Gestational diabetes mellitus (GDM) is defined as glucose intolerance of various degrees that is first detected during pregnancy. GDM is detected through the screening of pregnant women for clinical risk factors and, among at-risk women, testing for abnormal glucose tolerance that is usually, but not invariably, mild and asymptomatic. GDM appears to result from the same broad spectrum of physiological and genetic abnormalities that characterize diabetes outside of pregnancy. Indeed, women with GDM are at high risk for having or developing diabetes when they are not pregnant. Thus, GDM provides a unique opportunity to study the early pathogenesis of diabetes and to develop interventions to prevent the disease.

Historical perspective
For more than a century, it has been known that diabetes antedating pregnancy can have severe adverse effects on fetal and neonatal outcomes (1). As early as in the 1940s, it was recognized that women who developed diabetes years after pregnancy had experienced abnormally high fetal and neonatal mortality (2). By the 1950s the term "gestational diabetes" was applied to what was thought to be a transient condition that affected fetal outcomes adversely, then abated after delivery (3). In the 1960s, O'Sullivan found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy. He proposed criteria for the interpretation of oral glucose tolerance tests (OGTTs) during pregnancy that were fundamentally statistical, establishing cut-off values — approximately 2 standard deviations — for diagnosing glucose intolerance during pregnancy (4). In the 1980s those cut-off points were adapted to modern methods for measuring glucose and applied to the modern definition of gestational diabetes — glucose intolerance with onset or first recognition during pregnancy (5). While based on O'Sullivan's values for predicting diabetes after pregnancy, the diagnosis of gestational diabetes mellitus (GDM) also identifies pregnancies at increased risk for perinatal morbidity (6–8) and long-term obesity and glucose intolerance in offspring (9–11).

Population perspective
Clinical detection of GDM is carried out to identify pregnancies at increased risk for perinatal morbidity and mortality. Available data do not identify a threshold of maternal glycemia at which such risk begins or increases rapidly. A multinational study, the Hyperglycemia and Adverse Pregnancy Outcome study, is underway to explore this issue in a large multiethnic cohort. In the absence of a defined glucose threshold for perinatal risk, many different sets of glycemic criteria have been proposed and are employed worldwide for the diagnosis of GDM. The criteria currently recommended by the American Diabetes Association (12) are based on O'Sullivan's criteria (see above). The detection of GDM, a condition that is generally asymptomatic, involves screening in 2 sequential steps (Tables 1 and 2), followed by administration of a 2- or 3-hour OGTT (Table 3) to women determined to be at risk by screening. Women with very high clinical risk characteristics may be diagnosed with probable pregestational (preexisting) diabetes based on the criteria provided in Table 4. When the diagnostic criteria for a 3-hour OGTT presented in Table 3 was applied to a group of Caucasian women in Toronto, approximately 7% had GDM (6). The frequency of GDM may vary among ethnic groups (higher in groups with increased prevalence of hyperglycemia) (13–16) and with the use of different diagnostic criteria (higher when lower glucose thresholds are applied and vice versa) (4). Nonetheless, all approaches to GDM detection pinpoint — and thereby allow diagnosis of — women with glucose tolerance in the upper end of the population distribution during pregnancy. A small minority of those women have glucose levels that would be diagnostic of diabetes outside of pregnancy (Table 4). The great majority have lower glucose levels. Both groups impart to their offspring an increased risk of perinatal morbidity and long-term obesity and diabetes that appear to be related at least in part to fetal overnutrition in utero. They also incur for themselves a risk of diabetes after pregnancy that is the main focus of this paper.

Etiology and pathogenesis
Normal pregnancy
A detailed discussion of glucose regulation in pregnancy is beyond the scope of this paper. However, 2 points are important for the discussion that follows. First, pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in individuals with type 2 diabetes. The insulin resistance appears to result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta. The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. The second point is that pancreatic β cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy (see Figure 1, for example). As a result, changes in circulating glucose levels over the course of pregnancy are quite small compared...
with the large changes in insulin sensitivity. Robust plasticity of \( \beta \) cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy.

**Gestational diabetes**

GDM is a form of hyperglycemia. In general, hyperglycemia results from an insulin supply that is inadequate to meet tissue demands for normal blood glucose regulation. Studies conducted during late pregnancy, when, as discussed below, insulin requirements are high and differ only slightly between normal and gestational diabetic women, consistently reveal reduced insulin responses to nutrients in women with GDM (17–23). Studies conducted before or after pregnancy, when women with prior GDM are usually more insulin resistant than normal women (also discussed below), often reveal insulin responses that are similar in the 2 groups or reduced only slightly in women with prior GDM (18, 22–26). However, when insulin levels and responses are expressed relative to each individual’s degree of insulin resistance, a large defect in pancreatic \( \beta \) cell function is a consistent finding in women with prior GDM (23, 25, 27).

Potential causes of inadequate \( \beta \) cell function are myriad and not fully described. Outside of pregnancy, there are 3 general settings that are recognized — through classification as distinct forms of diabetes mellitus (12) — as separate categories of \( \beta \) cell dysfunction: (a) autoimmune; (b) monogenic; and (c) occurring on a background of insulin resistance. There is evidence that \( \beta \) cell dysfunction in GDM can occur in all 3 major settings, a fact that is not surprising given that GDM is detected by what is, in essence, population screening for elevated glucose levels among pregnant women.

**Autoimmune diabetes and GDM**

Type 1 diabetes results from autoimmune destruction of pancreatic \( \beta \) cells. It accounts for approximately 5–10% of diabetes in the general population (12). Prevalence rates vary by ethnicity, with the highest rates in Scandinavians and the lowest rates (i.e., 0%) in full-blooded Native Americans. Type 1 diabetes is characterized by circulating immune markers directed against pancreatic islets (anti–islet cell antibodies) or \( \beta \) cell antigens (such as glutamic acid decarboxylase [GAD]). A small minority (less than 10% in most studies) of women with GDM have the same markers present in their circulation (17, 28–31). Although detailed physiological studies of these women are lacking, they most likely have inadequate insulin secretion resulting from autoimmune damage to and destruction of pancreatic \( \beta \) cells. They appear to have evolving type 1 diabetes, which comes to clinical attention through routine glucose screening during pregnancy.

The frequency of anti–islet cell and anti-GAD antibodies detected in GDM tends to parallel ethnic trends in the prevalence of type 1 diabetes outside of pregnancy. Patients with anti–islet cell or anti-GAD antibodies often, but not invariably, are lean, and they can rapidly develop overt diabetes after pregnancy (30).

**Monogenic diabetes and GDM**

Monogenic diabetes mellitus has been identified outside of pregnancy in 2 general forms. Some patients have mutations in autosomes (autosomal dominant inheritance pattern, commonly referred to as maturity-onset diabetes of the young [MODY]), with genetic subtypes denoted as MODY 1, MODY 2, etc.). Others have mutations in mitochondrial DNA, often with distinct clinical syndromes such

### Table 1

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Clinical characteristics</th>
<th>Recommended screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (presence of any is sufficient)</td>
<td>Marked obesity</td>
<td>Blood glucose screening at initial antepartum visit or as soon as possible thereafter, repeat at 24–28 wk if not already diagnosed with GDM by that time</td>
</tr>
<tr>
<td>Average risk</td>
<td>Fits neither low- nor high-risk profile</td>
<td>Blood glucose screening between 24 and 28 wk gestation</td>
</tr>
<tr>
<td>Low risk (all required)</td>
<td>Age &lt;25</td>
<td>Blood glucose screening not required</td>
</tr>
<tr>
<td></td>
<td>Low-risk ethnicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No diabetes in first-degree relatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal prepregnancy weight and pregnancy weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No personal history of abnormal glucose levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No prior poor obstetrical outcomes</td>
<td></td>
</tr>
</tbody>
</table>

*aBased on recommendations of the American Diabetes Association (5). *bPerformed at initial antepartum visit. *cEthnicities other than Hispanic, African, Native American, South or East Asian, Pacific Islander, or indigenous Australian, all of which have relatively high rates of GDM. Adapted with permission from *N. Engl. J. Med.* (72). Copyright 1999, Massachusetts Medical Society. All rights reserved.

### Table 2

<table>
<thead>
<tr>
<th>Glucose cut point</th>
<th>Percentage of women with positive test</th>
<th>Sensitivity for GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 140 \text{ mg/dl (7.8 mmol/l)} )</td>
<td>14–18%</td>
<td>–80%</td>
</tr>
<tr>
<td>( \geq 130 \text{ mg/dl (7.2 mmol/l)} )</td>
<td>20–25%</td>
<td>–90%</td>
</tr>
</tbody>
</table>

*aThe test is a 50-g oral glucose challenge performed in patients with high or average clinical risk characteristics. No preparation is needed; the test can be done any time of day. Women with very high clinical risk characteristics may proceed directly to measurement of fasting glucose or to diagnostic OGTT (see Tables 3 and 4). *bMay vary with ethnicity and with diagnostic OGTT employed. Adapted with permission from *N. Engl. J. Med.* (72). Copyright 1999, Massachusetts Medical Society. All rights reserved.
as deafness. In both instances, onset tends to occur at an early age relative to other forms of nonimmune diabetes (e.g., type 2 diabetes, described below), and patients tend not to be obese or insulin resistant. Both features point to abnormalities in the regulation of β cell mass and/or function. Indeed, detailed metabolic studies have revealed abnormalities in glucose-mediated insulin secretion in some forms of MODY (32). Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes coding for: (a) glucokinase (MODY 2) (29, 33–35); (b) hepatocyte nuclear factor 1α (MODY 3) (29); (c) and insulin promoter factor 1 (MODY 4) (29). Together, these monogenic forms of GDM account for less than 10% of GDM cases (29, 33–36). They likely represent cases of preexisting diabetes that are first detected when the acquired insulin resistance of pregnancy abates, women have even greater insulin resistance than normal pregnant women. This finding, which has been measured directly (22, 23, 25, 26, 37–40), indicates that most women who develop GDM have chronic insulin resistance. Sequential measurements of insulin sensitivity performed in the same women before pregnancy, early in the second trimester, and in the third trimester have documented insulin resistance in both lean and obese women who go on to develop GDM (18, 24).

Only a small number of potential biochemical mediators of the chronic insulin resistance that frequently accompanies GDM and that likely contributes to the high risk of type 2 diabetes have been examined. It is likely that there is not a single underlying biochemical etiology. Women with GDM tend to be obese, so mechanisms promoting obesity and/or linking obesity to insulin resistance are likely to play a role. Small studies have revealed increased circulating levels of leptin (41) and the inflammatory markers TNF-α (42) and C-reactive protein (43) and decreased levels of adiponectin (44, 45) in women with GDM. Increased content of fat in liver (46) and muscle (47) has also been reported in women with previous gestational diabetes. All of these findings are consistent with the current understanding of some potential causes of obesity-related insulin resistance.

Defects in the binding of insulin to its receptor in skeletal muscle do not appear to be involved in the exaggerated insulin resistance of GDM (48). Alterations in the insulin signaling pathway (49–52), abnormal subcellular localization of GLUT4 transporters (53), reduced expression of PPARY (49), increased expression of the membrane glycoprotein PC-1 (51), and reduced insulin-mediated glucose transport (52, 53) have been found in skeletal muscle or fat cells of women with GDM or a history thereof compared with normal women. Whether any of these defects is primary or the result of more fundamental defects in insulin action is currently unknown. Given that GDM represents a cross-section of young women with glucose intolerance, mechanisms that lead to chronic insulin resistance in GDM are likely to be as varied as they are in the general population.

It has long been thought (and taught) that GDM develops in women who cannot increase their insulin secretion when faced with the increased insulin needs imposed by late pregnancy. Serial studies of women who develop GDM do not support that concept. As illustrated in Figure 1, insulin secretion in obese women who develop GDM can increase considerably over weeks or months in association with the acquired insulin resistance of pregnancy. However, the increase occurs along an insulin sensitivity-secretion curve that is approximately 50% lower (i.e., 50% less insulin for any degree of insulin resistance) than that of normal women. These short-term responses appear to occur on a background of long-term deterioration of β cell function that, over years, leads to progressive hyperglycemia and diabetes (see “Link to diabetes after pregnancy,” below). Longitudinal studies of lean and obese women before pregnancy, at the beginning of the second trimester, and in the third trimester also reveal an increase in insulin secretion in association with the acquired insulin resistance of pregnancy (18, 24). However, the increase is less than that which occurs in normal pregnant women despite somewhat greater insulin resist-

### Table 3

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Glucose cut pointsa</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Time (h) mg/dl mmol/l</td>
</tr>
<tr>
<td>100-g, 3-h OGTTb</td>
<td>Fast ing 95 5.3</td>
</tr>
<tr>
<td></td>
<td>1 180 10.0</td>
</tr>
<tr>
<td></td>
<td>2 155 8.6</td>
</tr>
<tr>
<td></td>
<td>3 140 7.8</td>
</tr>
<tr>
<td>75-g, 2-h OGTTb</td>
<td>Fast ing 95 5.3</td>
</tr>
<tr>
<td></td>
<td>1 180 10.0</td>
</tr>
<tr>
<td></td>
<td>2 155 8.6</td>
</tr>
</tbody>
</table>

aBased on recommendations of the American Diabetes Association (5). bVenous serum or plasma glucose measured by a certified clinical laboratory. cTwo or more values meeting or exceeding the cut points are required for diagnosis. Adapted with permission from N. Engl. J. Med. (72). Copyright 1999, Massachusetts Medical Society. All rights reserved.
Implications for clinical care

To date, insights into the mechanisms underlying impaired glucose regulation in GDM have not had an important impact on clinical management during pregnancy. The focus for antepartum care is on the use of standard antidiabetic treatments, mostly appropriate nutrition and exogenous insulin delivery but more recently administration of selected oral antidiabetic agents (63–65), to normalize maternal pre- and postprandial glucose levels and minimize fetal overnutrition. Fetal ultrasound measurements have also been used to refine the identification of pregnancies in which the fetus demonstrates signs of excessive adiposity — pregnancies in which the need to aggressively lower maternal glucose is the greatest (66, 67).

After pregnancy, the main focus of clinical care should be on reducing the risk of diabetes and detecting and treating diabetes that does develop. Measurement of fasting glucose in the immediate postpartum period will identify women with persistent fasting hyperglycemia in the diabetic range. Other women should have an OGTT sometime during the first 2–6 months postpartum and, if not diabetic, annual testing for diabetes. Family planning is important to reduce the occurrence of unplanned pregnancies in the presence of poorly controlled diabetes (68), a scenario that leads to serious birth defects in offspring (69).

Classification of patients into 1 of the 3 major subtypes of GDM discussed in this review can aid in clinical management. Lean patients are less likely to be insulin resistant than overweight or obese patients, so autoimmune and monogenic forms of diabetes should be considered in such patients. Screening for evolving autoimmune diabetes as obesity, weight gain, and increased age, that are known to be associated with type 2 diabetes. Relatively high glucose levels during and soon after pregnancy also correlate with increased risk of diabetes, perhaps because they identify women who are relatively close to developing diabetes when the diagnosis of GDM is made.

Longitudinal studies of the pathophysiology of diabetes that develops after GDM are limited to Hispanic women with clinical characteristics suggesting a risk for type 2 diabetes. Those studies have revealed much about the β cell defect that leads to type 2 diabetes after GDM in 1 ethnic group. First, weight gain and additional pregnancies, factors associated with chronic and acute insulin resistance, respectively, independently increase the risk of developing diabetes (59). Second, decreasing β cell function is associated with increasing hyperglycemia (Figure 2) (60). The impact of reduced β cell function on glucose levels is relatively small until the disposition index, which reflects acute insulin responses to glucose in relation to insulin resistance, is very low (approximately 10–15% of normal). Thereafter, relatively small differences in β cell function are associated with relatively large increases in glucose levels (60). Third, treatment of insulin resistance at the stage of impaired glucose tolerance results in a reciprocal downregulation of insulin secretion (61), which in turn is associated with a reduction in the risk of diabetes and with preservation of β cell function (62). Taken together, these 3 findings reveal a progressive loss of insulin secretion that appears to be caused by high insulin secretory demands imposed by chronic insulin resistance. Glycemia in the diabetic range is a relatively late consequence of the loss of insulin secretion. That loss can be slowed or stopped through the treatment of insulin resistance in order to reduce of high insulin secretory demands (62). Whether the same or similar mechanisms of progressive β cell dysfunction and opportunities for β cell preservation occur in other ethnic groups remains to be determined.

Link to diabetes after pregnancy

The hyperglycemia of GDM is detected at one point in a women’s life. If glucose levels are not already in the diabetic range, GDM could represent glucose intolerance that is limited to pregnancy, is chronic but stable, or is at a stage in the progression to diabetes. Long-term follow-up studies, recently reviewed by Kim et al. (57), reveal that most, but not all, women with GDM do progress to diabetes after pregnancy. Only approximately 10% of patients have diabetes soon after delivery (58). Incident cases appear to occur at a relatively constant rate during the first 10 years thereafter (57), and the few studies that have been conducted over a period of more than 10 years reveal a stable long-term risk of approximately 70% (57).

Most studies of risk factors for the development of diabetes after GDM fail to distinguish among the possible subtypes of GDM and diabetes discussed above. They generally reveal risk factors, such as obesity, weight gain, and increased age, that are known to be associated with type 2 diabetes. Relatively high glucose levels during and soon after pregnancy also correlate with increased risk of diabetes, perhaps because they identify women who are relatively close to developing diabetes when the diagnosis of GDM is made.

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Fig. 1: Insulin sensitivity-secretion relationships in women with GDM and normal women during the third trimester and remote from pregnancy. Values were measured at the end of 3-hour hyperglycemic clamps (plasma glucose, about 180 mg/dl) (22). Prehepatic insulin secretion rates were calculated from steady-state plasma insulin and C-peptide levels. Insulin sensitivity index was calculated as steady-state glucose infusion rate divided by steady-state plasma insulin concentration. FFM, fat-free mass. Figure reproduced with permission from J. Clin. Endocrinol. Metab. (27). Copyright 2001, The Endocrine Society.
by measuring antibodies to GAD may be warranted, particularly in women with no strong family history of diabetes who are from ethnic groups in which type 1 diabetes is relatively common. Although there are no established treatments to modify the progression to type 1 diabetes, careful monitoring of glucose levels is advised because patients can rapidly develop diabetes after pregnancy (30). Genotyping for monogenic diabetes is still primarily a research tool, but clinical tests are being developed. Early-onset diabetes with a relevant family history (autosomal dominant inheritance for MODY; maternal inheritance for mitochondrial mutations) may provide a clue to the diagnosis. In addition, Ellard et al. (34) have provided 4 clinical criteria that have relatively high specificity for identifying women with the glucokinase mutations that cause 1 form of MODY, MODY2: (a) persisting fasting hyperglycemia (105–145 mg/dl) after pregnancy; (b) a small (less than 82 mg/dl) increment in glucose above the fasting level during a 75-g, 2-hour OGTT; (c) insulin treatment during at least 1 pregnancy but subsequently controlled on diet; and (d) a first-degree relative with type 2 diabetes, GDM, or fasting serum or plasma glucose greater than 100 mg/dl. The constellation was infrequent in patients in the United Kingdom, but 80% of women who met all 4 criteria had glucokinase mutations. Identification of monogenic forms of diabetes is important for genetic counseling.

There is currently no clinical role for genetic testing for variants that have been associated with polygenic forms of type 2 diabetes (see “Insulin resistance, β cell dysfunction, and GDM,” above). The variants cannot be used reliably to discriminate between normal individuals and individuals affected with diabetes and, just as importantly, testing is not available to clinicians. On the other hand, recent advances in the understanding of mechanistic links between GDM and type 2 diabetes have been translated into clinical care aimed at reducing the risk of diabetes. At least 2 studies of diabetes prevention in high-risk individuals have included women with a history of GDM. In the US Diabetes Prevention Program (DPP) (70), intensive lifestyle modification to promote weight loss and increase physical activity resulted in a 58% reduction in the risk of type 2 diabetes in adults with impaired glucose tolerance. GDM was one of the risk factors that led to inclusion in the study. Protection against diabetes was observed in all ethnic groups. Treatment with metformin in the same study also reduced the risk of diabetes, but to a lesser degree and primarily in the youngest and most overweight participants. To date, specific results from women with a history of GDM have not been published.

The Troglitazone in Prevention of Diabetes (TRIPOD) study was conducted exclusively on Hispanic women with recent GDM. Assignment to treatment with the insulin-sensitizing drug troglitazone was associated with a 55% reduction in the incidence of diabetes. Protection from diabetes was closely linked to initial reductions in endogenous insulin requirements and ultimately associated with stabilization of pancreatic β cell function (62). Stabilization of β cell function was also observed when troglitazone treatment was started at the time of initial detection of diabetes by annual glucose tolerance testing (71). The DPP and TRIPOD studies support clinical management that focuses on aggressive treatment of insulin resistance to reduce the risk of type 2 diabetes and, at least in Hispanic women, to preserve pancreatic β cell function.

Taken together, these 2 studies suggest that postpartum management of women with clinical characteristics suggesting a risk for type 2 diabetes should focus on treatment of insulin resistance and monitoring of glycemia both to assess success (as reflected by stabilization of glucose levels) and to detect diabetes if it develops.

Future directions
Considerable work is needed to dissect the various mechanisms underlying maternal GDM and its evolution to diabetes after pregnancy. Large studies of screening for evolving autoimmune diabetes are necessary to more accurately define the clinical characteristics of women who need such screening as part of routine GDM management. Genetic studies may help identify women whose β cells will tolerate insulin resistance poorly, as well as women who develop poor insulin secretion for reasons unrelated to insulin resistance. Studies of gene-environment interactions and additional studies of insulin action in muscle and fat may identify causes of insulin resistance, especially as they relate to obesity. Better understanding of mechanisms that can lead to GDM should allow more rational development and administration of therapy during pregnancy, as well as more rational approaches to prevention of both GDM and diabetes after pregnancy. GDM is an especially attractive target for such studies because the disease is detected in the course of routine clinical care and it provides an opportunity to study relatively early stages of glucose dysregulation that may be fundamental to the long-term pathobiology of diabetes.

Acknowledgments
We thank our long-term collaborators Siri Kjos, Ruth Peters, and Richard Bergman for their contributions to studies on the pathogenesis of type 2 diabetes after GDM in Hispanic women. Our work cited in this paper was supported by research grants from the NIH (R01-DK46374, R01-DK61628, and M01-RR00043), the American Diabetes Association (Clinical Research Award and Distinguished Clinical Scientist Award), and Parke-Davis Pharmaceutical Research (the TRIPOD study).

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