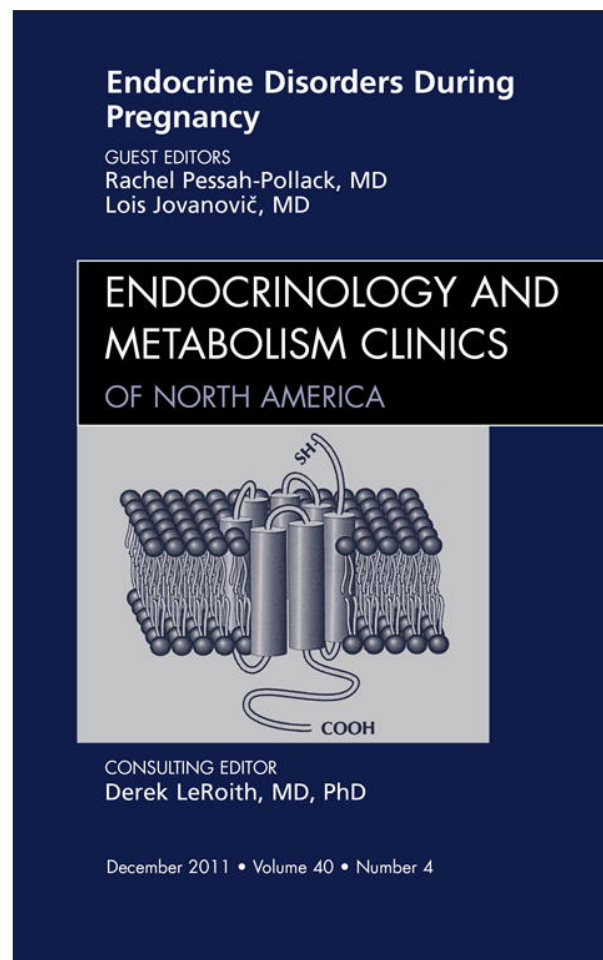


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# Diagnosis and Treatment of Hyperglycemia in Pregnancy

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## KEYWORDS

- Gestational diabetes mellitus • Type 2 diabetes
- Large for gestational age • Blood glucose
- Oral glucose tolerance test • Self-monitoring of blood glucose
- American Association of the College of Endocrinologists
- Certified diabetes educators

Gestational diabetes mellitus (GDM) has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy.<sup>1</sup> This definition is a misnomer in that it includes unrecognized overt diabetes that may have existed before pregnancy and hyperglycemia that is diagnosed concurrently with pregnancy. Those with suspected type 2 diabetes mellitus (T2DM) have been referred to as “hyperglycemia in pregnancy,” despite evidence of severe hyperglycemia consistent with pre-existing T2DM. Because the term “gestational diabetes mellitus” is confusing, the authors recommend use of the term “hyperglycemia in pregnancy,” as defined by the Endocrine Society.<sup>2</sup>

## SIGNIFICANCE

The prevalence of hyperglycemia in pregnancy varies in direct proportion to the prevalence of type 2 diabetes in a given population or ethnic group. Whereas in 1964 the prevalence of hyperglycemia in pregnancy was 1% to 4%,<sup>3</sup> the current estimate is 7%

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The authors have nothing to disclose.

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to 14%.<sup>3</sup> In 1964, the number of adults estimated to have type 2 diabetes in the United States was 2.3 million and in 2011 estimates were as high as 25.6 million, indicating that type 2 diabetes in America is increasing in an epidemic pattern. Likewise, hyperglycemia in pregnancy is a silent epidemic. If current trends continue, by 2050 one in three Americans will have diabetes.<sup>3</sup>

Hyperglycemia in pregnancy shares the pathophysiology of type 2 diabetes (increased insulin resistance and hyperinsulinemia) and confers an increased lifetime risk for future type 2 diabetes for both the mother and her newborn. Hyperglycemia in pregnancy is not just a pregnancy problem. Soon after giving birth, 90% to 95% of women with hyperglycemia in pregnancy are diabetes-free by a standard 2-hour 75-g oral glucose tolerance test (OGTT). By 6 to 12 weeks, 4% to 9% are diagnosed with T2DM. More than 20% have impaired glucose tolerance or impaired fasting glucose or both (prediabetes). By 36 months, 30% have metabolic syndrome (dysglycemia, abnormal lipid profile, hypertension, and central adiposity). By 5 years, 50% have T2DM. The cumulative risk over 10 years is 2.6% to 70%.<sup>4</sup> Fetal, neonatal, and adult consequences of uncontrolled maternal hyperglycemia include a variety of serious short- and long-term consequences (**Table 1**).

Detection and diagnosis of hyperglycemia in pregnancy provides an opportunity to assist women to establish healthy lifestyle habits and give them tools to reduce maternal and fetal risks (see **Table 1**) by facilitating normoglycemia. Providers who manage diabetes care during pregnancy are in the unique position to educate women about a healthy lifestyle and prevention of T2DM. The primary goals of hyperglycemia in pregnancy diagnosis are to reduce the short- and long-term risks associated with mild to moderate hyperglycemia during pregnancy through healthy lifestyle education.<sup>5,6</sup>

## SCREENING

For decades, the American Diabetes Association (ADA) published a two-step glucose screening and diagnosis of hyperglycemia in pregnancy that was solely based on the woman's risk for developing T2DM in the future.<sup>7</sup> The recommendations included the avoidance of screening in women considered low risk: less than 25 years of age, normal body weight, no family history of diabetes, and not a member of an ethnic or racial group at high risk for diabetes. The Fifth International Workshop on Gestational Diabetes in November 2005 recommended that hyperglycemia in pregnancy risk assessment should be ascertained at the first prenatal visit. The American College of Obstetricians and Gynecologists (ACOG) recommends that all pregnant patients

| <b>Table 1</b><br>Fetal, neonatal, and adult consequences of uncontrolled maternal hyperglycemia during pregnancy |                          |
|---|--------------------------|
| <b>Short Term (Fetal and Neonatal)</b>  | <b>Long Term (Adult)</b> |
| LGA   | Obesity                  |
| Organomegaly  | Visceral adiposity       |
| Neonatal hypoglycemia   | Hyperinsulinemia         |
| Transient tachypnea, respiratory distress   | Insulin resistance       |
| Birth trauma (Erb palsy, asphyxia, fractured bones)   | T2DM                     |
| Feeding abnormalities   | Cardiovascular disease   |
|   | Metabolic syndrome       |

be screened for hyperglycemia in pregnancy, whether by patient history, clinical risk factors, or a laboratory test to determine blood glucose (BG) levels early in pregnancy.<sup>8</sup> In 1996, the US Preventive Services Task Force concluded that evidence was insufficient to recommend for or against routine screening for hyperglycemia in pregnancy, and this recommendation remained unchanged in 2003.<sup>9</sup> Two subsequently published studies show benefit (particularly a reduction in macrosomia) when women are treated for hyperglycemia in pregnancy versus no treatment.<sup>5,6</sup>

Most American providers have used a two-step method involving a nonfasting 1-hour 50-g oral glucose screen (glucose loading test) with a subsequent diagnostic 3-hour 100-g OGTT for those who failed the initial screen. Screening reduces the number of women who would have to be subjected to a fasting plus 3-hour 100-g OGTT. Using a plasma glucose threshold greater than or equal to 140 mg/dL for screening has a sensitivity of 80% and specificity of 90% for a positive OGTT. Lowering the threshold to greater than or equal to 130 mg/dL increases the sensitivity to 90% but also increases the number of women requiring diagnostic testing by 60%. ACOG and ADA endorse either cut point.<sup>5,6</sup>

## DIAGNOSIS

Women who fail the 1-hour glucose loading test screen take a 3-hour 100-g glucola OGTT and are considered to have hyperglycemia in pregnancy if two of the four values equal or exceed the cut points of fasting BG 95 mg/dL, 1-hour after 100-g glucola of 180 mg/dL, 2-hour of 155 mg/dL, and 3-hour of 140 mg/dL.<sup>10</sup> If hyperglycemia in pregnancy is not diagnosed, the OGTT should be repeated at 24 to 28 weeks gestation or any time a patient presents with signs or symptoms suggestive of hyperglycemia.<sup>11</sup> Women with an abnormal 3-hour OGTT who are less than 24 weeks gestation may have undiagnosed T1DM, T2DM, or prediabetes but the diagnosis of preexisting diabetes or prediabetes can only be made definitively after delivery regardless of the severity of hyperglycemia.<sup>11</sup>

This method remained the gold standard in the United States with changes in the glucose cutoffs as glucose assays changed and the use of plasma replaced whole blood. Internationally, more than 10 different ways of diagnosing hyperglycemia in pregnancy included one- or two-step procedures primarily using a 2-hour 75-g OGTT but with a variety of different cut points and numbers of abnormal values required to diagnose hyperglycemia in pregnancy. Until now, no worldwide standard existed for the diagnosis of hyperglycemia in pregnancy.

## THE HYPERGLYCEMIA AND ADVERSE PREGNANCY OUTCOME STUDY

For the last 50 years, the diagnosis of hyperglycemia in pregnancy has been based on the 100-g, 3-hour OGTT that predicts the risk of the mother developing diabetes in the future.<sup>12</sup> Physicians have not had useful guidelines to link the diagnosis of hyperglycemia in pregnancy to neonatal outcomes. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study is a basic epidemiologic investigation designed to clarify unanswered questions about the association between various levels of glucose during the third trimester of pregnancy that indicate that the mother, fetus, and newborn are at increased risk for adverse outcomes. This 7-year international study was conducted in 15 centers in nine countries with 23,325 women participating in the study.

The women were given a 2-hour 75-g OGTT at 24 to 28 weeks of gestation. Providers and patients were blinded to the results unless they exceeded predefined cutoff values requiring treatment. The cutoffs were as follows: fasting BG greater than 105 mg/dL or 2-hour greater than 200 mg/dL or random BG at 34 weeks greater

than 160 mg/dL. The women who exceeded the cutoffs were removed from the study and treated for diabetes. The remainder received routine prenatal care, a random BG at 34 weeks, and fetal kick counts. Primary outcomes included those listed in **Boxes 1** and **2**.<sup>10</sup>

Results indicated that there is a continuous, positive, independent relationship between maternal BG and percent newborn body fat, and between cord C-peptide concentrations and percent newborn body fat.<sup>11</sup> This suggests that the relationship between maternal glycemia and fetal fat deposition is mediated by fetal insulin production. The association between hyperglycemia and poor outcomes was continuous, making it difficult to identify threshold criteria below which no risk is present. The task of translating these associations into diagnostic criteria was assigned to a committee of experts formed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG). In March 2010, the group published recommendations for a global method of diagnosing hyperglycemia in pregnancy using glucose cutoffs based on an odds ratio of 1.75 for having one of the primary adverse outcomes listed in **Box 1**.<sup>11</sup> **Table 2** provides a comparison of the old and new methods for diagnosing hyperglycemia in pregnancy. The 2011 ADA Standards of Medical Care published the IADPSG recommended method as the standard method of diagnosing hyperglycemia in pregnancy discontinuing all other methods.<sup>12</sup> This was in concert with many countries.

#### **PREGNANCY: A DIABETOGENIC STATE**

Normal pregnancy can be viewed as a progressive condition of insulin resistance, hyperinsulinemia, and mild postprandial hyperglycemia mediated by increasing placental secretion of antiinsulin hormones including, progesterone, human placental lactogen, cortisol, growth hormone, and tumor necrosis factor (TNF)- $\alpha$ . This prepares the mother for the increased demands of the fetus for amino acids and glucose in the latter half of pregnancy. Mild postprandial hyperglycemia serves to increase the amount of time that maternal glucose levels are elevated above the basal after a meal, thereby increasing the flux of ingested nutrients from mother to the fetus and enhancing fetal growth.<sup>13</sup>

The fetal demand for glucose in the third trimester is met during maternal fasting by hepatic glucose production, which increases 15% to 30% by late third trimester. The liver begins to supply glucose within 5 to 6 hours of the last meal when absorption of nutrients from the intestinal tract ceases. Depletion of glycogen stores results from this accelerated hepatic glucose production. Lower fasting values (55–65 mg/dL) offset the postprandial elevations resulting in 24-hour mean glucose values similar to non-gravid women.<sup>14</sup>

Fetal growth accelerates in the last trimester of pregnancy. During the last trimester, the fetus is constantly feeding while the mother alternates between fasting and

#### **Box 1**

##### **HAPO study primary neonatal outcomes**

- Birth weight above the 90th percentile for gestational age
- Primary cesarean delivery
- Clinically diagnosed neonatal hypoglycemia
- Cord-blood serum C-peptide level above the 90th percentile

*Data from* The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002.

**Box 2**

**Objectives of medical nutrition therapy in diabetes and pregnancy**

- Determine energy needs
- Set appropriate weight goals
- Develop an individualized, nutritionally balanced meal plan
- Provide education concerning nutrition-related lifestyle issue
- Counsel on the importance of normoglycemia before, during, and after pregnancy
- Evaluate adherence to the meal plan

*Adapted with permission from the California Department of Public Health, California Diabetes and Pregnancy Program Sweet Success Guidelines for Care 2006. Funding for the development of the original materials was provided by the Federal Title V block grant from the California Maternal, Child and Adolescent Health Division.*

feeding. Glucose is transported across the placenta from the mother to the fetus by facilitated diffusion. The concentration of glucose within the fetus is approximately 15% to 20% lower than maternal glucose.<sup>13</sup> Insulin does not cross the placenta. The fetus synthesizes its own insulin starting at 9 to 12 weeks gestation. From gestational weeks 9 to 15, maternal insulin requirements decrease. Reasons for this decrease are not well understood.

Fetal  $\beta$  cells respond to an increase in glucose and amino acids. Amino acids are transported against a concentration gradient from the maternal to fetal circulation. The fetal concentration of amino acids is three to four times that of the maternal concentration.

Late pregnancy has also been characterized as a catabolic phase or a period of accelerated starvation, which consists of an earlier switch from carbohydrate to fat metabolism (lipolysis) with fasting.<sup>14</sup> This metabolic response to fasting develops in 14 to 18 hours in pregnant women (accelerated starvation) and in 2 to 3 days in the nonpregnant state.<sup>13</sup> Ketones also cross the placenta in the direction of the concentration gradient. Ketones may be used as an alternate fuel for the fetus when glucose is not available. The hyperglycemia in pregnancy diet is designed to provide frequent

**Table 2**  
**Diagnosing hyperglycemia in pregnancy**

|                    | <b>Old Method<sup>10</sup></b>   | <b>New Method<sup>11</sup></b>   |
|--------------------|--|--|
| 24–28 wk gestation | Screen high-risk or all women  | Universal testing of all pregnant women  |
| Screen             | 1-h 50-g glucose load, nonfasting, glucose loading test; if $\geq 130$ or 140, proceed to diagnostic test    | None   |
| Diagnostic test    | After 8- to 12-h fast, obtain fasting; provide 100-g glucose load; then obtain 1-, 2-, and 3-h venous BG     | After 8- to 12-h fast, obtain fasting, provide 75-g glucose load, then obtain 1- and 2-h venous BG |
| Diagnosis of GDM   | If two of the following values meet or exceed: fasting 95 mg/dL, 1-h 180 mg/dL, 2-h 155 mg/dL, 3-h 140 mg/dL | If any 1 value meets or exceeds fasting 92 mg/dL, 1-h 180 mg/dL, 2-h 153 mg/dL                     |

Data from American Diabetes Association. Standards of medical care in diabetes–2011. Diabetes Care 2011;34(Suppl 1):S11–61.



sources of small amounts of carbohydrate by encouraging small frequent meals and a bedtime snack.

## HEALTHY EATING

The cornerstone for diabetes management is healthy eating and appropriate physical activity. The diagnosis of hyperglycemia in pregnancy gives women the opportunity to focus on healthy eating and staying active to improve their lifestyle for better health. The goal of the hyperglycemia in pregnancy meal plan is to attain and maintain euglycemia and adequate nutrition for the growth and development of the fetus. The achievement of these goals is based on the individualized medical nutrition therapy (MNT) plan developed by the woman and the registered dietitian. Registered dietitians should be central to the management team and should be included in the initial assessment and on an ongoing basis.

### *Creating a Meal Plan*

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Calories for pregnancy should be comprised of 40% to 50% carbohydrates, including high-fiber fruits and starches and milk as tolerated; 20% protein; and 35% fat, preferably unsaturated and monosaturated types.<sup>15</sup> Although caloric needs are determined, they no longer dominate the meal plan. The American Dietetic Association has abandoned the 1800- to 2200-calorie ADA diet. Instead, a carbohydrate-controlled meal plan that is culturally appropriate and individualized to take into account the individual's body habitus and physical activity is recommended to achieve treatment goals. The Institute of Medicine (IOM) has set dietary reference intakes as the minimum nutrient requirements for pregnancy.<sup>16</sup> The hyperglycemia in pregnancy meal plan should be built around these requirements. Women should be taught to read labels and recognize total carbohydrates and serving sizes. Ideally, they should keep food and BG records that allow providers to suggest strategies that lead to optimal nutrition and glycemic control. Nutritional interventions should emphasize overall healthy food choices, portion control, and cooking practices that can be continued throughout life. The carbohydrates should be distributed in three meals and several snacks to decrease postprandial hyperglycemia and the risk of between-meal hypoglycemia. Aspartame has been determined to be safe as a nonnutritive sweetener in pregnancy except in women with phenylketonuria. Saccharin does cross into placental circulation but there is no evidence of harmful fetal effects.<sup>17</sup>

Because healthy eating is central to adopting a healthy lifestyle, emphasis on nutrition education is fundamental. Assessment and reevaluation of the meal plan by a registered dietitian should occur at the first hyperglycemia in pregnancy visit and then on an ongoing basis thereafter, and finally in the postpartum period. Dietary adjustments are needed as a woman learns how certain foods influence her BG. "Principles of Healthy Eating during Pregnancy" modified from the California Diabetes and Pregnancy Program Sweet Success Guidelines for Care 2002, provides a general guide in **Box 3**.

## WEIGHT MANAGEMENT

In normal pregnancy, expected weight gain varies according to the prepregnancy weight. The IOM recommendations for nonpregnant women are listed in **Table 3**.<sup>18</sup>

After the release of the 2009 IOM guidelines, some investigators and experts expressed concern that higher weight gains among a population of normal and overweight women would not reduce adverse infant outcomes and would put women at risk for delivering macrosomic infants and for postpartum weight retention.<sup>19</sup> Since

**Box 3**

**Principles of healthy eating during pregnancy**

Distribute carbohydrates intake among three meals and three snacks spaced at 2.5- to 3-hour intervals. Skipping meals or snacks can result in hypoglycemia, ketone production, or overeating later in the day. Bedtime snack should provide 15–30 g of carbohydrates and approximately 7–15 g of protein

Sample distribution of carbohydrates (individualize)

Dietary reference intakes = 175 g carbohydrates per day in pregnancy

|                |                |                |
|----------------|----------------|----------------|
| Breakfast      | Lunch          | Dinner         |
| 15-----30----- | 45-----15----- | 45-----30----- |

= 180 g carb

*Macronutrient distribution:*

- Carbohydrates: ~40%–50%; ideally, carbohydrates should be combined with protein.
- Fat: <30%; use nuts, peanut butter, canola oil, or olive oil as primary sources of fat
- Protein: ~30%; look for lean meats, fish (check safety)

*Avoid high glycemic foods at breakfast:*

- Processed, ready to eat cold cereals (instant cereals)
- Milk
- Fruit
- Fruit juice
- A breakfast that consists of whole grain starch plus protein is suggested

*Limit fruit*

- Two to three fruit servings per day

*Encourage nonstarchy vegetables*

- Greens, tomatoes, carrots, and so forth, at least five servings per day

*Protein*

- 71 g/day: meat, poultry, fish, eggs, cheese, tofu, and so forth

*Fats*

- Minimum three servings per day: nuts, oils, and so forth; watch for excess calories with fats

*Adapted with permission from the California Department of Public Health, California Diabetes and Pregnancy Program Sweet Success Guidelines for Care 2006 Updates by the California Diabetes and Pregnancy Program. Funding for the development of the original materials was provided by the Federal Title V block grant from the California Maternal, Child and Adolescent Health Division.*

then, several studies have observed that the infants of women with pregnancy weight gains within the IOM recommendations are relatively less likely to be at the extremes of birth weight for a given gestational age.<sup>19</sup> In one study, women who gained more than recommended by the IOM were three times more likely to have an infant with large for gestational age (LGA) and nearly 1.5 times more likely to have an infant with hypoglycemia or hyperbilirubinemia, compared with women whose weight gain



| <b>Body Mass Index Category</b> | <b>Weight Gain Ranges</b> |
|---------------------------------|---------------------------|
| Underweight <18.5               | 28–40 lb                  |
| Normal 18.5–24.9                | 25–35 lb                  |
| Overweight 25–29.9              | 15–25 lb                  |
| Obese $\geq$ 30                 | 11–20 lb                  |

<sup>a</sup> Certain Asian populations may need lower body mass index cut points for each body mass index category and this might impact weight gain goals for pregnancy.<sup>76</sup>

Data from Institute of Medicine Report Brief. Weight gain during pregnancy reexamining the guidelines 2009. Available from: <http://www.iom.edu/w/media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf>. Accessed September 3, 2011.

was in the recommended range.<sup>20</sup> In another study, weight gain ranges based on adverse obstetric and neonatal outcome data were lower than the IOM recommendations, and the differences were most pronounced for overweight or obese women.<sup>21</sup> Excess gestational weight gain can be associated not only with fetal LGA but also with unhealthy maternal postpartum weight retention.<sup>22</sup>

Weight gain or loss should be monitored closely and the meal plan should be adjusted accordingly. Plotting weekly body weights on a weight gain grid specific to body mass index classification is encouraged to facilitate recognition of inadequate or excess weight gain. Sample weight gain grids for pregnancy are available online based on the 2009 IOM recommendations at <http://www.cdph.ca.gov/pubsforms/forms/Pages/MaternalandChildHealth.aspx>.

### **Obesity**

No discussion of weight during pregnancy can be adequate without a discussion of obesity. Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight, at least 300 million of them clinically obese. The epidemic of T2DM has paralleled the epidemic of obesity. The likelihood of developing T2DM and hypertension rises steeply with increasing body fat. Confined to older adults for most of the twentieth century, this disease now affects obese children even before puberty. Approximately 90% of people with diabetes have T2DM, and of these, 85% are obese or overweight.<sup>23</sup> The strong presence of obesity in a population makes it certain that a significant number of women with pregestational diabetes (type 1 and type 2 diabetes) and women who subsequently develop hyperglycemia in pregnancy will enter pregnancy obese. Obese women are at increased risk for morbidity and mortality during pregnancy.<sup>24</sup> Several studies have demonstrated that the risk of congenital malformations, especially neural tube defects, is double among obese women compared with fetus of normal-weight women, after correcting for diabetes as a potential confounding factor.<sup>25,26</sup> An increased incidence of miscarriage and intrauterine fetal demise has also been associated with obesity even in the absence of diabetes.<sup>27–29</sup>

Obesity confers a certain elevated level of insulin resistance and inflammation that may mediate these adverse outcomes. When combined with hyperglycemia, morbidities increase. Even lactation can be negatively impacted because overweight or obese women were found to have a lower prolactin response to suckling, and thus diminished milk production.<sup>30</sup> Limited or no weight gain in obese pregnant women has favorable pregnancy outcomes.<sup>31</sup> Obese women with hyperglycemia in pregnancy treated with diet therapy who achieved targeted levels of glycemic control

nevertheless had a twofold to threefold higher risk for adverse pregnancy outcomes compared with overweight and normal-weight patients with well-controlled hyperglycemia in pregnancy. In obese women with body mass index greater than 30 and hyperglycemia in pregnancy, achievement of targeted levels of glycemic control was associated with enhanced outcome only in women treated with insulin.<sup>32</sup> Several studies show a protective effect of reduced gestational weight gain and even weight loss on LGA births and cesarean delivery for obese women.<sup>33</sup> An upper limit on gestational weight gain should be considered to prevent comorbidities among obese women but controversy remains as to whether the 2009 IOM recommendation of 20 lb should be that upper limit.<sup>31</sup> Weight loss during pregnancy has not been recommended in the past, but women who are obese and adhere to the meal plan prescribed for managing diabetes during pregnancy are likely to lose weight while maintaining a healthy, nutrient-rich diet. The issue of starvation ketones emerges with weight loss. No correlation exists between ketonuria and ketonemia. Ketonemia is unlikely to exist when the meal plan includes at least 1800 calories and small frequent meals. However, obese women who want to become pregnant should be counseled about the increased risks, including gestational diabetes, associated with obesity and pregnancy. Immediate referral to a dietitian to address safe weight loss before pregnancy should occur.

Some women may choose bariatric surgery as a method of weight loss. Several studies have indicated that previous bariatric surgery in patients with GDM is not associated with adverse perinatal outcomes.<sup>34</sup> Many individuals who had T2DM no longer require medication to maintain normoglycemia. When screening for gestational diabetes, an alternate method for testing is necessary. Administration of a standard glucose solution would precipitate “dumping syndrome.” Women with previous bariatric surgery may need to test their blood sugars fasting and after meals for several days to determine if they are experiencing hyperglycemia. Some providers have used continuous glucose monitoring systems to help with diagnosis.<sup>35</sup>

### **Staying Active**

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Research over the past 22 years has focused on the safety of physical activity during pregnancy. The overwhelming results of most studies show primarily beneficial effects on the maternal–fetal unit and very few negative effects.<sup>36</sup> The role of physical activity for pregnant women with diabetes has also gained acceptance and has become an essential part of the treatment plan.

Exercise facilitates the glucose uptake that regulates glucose transport and intracellular metabolism and sustains insulin sensitivity and improves glucose clearance.<sup>37,38</sup> Furthermore, exercise regulates hepatic glucose output, evidenced in fasting BG levels and the counterregulatory hormones.<sup>39</sup> Additionally, weight-bearing exercise may moderate insulin resistance, improve caloric expenditure, favorably alter basal metabolic rate, and enhance weight loss. The effect of exercise on decreasing glucose and insulin concentrations is greatest with low-intensity, prolonged exercise that uses a large muscle mass shortly (<2 hours) after mixed caloric intake.<sup>38</sup> Regular exercise during pregnancy decreases TNF- $\alpha$  originating from the placenta, a substance that directly correlates with the level of insulin resistance throughout pregnancy.<sup>38</sup>

The ADA suggests that “women without medical or obstetric contraindications be encouraged to start or continue a program of moderate exercise as part of the treatment” of hyperglycemia in pregnancy.<sup>40</sup> The American College of Sports Medicine recommends that every adult accumulate at least 30 minutes of moderate-intensity aerobic activity on most, preferably all, days of the week.<sup>36</sup> Walking is the most popular form of aerobic exercise for adults, and walking at a normal-to-brisk pace

constitutes moderate-intensity exercise. Walking is also an activity that many women can fit into their lifestyles, even when pregnant. To reduce postmeal glucose excursions, three 10-minute walks can meet this requirement. Many women with gestational diabetes find this regimen reduces or in some cases eliminates the need for insulin therapy. A 10-minute activity session timed at 30 minutes after each meal may help to control postmeal glucose excursions and reduce the need for insulin.

### **Monitoring BG**

The consideration of glycemic goals in the pregnant diabetic woman must take into account the normal glucose ranges in nondiabetic pregnant women. Recently reexamined with the use of continuous glucose monitoring systems, mean fasting BG values have been shown to range from 61 to 75 mg/dL decreasing over the course of gestation.<sup>41</sup> In diabetic and nondiabetic pregnancies, maximal postprandial glucose excursions occur between 60 and 90 minutes after meal ingestion and correlate more closely with 1- than 2-hour postprandial measurements.<sup>42</sup> Understanding these nondiabetic pregnancy values, normal glucose ranges (**Table 4**) provide additional support to the previous observation that the LGA risk increases with increasing maximal postprandial hyperglycemia.<sup>43</sup>

During a healthy pregnancy, mean fasting blood sugar levels decline progressively to a remarkably low value of  $75 \pm 12$  mg/dL. However, peak postprandial blood sugar values rarely exceed 126 mg/dL. Meticulous replication of the normal glycemic profile during pregnancy has been demonstrated to reduce the LGA rate. **Table 5** shows the commonly held BG targets for hyperglycemia in pregnancy.

Daily BG self-monitoring, compared with weekly office-based testing, is associated with a reduction in the incidence of LGA infants in women with hyperglycemia in pregnancy.<sup>44</sup> Women should be taught to check their BG using a home meter. The frequency of testing is determined by whether or not they need medication and how well their blood sugars are controlled. Suggested frequencies are listed in **Box 4** but can be modified depending on the individual circumstances.

Because of the high frequency of self-monitoring blood glucose testing required in pregnancy, the use of alternative-site self-monitoring blood glucose testing is appealing, but the dynamically changing BG concentrations after eating may be identified at finger sites before being detected at the forearm or thigh sites. Because there

|   |           |
|---|-----------|
| Mean blood glucose (mg/dL)                                  | 83.7 ± 18 |
| Fasting glucose (mg/dL)                                     | 75 ± 12   |
| Preprandial glucose (mg/dL)                                 | 78 ± 11   |
| Peak postprandial glucose value (mg/dL)                     | 110 ± 16  |
| Peak postprandial time (min)                                | 70 ± 13   |
| Mean blood glucose of 3-h postprandial measurements (mg/dL) | 98 ± 12   |
| 1-h postprandial glucose value (mg/dL)                      | 105 ± 13  |
| 2-h postprandial glucose value (mg/dL)                      | 97 ± 11   |
| 3-h postprandial glucose value (mg/dL)                      | 84 ± 14   |
| Mean blood glucose at nighttime (mg/dL)                     | 68 ± 10   |

Data from Yogev Y, Ben-Haroush A, Chen R, et al. Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol* 2004;191:949–53.

**Table 5**  
**Blood glucose targets for hyperglycemia in pregnancy**

|                     |                            |                        |
|---------------------|----------------------------|------------------------|
| Fasting and premeal | 60–89 mg/dL <sup>a</sup>   | 95 mg/dL <sup>b</sup>  |
| Peak postprandial   | 100–129 mg/dL <sup>a</sup> | 140 mg/dL <sup>b</sup> |

<sup>a</sup> Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract* 2011;17(Suppl 2):1–53.

<sup>b</sup> American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 30, September 2001 (replaces Technical Bulletin Number 200, December 1994). Gestational diabetes. *Obstet Gynecol* 2001;98(3):525–38.

are no studies that have evaluated the use of BG values from alternative sites in pregnancy, alternative-site self-monitoring blood glucose testing must be discouraged.

### TREATMENT OF HYPERGLYCEMIA IN PREGNANCY

Although some women can attain normoglycemia through MNT and exercise alone, insulin or oral agents may be required for women to control BG levels during pregnancy. The percentage of women with hyperglycemia in pregnancy requiring insulin varies based on the population served. In 2009, the California Diabetes and Pregnancy Program Data System reported that of approximately 11,400 women with hyperglycemia in pregnancy, treated in the Sweet Success Program, about 40% (~4500) required medication in addition to meal plan and exercise to achieve normalization of BG during pregnancy complicated by hyperglycemia in pregnancy.<sup>45</sup>

When considering medication therapy for hyperglycemia in pregnancy, a number of considerations are important as described in **Box 5**.

Insulin has been the gold standard for achieving tight control during pregnancy. Initiating insulin with mild-to-moderate hyperglycemia can be accomplished with a simple approach as described in **Table 6**. For more severe hyperglycemia, dose calculations are similar to overt T2DM based on weight and gestational age.

A certified diabetes educator should teach the woman the safe and effective way to administer insulin and should follow-up in a few days. Compliance and success with insulin therapy has been positively correlated with provider contact.

#### *Hyperglycemia in Pregnancy and Oral Glucose-Lowering Agents*

Although insulin has been the gold standard for treatment of hyperglycemia during pregnancy, there are disadvantages that make some women refuse or comply poorly with the treatment plan when the treatment includes insulin. Some women restrict carbohydrate intake severely to avoid requiring insulin. The effects of severe

**Box 4**  
**Self-monitoring blood glucose suggested frequencies**

|                             |
|-----------------------------|
| Fasting                     |
| 1 hour postprandial         |
| Bedtime                     |
| Preprandial, when indicated |
| 3 AM, when indicated        |

**Box 5****When to initiate medication therapy for hyperglycemia in pregnancy**

*When BGs are greater than 20% beyond target despite meal plan and exercise adherence:*

- Three or more elevated fasting BGs and/or
- Six or more postmeal elevations in 1 week

*Before starting the woman with hyperglycemia in pregnancy on insulin evaluate for:*

- Persistent fasting plasma BG  $\geq 90$  mg/dL (three or more in 1 week)
- BG records that indicate a pattern (six or more in 1 week) of elevations despite adherence to the meal plan and exercise
- The degree of elevation above the target values: mild to moderate
  - Fasting plasma BG 90–120 mg/dL, postmeals 130–180 mg/dL
- Estimated LGA fetus >90th percentile or abdominal circumference >70th percentile on ultrasound (Buchanan et al, 2007)

restriction are not known, but women with an average BG of less than 87 mg/dL have an increased risk of a small-for-gestational-age infant.<sup>46</sup> There is some evidence that when carbohydrates have been severely restricted the pancreas is underdeveloped leading to T2DM in the offspring later in life.<sup>47</sup> Some women fear injections will be painful, hurt the fetus, or cause a reliance on injections for a lifetime. Although none of this is true, some women remain fearful and resist therapy. Insulin therapy is associated with risks of hypoglycemia and increase in appetite and weight.

As an alternative to insulin some providers are choosing to use oral medications, such as glyburide and metformin (glucophage), based on studies supporting relative safety and efficacy.<sup>48,49</sup> Langer and colleagues<sup>48</sup> have found that glyburide, a sulfonyl-urea drug, did not seem to pass through the placenta in the laboratory. The researchers speculated glyburide would be safe to use during pregnancy and designed a study to test the efficacy. Their randomized study of 404 women with gestational diabetes who received either insulin injections or glyburide pills confirmed this hypothesis. The outcomes in each group were similar. The percentage of newborns that were large for their gestational age was similar in both groups of women. In addition, there were no statistically significant differences in the infants' rates of birth defects, lung complications, or low blood sugar.

**Table 6****Starting doses of insulin with mild hyperglycemia**

|                                  |  |
|----------------------------------|--|
| Elevated fasting blood sugars    | 0.2 units/kg NPH at bedtime  |
| Elevated postbreakfast           | Insulin to carbohydrate ratio is $\sim 2:15$ at breakfast (2–4 units) rapid-acting analog                      |
| Elevated postlunch or postdinner | Insulin to carbohydrate ratio is $\sim 1:15$ at lunch (3–5 units) rapid-acting analog pre-lunch and pre-dinner |

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The researchers also did not detect glyburide in the umbilical-cord blood of the 12 newborns that were tested. Only eight of the women taking glyburide needed to switch to insulin to control their gestational diabetes. The number studied was insufficient to show statistical difference in this subgroup. The incidence of fetal LGA in both groups was greater than 12%. Glycemic control was not optimal in either group. Although the protocol in the study allowed for up to 10-mg glyburide twice a day, other authors have cautioned against such a high dose because hypoglycemia can accompany glyburide use.<sup>50,51</sup> **Box 6** describes one approach to dosing glyburide during pregnancy.

Although glyburide works by stimulating insulin secretion, it is also associated with risks of maternal hypoglycemia and weight gain. Metformin, an oral biguanide, may be a possible alternative to insulin for women with hyperglycemia in pregnancy who are unable to cope with the increasing insulin resistance of pregnancy. In another study, Rowan and associates<sup>49</sup> showed similar perinatal mortality and morbidity for women treated with metformin compared with insulin. There are data from over 30 years ago reporting use of metformin in women with hyperglycemia in pregnancy or T2DM in pregnancy in South Africa with no reports of adverse outcomes.<sup>52</sup> However, metformin does cross the placenta and little is known concerning long-term effects resulting from fetal exposure. There are ongoing studies. It should be noted that a total of 30% of metformin-treated women with hyperglycemia in pregnancy ultimately required insulin for adequate glucose control. **Box 7** provides a sample protocol for metformin use in pregnancy.

As with insulin, optimum care involves provider follow-up at frequent short intervals (every 3 days) until an adequate dose is achieved. As pregnancy progresses insulin resistance increases and doses need to be adjusted.

**Box 6****Glyburide protocol for hyperglycemia in pregnancy**

Begin with 1.25 mg/day either in the AM or PM depending on individual needs

After 2–3 days without achieving target blood sugars, increase by 1.25 mg so total dose at one time is 2.5 mg/day AM or PM

Next (after 2–3 days without achieving targets) add 2.5 mg to the opposite time of day so the patient is taking 2.5 mg twice daily

Increase every 3 days by 1.25–2.5 mg total until targets are reached or maximum daily dose is 20 mg per day

Maintain meal plan and exercise therapy

Comply with recommended self-monitoring blood glucose schedule

Conduct fetal surveillance as recommended for patients using insulin therapy

Be aware that hypoglycemia can occur

Adhere to MNT meal and snack regimen to avoid hypoglycemia

Ensure that the woman can recognize and treat hypoglycemia

Monitor weight and assess for appropriate weight gain because weight gain has been associated with this agent

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**Box 7****Metformin protocol for hyperglycemia in pregnancy**

Start at a dose of 500 mg once or twice daily with food or at bedtime depending on the target pattern of hyperglycemia

Increase by 500 mg every 3–5 days over a period of 1–2 weeks, to meet glycemic targets up to a maximum daily dose of 2500 mg

Obtain serum creatinine at start of therapy if renal dysfunction is suspected; metformin is cleared in the kidneys

Common side effects are nausea, vomiting, diarrhea, loss of appetite, stomach fullness, constipation, and heartburn

Drug should be discontinued before major surgery, or radiologic studies involving contrast materials

Metformin is associated with mild weight loss

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**Hypoglycemia**

Hypoglycemia is the result of insulin excess and compromised physiologic defenses against falling plasma glucose concentrations. Hypoglycemia has been classified as “asymptomatic” or “biochemical,” which is particularly common, and “symptomatic” or “severe,” which requires the assistance of another individual. The biochemical definition is a BG less than or equal to 70 mg/dL because in nondiabetic individuals, a BG of 65 to 70 mg/dL stimulates counterregulatory hormones epinephrine and glucagon but after repeated episodes of low BG, this response is blunted.<sup>53</sup> Episodes of hypoglycemia are infrequent but do occur when insulin or glyburide are used. When taking either of these agents, women must not further restrict their carbohydrates or skip meals and snacks to prevent hypoglycemia. The treatment of hypoglycemia as described in **Box 8** is limited to those women taking insulin or glyburide, and the recommendation is to eat a meal or snack containing a carbohydrate and a protein.

**Box 8****Hypoglycemia and the Rule of 15's**

Feeling low? Got symptoms? Check BG

If BG >50 mg/dL <70 mg/dL, treat with 15-g fast-acting carbohydrates (4 glucose tablets with water or 8 oz nonfat milk or 4 oz juice)

Check BG in 15 minutes

BG should increase at least 15 points

If not 15 points higher, repeat treatment

Once BG is >70 mg/dL, have a 15 g carbohydrate snack with 7 g protein

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## Hyperglycemia

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The Pedersen hypothesis, based on a glucocentric view of the pathophysiology of diabetes during pregnancy, theorizes that hyperglycemia mediates hyperinsulinemia in the fetus. Because insulin does not cross the placenta, spikes in maternal BG cause spikes in fetal BG, which stimulate fetal insulin production.<sup>52</sup> This process works well to encourage normal fetal growth when BG levels are in a normal range; however, high glucose levels produce high fetal insulin levels, promoting visceral fat deposition, abnormal growth, delay in lung maturation, and an overresponsive fetal pancreas.

Hyperglycemia is also known to cause oxidative stress and proinflammatory responses. The effects of these processes on the fetus are not well known. In adults with diabetes, hyperglycemia impairs the immune response and causes vascular damage that eventually results in end-organ disease.

As pregnancy progresses particularly in the third trimester, hyperglycemia increases as insulin resistance becomes greater. Increasing levels of progesterone, human placental growth hormones, and cytokines, such as TNF- $\alpha$ , are among the placental substances responsible for insulin resistance. Normoglycemia is more difficult to achieve without meticulous attention to meal plan, exercise, and for some, medication. Healthcare providers need to recognize situations that increase the risk for hyperglycemia, anticipate them, and assist women to adjust the variables that control BG levels to maintain normoglycemia (**Box 9**).

For example, individuals often have certain foods that trigger spikes in BG, such as sourdough bread, white rice, or cereal and milk at breakfast. Recognizing these patterns and intervening to avoid hyperglycemia is an integral part of problem solving. Obtaining BG measurements at the appropriate time and frequency allows evaluation of the appropriate intervention.

## Reducing Risks

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The three main goals of antepartum fetal surveillance are avoidance of fetal deaths, early detection of fetal compromise, and prevention of unnecessary premature birth and cesarean section. Fetal death in the final weeks of pregnancy has been associated with poor glycemic control, hydramnios, and fetal macrosomia.<sup>54</sup> All women with hyperglycemia in pregnancy are encouraged to do kick counts beginning around 26 to 28 weeks gestation.

## NONPLACENTAL INCREASED INSULIN NEEDS IN THE ANTEPARTUM PERIOD

Although specific detrimental outcomes of temporary hyperglycemia are not fully known, it is known that the fetal pancreas is stimulated to overproduce insulin in

### Box 9

#### High-risk situations for hyperglycemia

Stress

Sympathomimetics (terbutaline, ephedrine)

Steroids (eg, betamethasone)

Sepsis (infection)

Stout (obesity)

Advanced gestation (>24 weeks)

accordance with glucose levels in the maternal bloodstream.<sup>52</sup> The higher the maternal BG, the more insulin the fetus produces. Overproduction of fetal insulin is associated with adverse outcomes, described previously. Evidence-based literature suggests that normal nonpregnant individuals exposed to transient glucose elevations show rapid reduction in lymphocytes, including all lymphocyte subsets.<sup>55</sup> Hyperglycemia is similarly associated with reduced T-cell populations for CD4 and CD8 subsets. These abnormalities are reversed when glucose is lowered.<sup>55</sup> It is wise to avoid hyperglycemia associated with such conditions as fever, infection, betamimetics, or betamethasone administration. During these periods of “stress” all insulin doses generally need to be doubled.

The most common stress during pregnancy is preterm labor often requiring tocolysis. Use of betamimetics, such as terbutaline, should be avoided and either magnesium sulfate or nifedipine should be used if necessary. If delivery seems imminent before 35 weeks, betamethasone may be indicated to accelerate fetal lung maturation. Within about 4 hours after the first injection of 12 mg of betamethasone, hyperglycemia ensues. One method of avoiding hyperglycemia associated with betamethasone treatment is illustrated in **Table 7**.

For women with hyperglycemia in pregnancy, BG should be checked more frequently during betamethasone treatment. Women should check premeal and postmeal BG, at bedtime, and at 3 AM for the first 3 to 5 days after beginning betamethasone two-dose therapy. For hyperglycemia in pregnancy, a premeal correction algorithm should be instituted in addition to doubling doses of insulin to avoid postmeal excursions out of target ranges (**Table 8**).

A premeal correction algorithm must be individualized. If the premeal glucose is elevated, “correction insulin” according to the algorithm table is needed to prevent postmeal hyperglycemia; this is not a sliding scale. An algorithm is directed at preventing hyperglycemia, not chasing it, which often results in “stacking” of insulin and a deleterious cycle of hyperglycemia and hypoglycemia.

For hyperglycemia in pregnancy, basal insulin may be needed temporarily. Neutral protamine Hagedorn insulin at 0.2 units per kg may be necessary every 8 to 12 hours for 3 to 5 days.

## FETAL SURVEILLANCE AND TIMING OF DELIVERY

Well-controlled uncomplicated women with hyperglycemia during pregnancy may not require antenatal testing until 40 weeks and may await spontaneous labor.<sup>56</sup> Most are electively delivered by 41 weeks gestation. Women requiring medication with adequate control generally start weekly nonstress test and amniotic fluid index testing at 32 weeks gestation and twice weekly at 36 weeks gestation. A nonreactive nonstress test requires further testing, usually a biophysical profile and rarely a contraction

| <b>Table 7</b>   |  |  |  |
|--|--|--|--|
| <b>Recommendation for increased insulin needs with betamethasone</b> |  |  |  |
| <b>Day 1</b>   | <b>Day 2</b>   | <b>Day 3</b>   | <b>Day 4</b>   |
| Double insulin dose (if basic dose is 10 units, then give 20 units)  | Continue with increased dose; modify as needed for BG (+) doubled dose of 20 units | Decrease the previous day's increased dose by 50% and add to the basic dose (ie, 15 units) | Revert to pre-betamethasone insulin dose and regime (ie, 20 units) |

Data from Kitzmiller J, Gavin L, Inturrisi M. Diabetes and pregnancy pocket guide. UCSF, 2002.

| Table 8<br>Premeal correction algorithm |   |   |
|---|---|---|
| If Premeal BG is                        | Correct the Basic Dose by               | And   |
| <70 mg/dL                               | 2 units less                            | Eat right away, inject insulin after the meal |
| 70–99 mg/dL                             | Give basic dose                         | Inject, eat carbohydrates right away          |
| 100–129 mg/dL                           | 1 unit more                             | Inject, eat right away                        |
| 130–159 mg/dL                           | 2 units more                            | Inject, check BG in 15 min, eat when <110     |
| 160–189 mg/dL                           | 3 units more                            | Inject, check BG in 15 min, eat when <110     |
| >190 mg/dL                              | Add 4 units, call doctor, check ketones | May need to wait up to 1 h                    |

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stress test. Delivery before 39 weeks carries a risk of delivering an infant with immature lungs; therefore, most physicians opt for amniocentesis and lung maturity studies before elective induction of labor or cesarean delivery before 39 weeks. If the lung indices are immature and the gestational age is less than 35 weeks, betamethasone should be considered. Poor metabolic control or history of stillbirth is also an indication for amniocentesis and scheduled delivery before 39 weeks. Suspected LGA as an indication for delivery is controversial and contributes to the high cesarean section rate in women with diabetes.<sup>54</sup>

### INTRAPARTUM RISKS

Intrapartum risks include prolonged labor, shoulder dystocia, operative delivery, poor metabolic control resulting in fetal hypoxia and neonatal hyperinsulinemia and reactive hypoglycemia, and birth injuries to the mother and newborn. A plan of care should be coordinated by the outpatient diabetes team well in advance of delivery so that the woman, her partner, and the delivery team is well informed and everyone understands the same plan. The plan must be clearly communicated in written and oral form. One approach is for the diabetes team to send a plan of care with the patient and to the labor delivery unit on or before the 36th week gestation.

#### ***Dystocias***

A greater risk for labor abnormalities (dystocias) is unknown for women with diabetes. Arrest disorders were described in 9%, 19.4%, and 23.9% of women with diabetes in three reports compared with 6% to 8% in nondiabetic women with newborns of similar birth weights (3000–4500 g).<sup>57,58</sup> Risk for shoulder dystocia increases with increasing birth weight in both diabetic and nondiabetic women, varying from 8% to 23% across the 4000- to 4500-g range.<sup>59</sup> In one study fetal LGA predicted shoulder dystocia in 84% of the cases.<sup>60</sup> Because of wider shoulder width and central adiposity in infants of diabetic mothers in addition to increased obesity in diabetic mothers, the risk of shoulder dystocia maybe greater than in nondiabetic women even at birth weights of 3000–3900 g.<sup>57,59,60</sup> Birth trauma was found in 20% to 40% of the cases of shoulder

dystocia, including fracture of the clavicle or humerus, facial palsy, or brachial plexus palsy.<sup>59,60</sup> Women with labor complicated by shoulder dystocias also incurred injuries, such as third- and fourth-degree perineal lacerations.<sup>61</sup>

Another approach to reduce the risks associated with dystocias is to induce labor before LGA becomes too severe or to electively perform a cesarean at 39 weeks gestation.<sup>62</sup> The ACOG clinical practice guideline does not endorse induction before 40 weeks (in nondiabetic pregnancies) because accurate determination of fetal size is difficult to determine.<sup>63</sup> The ADA recommendation is to induce labor or perform a cesarean delivery on an individualized basis when the estimated fetal weight is between 4000 and 4500 g. Primary cesarean is recommended in most cases when the estimated fetal weight is greater than 4499 g.<sup>64</sup> Labor induction protocols do not differ for women with diabetes versus no diabetes. However, continuous electronic fetal heart rate monitoring is advised.<sup>64</sup> There are no contraindications to epidural anesthesia, although the use of betamimetics for hypotension may raise the maternal BG for several hours.

Cesarean delivery raises the risk for infection, both uterine (endometritis) and wound infection, if BG is not meticulously controlled peripartum. The risk for deep vein thrombus after cesarean delivery is five times higher than that after a vaginal birth. Obesity increases these risks and women with diabetes are more likely to be obese. Prevention generally includes use of pneumatic pressure stockings intraoperatively and postoperatively until the woman is fully ambulatory. Heparin prophylaxis has no advantage over stockings in this setting and may cause heparin-induced thrombocytopenia.<sup>65</sup>

### ***Intrapartum Insulin Management***

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The goals of intrapartum insulin management are to maintain maternal normoglycemia (BG 70–110 mg/dL) to optimize fetal tolerance of labor and prevent neonatal hypoglycemia. In the largest published experience with 233 insulin-treated pregnant women, the lowest risk of neonatal hypoglycemia occurred when intrapartum maternal glucose was maintained at less than 100 mg/dL. Intrapartum hyperglycemia had more effect on neonatal hypoglycemia than did antepartum glucose levels.<sup>66</sup>

Women with hyperglycemia in pregnancy generally do not require insulin during labor because the uterine muscle contractions of the labor process increase insulin sensitivity and reduce insulin needs. Even women with hyperglycemia in pregnancy may not require insulin during labor if carbohydrate intake (intravenous and oral) is restricted. To determine the need for insulin the BG should be followed closely as described in the section on monitoring.<sup>63</sup>

When intrapartum insulin is needed it is optimally delivered by intravenous drip (**Table 9**). The usual dose of intermediate-acting subcutaneous insulin is given at bedtime the night before induction of labor but the morning dose is withheld.<sup>63</sup>

### **POSTPARTUM RISKS**

The most immediate risk postpartum is the risk for neonatal hypoglycemia. BG cutoffs for neonatal hypoglycemia vary slightly but on average the value of 45 mg/dL or less is consistent with the need for intervention. This risk, however, can also be attenuated by early (within the first hour of life) and often (every 2 hours) breastfeeding. The healthy newborn should be dried off and kept warm (preferably skin-to-skin with the mother) and placed at breast as soon after birth as possible. Acquisition of colostrum by the newborn may stimulate hepatic gluconeogenesis to help stabilize the newborn's BG. The newborn will have heel-stick glucose levels checked beginning around 30 minutes after birth. Various protocols exist to monitor the newborn's glucose until stable. Breastfeeding provides numerous health benefits to women with diabetes

| Capillary BG  | 1 Unit<br>Insulin = 1 mL                               | Intravenous<br>Fluids | BG Checks                    |
|---------------|--|-----------------------|------------------------------|
| <70 mg/dL     | 0  | D5 0.5 NS at 200 mL/h | Every 15 min<br>until >70 x2 |
| 70–110 mg/dL  | 0  | D5 0.5 NS at 100 mL/h | Every 1–2 h                  |
| 111–130 mg/dL | 1  | NS or LR at 100 mL/h  | Every 30 min                 |
| 131–150 mg/dL | 2  | NS or LR at 100 mL/h  | until <110                   |
| 151–170 mg/dL | 3  | NS or LR at 100 mL/h  | Then every 1 hour            |
| 171–190 mg/dL | 4  | NS at 150/h           | while on                     |
| >190 mg/dL    | Check urine ketones<br>call doctor for<br>insulin dose | NS at 150/h           | intravenous<br>insulin drip  |

*Abbreviations:* D5, 5% dextrose; LR, lactated Ringers solution; NS, normal saline.

*Data from* Palmer D, Inturrisi M. Insulin infusion therapy in the intrapartum period. *J Perinat Neonat Nurs* 1992;6(1):B14–25.

and offspring. Among those benefits is improved glucose use and reduced lipid levels in the mother.<sup>67</sup> A relationship has also been shown between breastfeeding and reduction of type 2 diabetes in Pima Indian children.<sup>68</sup> Infants of women with mild to severe glucose intolerance are at risk for infant and childhood obesity.<sup>69,70</sup> Breastfed infants tend to be leaner than formula-fed infants.<sup>71</sup> Lactation removes glucose from the maternal blood to create lactase for the breast milk, thus lowering maternal BG independent of the action of insulin.

### **Contraception for Women with a History of Hyperglycemia in Pregnancy**

The use of progestin-only oral contraceptives almost tripled the conversion to type 2 diabetes in the 2 years after hyperglycemia in pregnancy in a study of Latina women who were breastfeeding compared with equivalent use of low-dose combination pills.<sup>72</sup> Because the underlying mechanism for conversion to type 2 diabetes in Hispanic women is the same for most other women (impaired  $\beta$  cell function and insulin resistance), the recommendation is that progesterone-only birth control be avoided when possible in previous hyperglycemia in pregnancy. Low-dose combination pills can be used safely in breastfeeding women with previous hyperglycemia in pregnancy.<sup>72</sup>

The interaction of medroxyprogesterone acetate (Depo-Provera) with breastfeeding is similar to that of progestin-only contraception with breastfeeding, adversely affecting diabetes risk.<sup>72</sup> Thus, medroxyprogesterone acetate should be used with caution in breastfeeding women and those with elevated triglyceride levels ( $\geq 150$  mg/dL). Close attention should be paid to weight gain, which also has been demonstrated to increase the risk of subsequent diabetes.<sup>72</sup>

Progesterone does increase insulin resistance and lowers low-density lipoprotein and raises high-density lipoprotein. The lowest dose and potency of progestin should be used to minimize adverse effects on lipids and glucose control. The intrauterine device is metabolically neutral and highly efficacious. This is a good choice for most women with diabetes. The guidelines for use follow the same guidelines as healthy parous women, such as low risk for sexually transmitted disease and pelvic inflammatory disease.

### **Reducing Future Risk for T2DM in Hyperglycemia in Pregnancy**

Hyperglycemia in pregnancy is not just a pregnancy problem. Approximately 55% of women with diagnosed hyperglycemia in pregnancy have overt T2DM, and another



20% to 30% have prediabetes.<sup>73</sup> Independent antepartum predictors of conversion from hyperglycemia in pregnancy to T2DM include low insulin sensitivity (elevated postmeal requiring insulin); high basal glucose production (elevated fasting BG requiring insulin); and abnormal 1-hour value on the OGTT.<sup>74</sup> Postpartum predictors of conversion from hyperglycemia in pregnancy to T2DM include obesity, pregnancy weight gain, high-fat diet, inactivity, and progesterone contraception.<sup>74</sup>

A woman who had hyperglycemia in pregnancy but has a negative test for preexisting diabetes should be counseled on the increased risk for developing hyperglycemia in pregnancy in future pregnancies. Women with a history of hyperglycemia in pregnancy have an increased risk for presenting with undiagnosed diabetes at the first prenatal visit in subsequent pregnancies. Counseling should include discussing the lifetime risk for developing T2DM and dyslipidemias. Because approximately one-third of women with a history of hyperglycemia in pregnancy have abnormal lipid profiles, lipid testing is recommended 1-year postpartum and annually thereafter. The 2-hour adult OGTT more accurately identifies this population than the fasting plasma glucose test.<sup>75</sup> The current recommendation is to obtain a 2-hour 75-g OGTT at 6 to 8 weeks postpartum and at 1 year. If within normal limits, then obtain fasting or hemoglobin A<sub>1C</sub> yearly and OGTT every 3 years.

## SUMMARY

Women who had hyperglycemia in pregnancy and have prediabetes on the OGTT should be referred for management that includes nutrition and exercise counseling and possibly treatment with metformin to prevent the conversion to T2DM. Women with prediabetes need to be tested for overt diabetes every year thereafter.

Women who have a history of hyperglycemia in pregnancy and have a subsequent positive test for T2DM should be referred for appropriate follow-up with a healthcare provider familiar with diabetes care. Women should be counseled on the importance of preconception care and also advised of the long-term complications associated with poor glycemic control. Attention should be given to attainment and maintenance of appropriate weight.

Hyperglycemia in pregnancy is an opportunity for women at risk for complications during pregnancy and beyond to change their life course to improve outcomes for themselves and their offspring. Providers of diabetes care during pregnancy complicated by hyperglycemia in pregnancy have the unique opportunity to make a significant difference.

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