no significant differences in perinatal outcome, rates of cesarean delivery, or shoulder dystocia among the two study groups. In contrast, a follow-up prospective study from the same institution of 96 insulin-requiring patients with GDM demonstrated that induction at 38–39 weeks was associated with a 1.4% shoulder dystocia rate compared with 10.2% in historic control groups.

Kjos and colleagues conducted a prospective randomized trial of active induction of labor at 38 weeks of gestation compared with expectant management in a series that included 187 insulin-requiring women with GDM. The cesarean delivery rate was not significantly different in the expectant-management group (31%) from the active-induction group (25%). However, an increased prevalence of LGA neonates (23% compared with 10%) was observed in the expectant management group. Moreover, the frequency of shoulder dystocia was 3% in this group with no cases reported in those undergoing induction at 38 weeks of gestation. These data led the authors to conclude that scheduled elective induction be considered in insulin-requiring patients with GDM because it does not increase the risk of cesarean delivery and lowers the risk for fetal death. With this single randomized controlled trial and few observational studies addressing the issue of timed delivery in GDM, further studies that evaluate a broader range of out-
comes are needed to provide evidence to inform clinical practice.61

Choosing the route of delivery for the woman with GDM remains a challenge. Contributing to this clinical dilemma is the observation that the overall risk for shoulder dystocia in the macrosomic infant of a diabetic mother is greater than in large infants of normal pregnancy. The risk for shoulder dystocia with a fetal weight greater than 4,000 g in diabetic pregnant women is approximately 30%.62 Somewhat less impressive yet significantly greater frequencies of shoulder dystocia for delivery of macrosomic infants in pregnant women with diabetes has been reported by Nesbitt and colleagues (Fig. 2).63

The increased rate of shoulder dystocia and brachial plexus injury in the offspring of diabetic women has prompted adoption of early induction strategies as well as selection of patients for cesarean delivery based on ultrasonographic estimation of fetal size. Such approaches are limited by the relative inaccuracy of ultrasonographic prediction of birth weight. Conway and colleagues evaluated the effect of implementation of a protocol in which cesarean delivery was recommended in women with GDM with ultrasonography-estimated fetal weight of 4,250 g or greater and induction was carried out if estimated fetal weight was between 4,000 and 4,249 g.64 These authors noted a reduction in cases of shoulder dystocia from 2.4% to 1.1% with a modest increase in cesarean delivery from 21.7% to 25.1%.64 There is general agreement that prophylactic cesarean delivery can reduce the frequency of shoulder dystocia and related brachial plexus injury. However, maternal risk of operative delivery must be weighed against fetal risks in such a discussion. In a decision tree analysis of cost-effectiveness, Rouse and colleagues found that elective cesarean delivery for macrosomia to prevent permanent brachial plexus injury was prohibitively expensive in the nondiabetic woman, at a cost of several million dollars per permanent brachial plexus injury prevented.65 For pregnancies complicated by diabetes, 489 cesarean deliveries at a cost per avoided birth injury of $880,000 per case with an estimated fetal size greater than 4,000 g seemed to be at least tenable.65

Others have similarly attempted to theoretically calculate the number of cesarean deliveries required at various estimated fetal weights to prevent a case of permanent brachial plexus injury.66 A range of 58–588 cesarean deliveries with an estimated fetal weight of 4,500 g and 148–962 cesarean deliveries with estimated fetal weight of 4,000 g have been suggested as needed to prevent a single case of permanent palsy.67 Some of these analyses have considered cost, whereas others have not evaluated either medical or medicolegal economic effect. Potential flaws exist in all of these analyses inasmuch as the frequency of shoulder dystocia in diabetic pregnancies has been derived from selected populations in which the highest risk cases may have been delivered by cesarean delivery without labor. Additionally, the rate of permanent brachial plexus palsy after transient injury used in such analyses is based on limited data from studies nearly 40 years ago. At present, the College recommends consideration of cesarean delivery in diabetic women when estimated fetal weight exceeds 4,500 g.68 Our approach is to individualize and thereby consider cesarean delivery when the estimated weight is 4,000–4,500 g after carefully evaluating both obstetric history and clinical pelvimetry.

POSTPARTUM FOLLOW-UP AND PREVENTION OF TYPE 2 DIABETES

Women with GDM have a sevenfold increased risk of eventually developing type 2 DM relative to women who do not have diabetes during pregnancy.69 O’Sullivan’s original cohort of women with former GDM indicated a prevalence of diabetes of 50–60% at 28 years of follow-up.5 A recent follow-up study of up to 10 years in 11,270 patients with GDM com-
pared with 174,146 patients in a control group revealed a 15.7% frequency of diabetes in patients who had GDM compared with 1% in the non-GDM population. Abnormal carbohydrate intolerance may persist in the postpartum period depending on the population studied and its associated risk factors. As many as one-third of women with GDM will have overt diabetes, impaired fasting glucose, or impaired glucose tolerance identified during postpartum testing conducted within 6–12 weeks of delivery. Thus, both the American Diabetes Association and the College (Fig. 3) recommend postpartum glucose testing after a diagnosis of GDM. Despite these guidelines, the prevalence of postpartum glucose screening with either a fasting plasma glucose or a 2-hour OGTT has ranged from only 23% to 58% in seven reported studies.

Recognizing that the 2-hour 75-g OGTT has been traditionally recommended for postpartum evaluation, there is some debate as to whether postpartum glucose testing can be limited to a fasting glucose determination alone. Whereas some have reported sufficiently high sensitivity using a fasting glucose alone (cutoff 6.0 mmol/L or 108 mg/dL) to detect diabetes in prior GDM, more recent reports indicate the need for a complete 2-hour 75-g OGTT to achieve satisfactory sensitivity. Currently, the College recommends using either a fasting plasma glucose or a 75-g 2-hour OGTT at 6–12 weeks postpartum. The optimal frequency of subsequent testing has not been established. However, we follow the American Diabetes Association recommendation to repeat testing at least every 3 years for women with prior GDM and normal results of postpartum screening.

As a high risk for subsequent diabetes exists in former GDM, this population is ideally suited for preventive strategies to lower their risk for deteriorating carbohydrate tolerance. The American Diabetes Association recommends that women with prior GDM should receive education about lifestyle modifications, whereas those with impaired glucose tolerance at postpartum screening should receive medical nutrition therapy and an individualized exercise program. There is substantial evidence that both lifestyle changes and pharmacotherapy can prevent or delay the progression of impaired glucose tolerance to type 2 DM after GDM. In the Diabetes Prevention Program, which compared lifestyle changes with metformin therapy, intensive lifestyle changes of diet and exercise resulted in an average weight loss of 15 pounds, most of which was sustained throughout the study. Fewer individuals randomized to lifestyle intervention developed diabetes (14%) compared with 22% in the metformin group and 29% in placebo-treated patients. In contrast to the findings in the entire study group, Ratner and colleagues found that metformin and lifestyle intervention were similarly effective in reducing the incidence of diabetes in women with prior GDM. In women with a history of GDM and impaired glucose tolerance, the incidence of subsequent diabetes was reduced by 50% and 53% in patients receiving metformin and lifestyle intervention, respectively, compared with placebo. It follows that women with GDM found to have impaired glucose tolerance on postpartum glucose tolerance testing should be referred for preventive therapy. Additional study is needed to determine if such interventions are of benefit in women who do not have impaired glucose tolerance on postpartum testing.

Women with GDM are at high risk for recurrence in future pregnancies. Getahun and colleagues found a 41.3% incidence in second pregnancies. Because of the high recurrence risk of GDM, we recommend first-trimester screening or testing followed by 24- to 28-week screening or testing in those not found to have GDM earlier in pregnancy.
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