CHAPTER 4

GESTATIONAL DIABETES

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SUMMARY

Since the 1979 publication on "classification and diagnosis of diabetes mellitus and other categories of glucose intolerance" by the National Diabetes Data Group, gestational diabetes has been defined as "carbohydrate intolerance of variable severity with onset or recognition during pregnancy." The diagnosis and treatment of gestational diabetes focus on the prevention or reduction of adverse outcomes. However, the criteria that were proposed in 1964 by O'Sullivan and Mahan for interpretation of an oral glucose tolerance test (OGTT) during pregnancy focused on the level of risk for the development of diabetes in the mother. With modifications, these criteria remain in use in the United States in 2016.

There is a longstanding controversy about the value of detecting and treating gestational diabetes. Two issues are the focus of concern. The first is whether the adverse outcomes that occur in pregnancies complicated by gestational diabetes are independently linked to maternal hyperglycemia or to confounding factors, such as obesity and/or higher maternal age. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study addressed this question. The HAPO Study demonstrated an independent association between maternal glucose from 75 g OGTTs performed at 24–32 (mean 27.8) weeks of gestation and the four independent primary study outcomes of birth weight above the 90th percentile, cord blood C-peptide above the 90th percentile, neonatal hypoglycemia, and primary cesarean delivery. Odds ratios were calculated for risk of outcomes associated with a one standard deviation increase in glucose at each of the three time points (fasting, 1-hour, and 2-hour) of the OGTT. The odds ratios, all of which were statistically significant, were in the range of 1.38–1.46 for birth weight above the 90th percentile, 1.37–1.55 for cord blood C-peptide above the 90th percentile, 1.08–1.11 for primary cesarean delivery, and 1.08–1.13 for neonatal hypoglycemia. There were no obvious thresholds at which risks increased.

The second issue, whether diagnosing and treating mild gestational diabetes reduces adverse outcomes, was the focus of two large randomized clinical trials. Both trials showed significant improvement in some perinatal outcomes when gestational diabetes was diagnosed and treated compared to when caregivers were blinded to the diagnosis and gestational diabetes was not treated. For example, rates of macrosomia (birth weight ≥4,000 g) were reduced from 21% and 14% in the untreated groups to 10% and 6%, respectively, in the treated groups of the two studies. Rates of the combined outcome of preeclampsia and gestational hypertension decreased from 18% and 14% in untreated to 12% and 9%, respectively, in treated groups in the two studies.

The prevalence of gestational diabetes has increased substantially from the 1980s onward in parallel with increases in the frequency of obesity and overweight, type 2 diabetes, impaired glucose tolerance, and impaired fasting glucose in the general population. For example, in pregnant women receiving prenatal care in the Northern California Kaiser Permanente Clinics, the overall frequencies of gestational diabetes were 4.7% in 1991 and 7.2% in 2000. The rate increased progressively with some year-to-year variation related to differences in age and racial/ethnic mix of the cohort.

Based primarily on associations between glucose values and perinatal outcomes in the HAPO Study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended new glucose threshold values for the diagnosis of gestational diabetes (fasting, 1-hr, and 2-hr plasma glucose concentrations of 92, 180, and 153 mg/dL, respectively, with one or more values meeting or exceeding the threshold being diagnostic of gestational diabetes). Use of the IADPSG diagnostic thresholds leads to an additional increase in the prevalence of gestational diabetes. For this reason, some have recommended that more randomized treatment trials should be conducted to specifically assess the benefit of treating gestational diabetes cases that meet the IADPSG diagnostic thresholds but not older criteria for gestational diabetes. Thus, in the future as in the past, controversy about gestational diabetes is likely to remain part of diabetes in the United States.

DEFINITION

Since the 1979 National Diabetes Data Group (NDDG) publication titled "Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance" (1), gestational diabetes has been defined as "carbohydrate intolerance of variable severity with onset or recognition during pregnancy."

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BACKGROUND

Diabetes occurring during pregnancy was recognized early in the 19th century (2), and in 1882, J. Matthews Duncan described what would later be called gestational diabetes mellitus when he indicated that "diabetes may occur only during pregnancy being absent at other times or may cease with the termination of pregnancy recurring some time afterwards" (3). With the advent of insulin treatment in 1922, pregnancy among women with diabetes occurred more frequently than it had previously. Information on pregnancy in women with preexisting diabetes is discussed in Chapter 5 *Pregnancy With Preexisting Diabetes*. It was soon found that "problems of fetal abnormality exist not only among diabetic women but also among those whom we have come to describe as 'prediabetic,' that is those in whom a diagnosis of diabetes is established at some time later" (4,5). Studies were initiated to determine whether treatment of prediabetes in pregnancy with insulin could reduce fetal complications (5). However, the criteria that were proposed by O'Sullivan and Mahan in 1964 for interpretation of an oral glucose tolerance test (OGTT) during pregnancy (6) focused on the level of risk for the development of diabetes in the mother.

The term "gestational diabetes" had been used (7,8) before the O'Sullivan-Mahan criteria (6) were proposed in 1964. In 1971, Mestman *et al*. also proposed criteria for a normal OGTT in pregnancy (9). Focusing on gestational diabetes and fetal risks, the American College of Obstetricians and Gynecologists (ACOG) recommended in 1978 screening for diabetes in pregnancy be carried out in patients with historical risk factors for diabetes using an OGTT (10), interpreted by the criteria of either O'Sullivan and Mahan (6) or by a separate set of criteria proposed by Mestman *et al.* (9). When the NDDG International Working Group published comprehensive guidelines for the classification and diagnosis of diabetes and other categories of glucose intolerance in 1979 (1), the term gestational diabetes was restricted to pregnant women in whom the onset or recognition diabetes or impaired glucose tolerance occurred during pregnancy. Data linking maternal glycemia to perinatal outcomes were not available to define diagnostic criteria for gestational diabetes. Instead, use of the O'Sullivan-Mahan criteria (6) was recommended with a correction to apply the criteria to plasma glucose concentrations rather than the whole blood glucose values (1).

In the 1980s, the World Health Organization (WHO) published recommendations that equated gestational diabetes with diabetes detected during pregnancy and with values used for diagnosis of impaired glucose tolerance in nonpregnant persons (11,12). In the absence of diagnostic criteria based on pregnancy outcome, numerous other strategies have been used in addition to the NDDG or WHO recommendations (13).

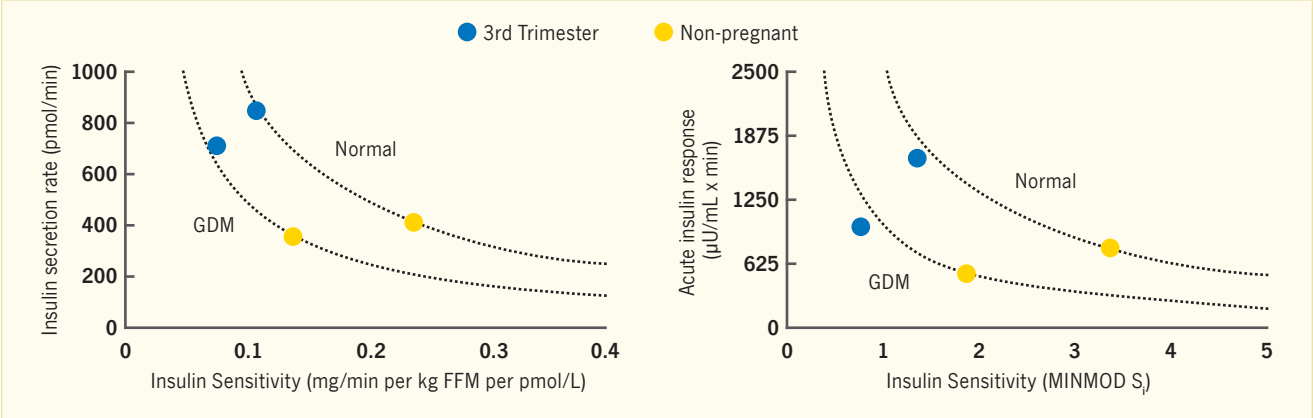
With each of these strategies for the diagnosis of gestational diabetes, a diagnostic OGTT is administered only to pregnant women deemed high-risk by historical factors (glycosuria, family history of diabetes, obesity, maternal age [>35 or >40 years], previous fetal loss, malformations or birth of large for gestational age [LGA] infant), or a positive 50 g glucose challenge test (GCT), i.e., plasma glucose value at 1 hour of 135 or 140 mg/dL (7.49 or 7.77 mmol/L). This is discussed in detail in the section *Detection and Diagnosis*.

Clinical and epidemiologic interest in gestational diabetes increased steadily during the last quarter of the 20th century. A series of five International Workshop-Conferences served to summarize the work and to promote specific areas of research. In 1985, the Second International Workshop-Conference on Gestational Diabetes Mellitus (14) recommended universal use of a GCT to exclude the majority of women with very low risk of gestational diabetes from full testing with an OGTT, leaving that testing to a minority with increased risk. In 1986, that recommendation was adopted by the American Diabetes Association (ADA) (15). The same year, ACOG also issued guidelines for screening for gestational diabetes (16). ACOG recommended administering a 50 g GCT to pregnant women age <30 years with risk factors for diabetes and to all pregnant women age ≥30 years. Both ADA and ACOG provided guidelines for treatment of gestational diabetes, including thresholds for initiating insulin therapy. In 1990, a survey of general obstetricians (ACOG Fellows) and specialists (Society of Perinatal Obstetricians) found that 90% of specialists and approximately 77% of generalists conducted universal screening for gestational diabetes, primarily using a GCT followed by a 100 g OGTT in patients whose GCT value met or exceeded a cutoff value (17).

Despite the endorsements and guidelines for diagnosis and treatment of gestational diabetes by two major U.S. professional organizations and widespread testing for gestational diabetes in clinical practice (17), there has been longstanding controversy about the value of detecting and treating gestational diabetes (18,19). Two issues have been the focus of concern. The first is whether the adverse outcomes that occur in pregnancies complicated by gestational diabetes are independently linked to maternal hyperglycemia or to confounding factors, such as obesity and/or higher maternal age. The second is whether treatment of hyperglycemia in gestational diabetes reduces adverse outcomes. In 2003 and again in 2008, the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to make a recommendation for or against routine screening for gestational diabetes before or after 24 weeks of gestation (20,21).

Since 2005, much evidence has been published to address both of these issues. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study demonstrated that there is indeed an independent association between maternal glucose from OGTTs performed

FIGURE 4.1. Beta Cell Compensation During and After Pregnancy in Women With and Without Gestational Diabetes



Left panel: Relationships between pre-hepatic insulin secretion rates and insulin sensitivity measured during steady-state hyperglycemia (3 hours, 180 mg/dL) in women with GDM (n=7) or normal glucose tolerance during pregnancy (n=8). Right panel: Relationships between acute insulin response to intravenous glucose (AIRg) and insulin sensitivity (minimal model Si) in Hispanic women with GDM (n=99) or normal glucose tolerance during and after pregnancy (n=7). Curved lines represent insulin sensitivity-secretion relationships defined by the product of sensitivity and secretion in each study group. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. FFM, fat-free mass; GDM, gestational diabetes mellitus.

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at 24–32 (mean 27.8) weeks of gestation and several adverse perinatal outcomes (22). In parallel, two large randomized clinical trials investigated whether adverse outcomes were reduced by treatment of "mild" gestational diabetes (23,24). Both trials showed reductions in some perinatal outcomes in association with identification and treatment of gestational diabetes. In 2013, a USPSTF report found "adequate evidence that treatment of screen-detected gestational diabetes with dietary modifications, glucose monitoring, and insulin (if needed) can significantly reduce the risk of preeclampsia, fetal macrosomia, and shoulder dystocia. When these outcomes are considered collectively, there is a moderate net benefit for both mother and infant" (25). However, the USPSTF went on to conclude that the evidence was inadequate "to determine whether there are benefits to screening for gestational diabetes in women before 24 weeks of gestation" (25).

PATHOPHYSIOLOGY

From the physiological standpoint, gestational diabetes identifies women whose pancreatic beta cells compensate inadequately for insulin resistance during pregnancy. Available evidence indicates that this beta cell defect is not specific to pregnancy: it exists before and after pregnancy in many, probably most, cases (26,27,28). As shown in Figure 4.1, women with gestational diabetes compensate for pregnancy-related changes in insulin resistance on a curve that is parallel to, but lower than, women without gestational diabetes (27,28). In other words, defects in beta cell compensation for insulin resistance, one of the best measures of beta cell function, are not dependent on pregnancy; they exist when the women are not pregnant as well. Data from Catalano *et al.* (26) indicate the defects antedate pregnancy as well. Thus, gestational diabetes can be thought of as detection of an underlying beta cell defect through routine glucose screening in pregnancy. In many cases, the beta cell defect that causes gestational diabetes worsens over time, imparting a high risk of diabetes following the index pregnancy. The beta cell defects of gestational diabetes result from many causes, including autoimmunity typical of type 1 diabetes (29,30,31), single gene variants typical of maturity-onset diabetes of youth (32,33) or maternally inherited diabetes (34), and chronic insulin resistance typical of type 2 diabetes (26,28). The majority of women have phenotypic characteristics suggesting chronic insulin resistance and evolving type 2 diabetes (35).

DETECTION AND DIAGNOSIS

The diagnostic thresholds for gestational diabetes recommended by O'Sullivan and Mahan (6) represented the mean plus two standard deviation values for each sample (fasting and 1-, 2-, and 3-hour postload) of the 100 g OGTT that was performed on all 752 participants of the study cohort. Thus, by definition, the frequency of gestational diabetes was low in that population and in others with similar characteristics. Since gestational diabetes is usually asymptomatic, it was necessary to formulate a strategy to screen pregnant women to determine in whom and when to do a diagnostic test (i.e., OGTT).

SCREENING FOR GESTATIONAL DIABETES

When Wilkerson and O'Sullivan developed a strategy to detect prediabetes or impaired glucose metabolism in pregnancy, they initially applied an approach and criteria that were used in nonpregnant persons (36). They compared the

predictive value of historical factors that they (4,5) and others (7) had associated with maternal prediabetes with the presence of a positive GCT. The GCT results were clearly more predictive. In 1973, O'Sullivan *et al.* (37) compared the GCT and OGTT results from the cohort of 752 pregnant women that had been used to define gestational diabetes (6). In this two-step analysis, they established that a GCT screening threshold of ≥130 mg/dL (whole blood; ≥7.22 mmol/L) had a sensitivity of 79% and specificity of 87% for the identification of women with gestational diabetes. Clinical risk factors alone or in combination were again found to be insensitive for detecting gestational diabetes (37). Accordingly, for many years, the standard practice in the United States has been to do a 50 g GCT in all women (14,15,16,17) or in all except those who qualify clinically as "low-risk" (38,39), followed by a diagnostic OGTT in women with screening values above a threshold designed for high sensitivity but low specificity for possible gestational diabetes.

Worldwide, there are many different approaches to screening for gestational diabetes. In many areas outside of the United States, the GCT is not used at all or is administered only to women with clinical risk factors for diabetes or gestational diabetes. Many different values are used to discriminate between low-risk and at-risk results (40), due in part to inconsistent approaches to extrapolating plasma glucose values to replace whole blood glucose concentrations that were originally used to define a positive GCT (1,14,15,16,37,38,39,40,41). This problem and the concerns related to different laboratory methods and analyzers used to measure glucose were reviewed in detail in *Diabetes in America, 2nd edition* (42). Furthermore, a positive GCT is combined with either a 75 or 100 g OGTT and the application of a variety of diagnostic criteria (40).

Lowering the threshold for venous plasma glucose from 140 mg/dL (14) to 130 or 135 mg/dL increases the number diagnosed with gestational diabetes (greater sensitivity) but requires doing substantially more OGTTs (lower specificity) (41,42). However, few studies using different GCT thresholds in combination with specific diagnostic criteria have included a GCT and an OGTT in all participants (25,40).

Systematic reviews published in 2012 (40) and 2013 (43) indicate that despite a number of limitations, using a GCT to identify women at risk for gestational diabetes is an acceptable screening procedure. However, differences in the application of the GCT as a screening tool are among several factors that contribute to the widely varying rates of gestational diabetes that have been reported across the globe (40,44). Furthermore, using only a postload glucose value for screening, as in the GCT, does not take advantage of the fact that the concentration of fasting plasma glucose (FPG) is also strongly and independently associated with several perinatal outcomes (22,45).

The optimal time in pregnancy to screen and test for gestational diabetes is also an important question. Historically, pregnancy has been considered to be diabetogenic, particularly after the first trimester (46). The Second International Workshop-Conference on Gestational Diabetes Mellitus (14) and the ADA (15) recommended that "All pregnant women who have not been identified as having glucose intolerance before the 24th week should have a screening glucose load between the 24th and 28th week consisting of 50 g oral glucose given without regard to time of the last meal or the time of day. A value of >140 mg/dL… is recommended as a threshold to indicate the need for a full diagnostic glucose tolerance test." While some women could be identified as having gestational diabetes after screening and testing in the first trimester, a higher yield of abnormal results was found with testing in the second and/or third trimester (47,48). Early detection and treatment of previously undiagnosed diabetes are clearly of value; however, it remains uncertain that early detection and treatment of gestational diabetes are beneficial (25). Testing late in gestation may yield the largest number of cases of gestational diabetes (47,48), but making the diagnosis of gestational diabetes late in the third trimester leaves little opportunity for treatment to have an effect on perinatal outcome.

Performing a diagnostic OGTT in all pregnancies or in those considered at high risk for gestational diabetes and/or lifetime risk of diabetes (one-step procedure) is an alternate strategy for detection and diagnosis of gestational diabetes. In general, this approach to disease detection is most applicable if the diagnostic test is accurate and relatively inexpensive and the condition tested for is not rare. The merits, or lack thereof, of an OGTT as a diagnostic test have been debated historically (18,19) and remain controversial (49,50,51). Nevertheless, an OGTT is one accepted standard for making a diagnosis of diabetes outside of pregnancy (52).

Whether the one-step or two-step approach to the diagnosis of gestational diabetes is most cost-effective has also been a concern. Meltzer *et al.* (53) conducted a randomized controlled clinical trial comparing costs and effectiveness of the diagnostic process with one- and two-step procedures for the detection and diagnosis of gestational diabetes. Itemized costs included the time the women had to devote to complete the testing. Two versions of the two-step approach were included: in one, a positive 50 g GCT was followed by a 3-hour 100 g OGTT; in the other, a positive GCT was followed by a 2-hour 75 g OGTT. In the third group, all women had a 2-hour 75 g OGTT. Canadian Diabetes Association guidelines and diagnostic criteria for gestational diabetes (54), which are similar to the NDDG criteria (1), were followed. Overall, the two-step approach was modestly, but significantly, less costly. However, in Asian women, who had a much higher prevalence of gestational diabetes than the population overall, costs of the one-step and two-step approaches did not differ (53). Of note, gestational age at diagnosis of gestational diabetes was significantly earlier with the one-step approach.

TABLE 4.1. Diagnosis of Gestational Diabetes

	100 G ORAL GLUCOSE LOAD			75 G ORAL GLUCOSE LOAD
GLUCOSE VALUE	O'Sullivan-Mahan (Ref. 6) Whole blood (mg/dL)*	NDDG (Ref. 1) Plasma AutoAnalyzer (mg/dL)*	Carpenter-Coustan (Ref. 41) Plasma glucose oxidase (mg/dL)*	IADPSG (Ref. 67) Plasma enzymatic (mg/dL)†
Fasting	90	105	95	92
1-hour	165	190	180	180
2-hour	145	165	155	153
3-hour	125	145	140	‡

The test should be performed in the morning after an overnight fast of at least 8 hours but not more than 14 hours and after at least 3 days of unrestricted diet (≥150 g carbohydrate per day) and physical activity. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. IADPSG, International Association of Diabetes and Pregnancy Study Groups; NDDG, National Diabetes Data Group.

* For the diagnosis, two or more of the glucose values must be met or exceeded.

† For the diagnosis, one or more of the glucose values must be met or exceeded.

‡ IADPSG diagnostic criteria are based on a 2-hour, 75 g oral glucose tolerance test.

SOURCE: References are listed within the table.

Measuring the concentration of glycosylated hemoglobin (A1c) or other glycosylated moieties as a screening tool for gestational diabetes detection has been examined in numerous reports based on small to moderate sized groups of subjects (42). In general, limited sensitivity and specificity were found compared to a diagnosis based on plasma glucose values. A similar conclusion was reached from the subset of >21,000 women in the HAPO Study who had A1c measured; perinatal outcome was the gold standard in that study (55).

DIAGNOSIS OF GESTATIONAL DIABETES

Ideally, the diagnosis of gestational diabetes should distinguish a group of pregnant women in whom an important clinical risk, whether to the mother or fetus, is higher than in another group. Despite shortcomings in the use of an OGTT as a tool for classifying the status of glucose tolerance (18,19,49,50,51), such tests remain the standard for diagnosing gestational diabetes. However, no widespread agreement has been reached on the type or timing of the OGTT for diagnosing gestational diabetes. In 2006, Cutchie *et al.* summarized guidelines for diagnosis and treatment of gestational diabetes from 11 organizations or countries (13). In all instances, either a 75 or 100 g glucose load was used for the diagnostic test. In 3 of 11, a 100 g diagnostic test was used, but diagnostic thresholds were not consistent. A 75 g 2-hour OGTT was used in the other eight programs; however, six different combinations of fasting and 2-hour plasma glucose threshold values were used for the diagnosis of gestational diabetes. The criteria that are widely used for the diagnosis of gestational diabetes in the United States are shown in Table 4.1.

Clearly, variance in strategies for screening to determine on whom to perform a diagnostic OGTT, the diagnostic test that is used, and the diagnostic thresholds that are used all contribute to the limitations of efforts to compare the frequency, complications, and the effectiveness of treating gestational diabetes within and among countries. This situation is very reminiscent of the problems that prevailed regarding diabetes in the general population before the 1979 and 1980 recommendations of the NDDG (1) and WHO (11), respectively.

PREVALENCE OF GESTATIONAL DIABETES

The lack of standardized methods for the detection and diagnosis of gestational diabetes described above represents a major challenge to providing estimates of the prevalence of gestational diabetes (56,57). Engelgau *et al.* (58) used data from the National Maternal and Infant Health Survey (NMIHS) to estimate the prevalence of diabetes and pregnancy in the United States in 1988. With adjustments for many factors, including lack of information on diabetes in 26% of the sample, the estimated prevalence of diabetes and pregnancy was 4%, and of those, 88% had gestational diabetes. Increasing maternal age and body mass index (BMI, kg/m^2) were associated with higher rates of gestational diabetes.

Getahun *et al.* (59) used National Hospital Discharge Survey data that included information on hospital discharge records of birth in the United States during the period of 1989–2004 to estimate temporal trends in the prevalence of gestational diabetes. The prevalence of gestational diabetes increased by 80% in white women and by 172% in black women during this interval (Table 4.2). The increase in prevalence was most striking in black women age <25 years; the rate more than tripled from 0.6% to 2.1% between 1989 and 2004 (59). Information was not available on factors such as maternal weight and method of detection of gestational diabetes that might have contributed to these temporal trends.

Bardenheier *et al.* (60) used discharge-level and hospital-level data from the Healthcare Cost and Utilization Project and discharge-level data from the State Inpatient Databases for 2008 to estimate the prevalence rate of gestational diabetes in 23 states (Table 4.3).

TABLE 4.2. Prevalence of Gestational Diabetes and Percent Changes by Periods Among Hospitalized Women, by Age and Race, U.S., 1989–2004

AGE (YEARS) AND RACE	PERCENT									PERCENT CHANGE (95% CI) 2003–2004 VS. 1989–1990
	1989–1990*	1991–1992	1993–1994	1995–1996	1997–1998	1999–2000	2001–2002	2003–2004	Average	
White women										
Total	2.0	2.1	2.7	2.8	2.9	3.2	3.4	3.6	2.8	80 (79–82)
<25	1.2	1.0	1.1	1.5	1.3	1.7	1.8	1.4	1.4	13 (11–16)
25–34	2.2	2.6	3.1	3.0	3.1	3.1	3.8	4.2	3.2	94 (91–96)
≥35	4.1	4.0	5.0	5.5	6.0	6.1	5.4	7.0	5.4	70 (66–73)
Black women										
Total	1.5	1.9	1.8	2.6	3.1	2.5	3.0	4.1	2.8	172 (166–178)
<25	0.6	0.8	0.9	1.4	2.0	0.8	1.4	2.1	1.3	260 (243–279)
25–34	1.9	2.9	2.4	3.4	3.7	3.8	4.4	5.7	3.5	197 (187–207)
≥35	6.4	4.7	4.4	5.8	6.7	6.7	6.4	8.7	6.2	35 (30–41)

CI, confidence interval.
* Period-specific rates

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TABLE 4.3. Prevalence of Gestational Diabetes Among Hospital Discharges for Obstetric Deliveries in 23 States, by Race/Ethnicity, State Inpatient Databases, 2008

STATE	GESTATIONAL DIABETES RATES PER 100 DELIVERIES (STANDARD ERROR)				
	All	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian
All 23 states	5.32 (0.02)	4.40 (0.02)	5.30 (0.05)	7.02 (0.04)	8.14 (0.08)
Arizona	4.78 (0.07)	3.44 (0.09)	4.18 (0.34)	5.81 (0.12)	6.68 (0.43)
Arkansas	5.01 (0.13)	3.24 (0.11)	2.73 (0.21)	8.03 (0.46)	4.62 (0.88)
California	5.88 (0.03)	4.67 (0.05)	5.43 (0.15)	8.06 (0.06)	8.73 (0.11)
Colorado	4.34 (0.09)	3.09 (0.09)	4.24 (0.42)	6.79 (0.26)	6.42 (0.62)
Florida	5.61 (0.05)	4.96 (0.07)	4.95 (0.10)	5.58 (0.11)	8.37 (0.40)
Hawaii	5.26 (0.16)	4.29 (0.30)	6.01 (1.36)	6.63 (1.27)	8.23 (0.26)
Iowa	6.04 (0.15)	4.59 (0.12)	3.76 (0.55)	*	6.67 (1.04)
Kentucky	7.14 (0.13)	5.24 (0.11)	4.09 (0.32)	6.23 (0.57)	5.42 (0.92)
Maine	6.97 (0.25)	5.55 (0.21)	*	*	7.12 (1.76)
Maryland	5.86 (0.09)	4.74 (0.11)	5.60 (0.16)	8.11 (0.31)	9.73 (0.46)
Massachusetts	4.67 (0.08)	4.22 (0.09)	6.32 (0.32)	6.20 (0.26)	8.78 (0.39)
Michigan	6.77 (0.10)	5.29 (0.09)	5.38 (0.18)	8.22 (0.49)	7.70 (0.62)
Nevada	3.92 (0.10)	2.78 (0.13)	3.53 (0.35)	5.05 (0.19)	5.71 (0.47)
New Jersey	5.03 (0.07)	4.33 (0.09)	5.59 (0.20)	6.96 (0.19)	9.47 (0.28)
New York	5.06 (0.05)	4.47 (0.06)	5.64 (0.12)	6.08 (0.13)	8.98 (0.21)
North Carolina	6.71 (0.10)	5.32 (0.10)	6.27 (0.19)	†	8.56 (0.57)
Oregon	5.75 (0.33)	4.56 (0.32)	*	8.36 (1.20)	6.46 (1.08)
Rhode Island	7.15 (0.24)	6.21 (0.26)	8.51 (0.99)	8.27 (0.63)	11.08 (1.57)
South Dakota	6.43 (0.30)	4.98 (0.24)	*	†	*
Utah	3.47 (0.09)	2.42 (0.08)	2.47 (0.70)	5.01 (0.25)	4.68 (0.61)
Vermont	3.78 (0.29)	3.01 (0.24)	*	*	*
Washington	6.48 (0.16)	5.16 (0.17)	7.71 (0.89)	8.65 (0.40)	8.70 (0.61)
Wisconsin	4.89 (0.09)	3.77 (0.08)	4.48 (0.28)	6.74 (0.34)	6.63 (0.53)

Logistic regression analysis was used to estimate age- and race-adjusted gestational diabetes rates for each state and region and age-adjusted gestational diabetes rates by race and ethnicity.
* Number of cases ≤10
† State does not collect data for Hispanic ethnicity.

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TABLE 4.4. Crude and Adjusted Yearly Cumulative Incidence of Gestational Diabetes in Women Age 15–49 Years Who Were Screened, by Age and Race/Ethnicity, the Kaiser Permanente Northern California Gestational Diabetes Registry, 1991–2000

CHARACTERISTICS	PERCENT (STANDARD ERROR)									
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
All										
Crude	4.7 (0.15)	4.8 (0.14)	5.2 (0.15)	5.9 (0.15)	6.2 (0.16)	6.8 (0.16)	7.5 (0.16)	6.5 (0.15)	7.3 (0.16)	7.2 (0.15)
Age-adjusted	4.9 (0.15)	4.9 (0.14)	5.2 (0.15)	5.9 (0.15)	6.1 (0.16)	6.8 (0.16)	7.5 (0.16)	6.5 (0.15)	7.3 (0.16)	7. 1 (0.15)
Age- and race/ethnicity-adjusted	5.1 (0.16)	5.1 (0.15)	5.4 (0.16)	6.0 (0.16)	6.2 (0.16)	6.8 (0.16)	7.4 (0.16)	6.4 (0.15)	7.1 (0.16)	6.9 (0.15)
Age (years)										
15–24	1.4 (0.04)	1.6 (0.04)	1.9 (0.05)	2.2 (0.05)	2.8 (0.05)	2.7 (0.05)	3.0 (0.05)	2.5 (0.05)	2.9 (0.05)	2.7 (0.05)
25–34	4.9 (0.11)	4.8 (0.11)	5.2 (0.11)	6.1 (0.12)	6.4 (0.12)	7.2 (0.12)	7.6 (0.12)	6.6 (0.11)	7.5 (0.12)	7.8 (0.11)
35–49	10.2 (0.08)	10.2 (0.08)	10.5 (0.08)	11.1 (0.08)	10.6 (0.08)	11.6 (0.09)	14.0 (0.09)	12.1 (0.09)	13.3 (0.90)	13.3 (0.09)
Race/ethnicity										
White										
Crude	3.8 (0.10)	3.8 (0.11)	4.1 (0.11)	4.9 (0.12)	5.3 (0.12)	5.6 (0.13)	6.0 (0.13)	5.1 (0.12)	6.4 (0.13)	6.1 (0.13)
Age-adjusted	3.9 (0.18)	3.8 (0.16)	4.1 (0.17)	4.8 (0.18)	5.1 (0.19)	5.4 (0.20)	5.7 (0.20)	5.9 (0.19)	6.0 (0.21)	5.7 (0.20)
African American										
Crude	3.2 (0.08)	3.9 (0.04)	4.3 (0.04)	4.8 (0.05)	4.0 (0.04)	4.8 (0.05)	5.2 (0.05)	5.4 (0.05)	5.2 (0.05)	5.8 (0.05)
Age-adjusted	4.1 (0.62)	4.7 (0.60)	5.1 (0.60)	5.7 (0.54)	4.7 (0.49)	5.6 (0.52)	5.8 (0.53)	5.8 (0.55)	5.9 (0.58)	6.4 (0.55)
Hispanic										
Crude	6.2 (0.06)	5.7 (0.07)	6.1 (0.07)	7.3 (0.12)	7.1 (0.08)	7.3 (0.09)	8.5 (0.11)	7.1 (0.10)	7.7 (0.11)	7.6 (0.11)
Age-adjusted	7.2 (0.53)	6.5 (0.46)	6.9 (0.47)	8.2 (0.47)	8.1 (0.48)	8.2 (0.44)	9.8 (0.44)	8.3 (0.39)	8.5 (0.38)	8.3 (0.35)
Asian										
Crude	7.8 (0.07)	8.7 (0.08)	8.8 (0.08)	8.8 (0.09)	9.4 (0.09)	11.3 (0.10)	12.1 (0.11)	10.4 (0.10)	10.7 (0.10)	10.9 (0.11)
Age-adjusted	7.2 (0.47)	7.9 (0.46)	8.0 (0.47)	8.0 (0.43)	8.3 (0.45)	10.0 (0.46)	11.0 (0.48)	9.3 (0.43)	9.6 (0.43)	9.7 (0.44)

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The age and race/ethnicity-adjusted rates varied from 3.47% in Utah to 7.15% in Rhode Island. Differences in age, race/ethnicity, frequency of obesity (state level only), hospital, and insurance accounted for 86% of the variance. Differences in the proportion of pregnancies screened and diagnostic criteria used could not be measured and likely contributed to some of the unmeasured variance, as well as differences linked to hospitals and insurance.

Reports of gestational diabetes prevalence among participants in specific health care systems have included information about screening methods and diagnostic criteria and have provided convincing evidence of substantial increases in gestational diabetes in the 1990s and 2000s. Between 1991 and 2000, the Kaiser Permanente Medical Care Program in Northern California provided care to approximately 30% of the population in a 14-county region (61). Screening for gestational diabetes was performed in 267,051 pregnancies during the 10 years of the study (86.8% of the total) using a two-step process (50 g GCT and 100 g OGTT and the Carpenter-Coustan diagnostic thresholds (41) in 98.2% of the cases). As indicated in Table 4.4, the overall (crude) cumulative incidence of gestational diabetes among screened pregnancies increased by 53%, from 4.7% in 1991 to 7.2% in 2000. An increase was seen in all age and race/ethnicity groups. The cumulative incidence of gestational diabetes leveled off in 1998–2000 in all except African Americans (61). In a report from Kaiser Permanente Colorado (KPCO), based on 36,403 pregnancies in residents of the Denver region seen between 1994 and 2002, Dabelea *et al.* (62) found very similar trends to those reported from Northern California (61). Overall, the prevalence of gestational diabetes doubled from 2.1% in 1994 to 4.1% in 2002. The substantially lower absolute frequencies were due at least in part to the fact that the diagnostic thresholds recommended by NDDG (1) were used in KPCO, while the lower Carpenter-Coustan diagnostic threshold values (41) were used in Northern California.

Lawrence *et al.* (63) reported on trends in prevalence of both preexisting diabetes and gestational diabetes in 209,287 pregnancies in women who received their medical care from Kaiser Permanente Southern California (KPSC) between 1999 and 2005. The proportion of women screened and tested for gestational diabetes predominately using the two-step approach was very high (96.5%). In 1999, the crude prevalence of gestational diabetes in KPSC (7.1%), where the Carpenter-Coustan diagnostic thresholds (41) were used, was similar to that found in Northern California (7.3%) (61) and higher than the 4.1% 2002 rate in Colorado (62). The age- and race/ethnicity-adjusted rates of gestational diabetes were nearly constant between 1999 and 2005, 7.5% and 7.4%, respectively. This is similar to the stable rate of gestational diabetes that was found in Northern California between 1998 and 2000 (61). In this context, the data on rates of preexisting diabetes that were found in the KPSC study (63) are important to consider (Table 4.5). The age-adjusted rate of preexisting diabetes increased progressively from

TABLE 4.5. Crude and Adjusted Prevalence of Preexisting Diabetes and Gestational Diabetes, Kaiser Permanente Southern California, 1999–2005

	PREVALENCE PER 100 (STANDARD ERROR)							
	1999	2000	2001	2002	2003	2004	2005	P_{trend}
Preexisting diabetes*								
Crude	0.76 (0.05)	1.06 (0.06)	1.05 (0.06)	1.26 (0.06)	1.52 (0.07)	1.87 (0.08)	1.90 (0.08)	<0.0001
Age-adjusted	0.81 (0.02)	1.10 (0.02)	1.06 (0.02)	1.25 (0.02)	1.50 (0.03)	1.81 (0.03)	1.83 (0.03)	<0.0001
Age- and race/ethnicity-adjusted	0.81 (0.02)	1.10 (0.02)	1.06 (0.02)	1.24 (0.02)	1.50 (0.03)	1.82 (0.03)	1.82 (0.03)	<0.0001
Gestational diabetes†								
Crude	7.1 (0.15)	7.4 (0.15)	7.6 (0.06)	8.2 (0.16)	7.4 (0.16)	7.6 (0.16)	7.8 (0.16)	0.0176
Age-adjusted	7.4 (0.06)	7.6 (0.06)	7.9 (0.06)	8.1 (0.06)	7.2 (0.06)	7.4 (0.06)	7.5 (0.06)	0.4104
Age- and race/ethnicity-adjusted	7.5 (0.06)	7.6 (0.06)	7.9 (0.06)	8.1 (0.06)	7.2 (0.06)	7.3 (0.06)	7.4 (0.06)	0.0655

* P-values are derived from Poisson regression models using preexisting diabetes as the outcome variable and year as a continuous variable in the model after adjustment for other variables specified for the row.

† P-values are derived from Poisson regression models using gestational diabetes as the outcome variable and year as a continuous variable in the model after adjustment for other variables specified for the row.

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0.81% to 1.83% between 1999 and 2005; the increase was seen in all race/ethnicity groups. The greatest increase in prevalence of preexisting diabetes was found in the youngest age group (age 13–19 years). While it was not possible to distinguish between preexisting type 1 and type 2 diabetes, the demographics of this population suggest that much of the temporal trend represented an increase in type 2 diabetes and that the appearance of more type 2 diabetes in the younger women may have contributed to the leveling of the rate of gestational diabetes.

The 6th edition of the *International Diabetes Federation (IDF) Diabetes Atlas* includes estimates of the prevalence of diabetes in 2013 and projections for 2035 (64). The estimates are based on reports from throughout the world that at a minimum included age-specific prevalence of diabetes in three age groups of adults between 20 and 79 years (65). The estimated prevalence of gestational diabetes for 2013 was 16.8% (64).

GLUCOSE TOLERANCE IN NONPREGNANT WOMEN

The prevalence of gestational diabetes is associated with the prevalence of alterations of glucose metabolism (tolerance) in the general population. Table 4.6 shows National Health and Nutrition Examination Survey (NHANES) data analyzed for *Diabetes in America, 3rd edition*, on the status of glucose tolerance and BMI among women age 20–44 years in the periods 1976–1980 and 2007–2010. During this interval of 30 years, the frequencies of diagnosed diabetes, undiagnosed diabetes, and undiagnosed prediabetes each more than doubled. In parallel, the rate of obesity became nearly threefold higher, and the rate of overweight increased modestly. Comparable data from other countries are limited. The documented increases in prevalence rates of gestational diabetes and preexisting diabetes during pregnancy (above) occurred during the same general timeframe in which the epidemic of obesity and type 2 diabetes developed in the general population in the United States and globally. This is in keeping with the theme that gestational diabetes represents detection of existing abnormalities of glucose tolerance in the population (66). As noted, data on BMI were not available for the studies that demonstrated the increasing prevalence of gestational diabetes specifically (59,61,62).

TABLE 4.6. Weighted Distribution of Glucose and BMI Categories Among Women Age 20–44 Years, U.S., 1976–1980 and 2007–2010

	WEIGHTED PERCENT (STANDARD ERROR)	
DIABETES/BMI* STATUS	1976–1980	2007–2010
Diagnosed diabetes†	1.2 (0.20)	2.3 (0.29)
Undiagnosed diabetes‡	1.2 (0.40)	2.6 (0.48)
Undiagnosed prediabetes‡	11.9 (1.15)	24.0 (1.87)
Normal glucose levels‡	85.8 (1.23)	71.2 (2.11)
Obese	12.1 (1.05)	32.7 (1.79)
Overweight	21.6 (1.67)	26.4 (1.67)
Normal	66.3 (1.80)	40.9 (2.30)

Women currently pregnant were excluded from the analysis. BMI, body mass index (weight/height in kg/m^2).

* BMI is defined as obese (≥30 kg/m^2), overweight (25–<30 kg/m^2), normal (<25 kg/m^2).

† Diagnosed diabetes is self-reported.

‡ Undiagnosed diabetes, prediabetes, and normal glucose levels are defined by fasting plasma glucose or 2-hour plasma glucose from an oral glucose tolerance test using American Diabetes Association cutpoints (Reference 73).

SOURCE: National Health and Nutrition Examination Surveys 1976–1980 and 2007–2010

THE HYPERGLYCEMIA AND ADVERSE PREGNANCY OUTCOME (HAPO) STUDY

The objective of the HAPO Study was to clarify associations of levels of maternal glucose lower than those diagnostic of diabetes with perinatal outcome (22). A 75 g OGTT was performed on unselected consenting pregnant women at 24–32 weeks of gestation (mean 27.8 weeks) in 15 centers in nine countries. In 23,316 participants with glucose values blinded to participants and caregivers, continuous, linear associations were found between each venous plasma glucose measure (fasting, 1-hour, and 2-hour post glucose

TABLE 4.7. Frequency of Gestational Diabetes by Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Field Center and Participants With Elevated Fasting, 1-Hour, and 2-Hour Plasma Glucose, 2000–2006

		PERCENT									
			GDM diagnosed by each glucose measure			All women with individual glucose measures *at or above* the threshold			Women with GDM with individual glucose measures *at or above* the threshold		
FIELD CENTER*	PARTICIPANTS/ CENTER	GDM	FPG†	1-hour PG‡	2-hour PG§	FPG	1-hour PG	2-hour PG	FPG	1-hour PG	2-hour PG
HAPO overall	23,957	17.8	55	33	12	9.8	9.7	6.7	55	55	38
Bellflower, California	1,981	25.5	73	21	6	18.7	12.4	6.9	73	49	27
Singapore, Singapore	1,787	25.1	47	39	14	11.9	16.3	11.7	47	65	47
Cleveland, Ohio	797	25.0	64	27	10	15.9	12.0	9.4	64	48	38
Manchester, United Kingdom	2,376	24.3	67	26	7	16.2	13.8	8.5	67	57	35
Bangkok, Thailand	2,499	23.0	24	64	12	5.5	17.4	10.0	24	76	43
Chicago, Illinois	753	17.3	53	28	19	9.2	8.0	8.0	53	46	46
Belfast, United Kingdom	1,671	17.1	63	30	7	10.7	7.8	4.2	63	46	25
Toronto, Canada	2,028	15.5	66	24	9	10.3	7.5	5.2	66	48	34
Providence, Rhode Island	757	15.5	73	19	9	11.2	5.9	5.3	73	38	34
Newcastle, Australia	668	15.3	64	25	11	9.7	7.2	5.7	64	47	37
Hong Kong, China	1,654	14.4	26	45	29	3.8	8.9	9.4	26	62	65
Brisbane, Australia	1,444	12.4	50	31	18	6.2	5.9	4.8	50	47	39
Barbados, West Indies	2,093	11.9	74	9	17	8.8	3.8	5.1	74	32	43
Petah Tiqva, Israel	1,818	10.1	43	45	13	4.3	6.3	3.4	43	62	33
Beersheba, Israel	1,631	9.3	57	28	15	5.3	3.8	2.4	57	41	26

Gestational diabetes is defined by International Association of Diabetes and Pregnancy Study Groups criteria (see Table 4.1 or Reference 67). FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcome Study; PG, plasma glucose.

* Centers are listed from highest to lowest unadjusted frequency of gestational diabetes.

† Includes all with FPG *at or above* the threshold without regard to 1-hour and 2-hour values.

‡ Includes all with FPG less than the threshold and 1-hour *at or above* the threshold without regard to 2-hour value.

§ Only 2-hour value is *at or above* the threshold.

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load) and multiple pregnancy outcomes (birthweight, cord serum C-peptide, percent infant body fat [each >90th percentile], primary cesarean delivery, neonatal hypoglycemia, preterm delivery, and preeclampsia). No obvious thresholds at which risks increased were observed (22).

The HAPO Study was expected to provide data on associations between maternal glycemia and risk of specific adverse outcomes that could be used to derive internationally acceptable criteria for diagnosis and classification of gestational diabetes. Since no apparent glucose threshold for perinatal risks was identified, derivation of such criteria has been approached by consensus of experts. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) sponsored a Workshop-Conference on Gestational Diabetes Diagnosis and Classification attended by more than 225 conferees from 40 countries. Published and unpublished HAPO results and other work on associations of maternal glycemia with perinatal and long-term outcomes in offspring were reviewed. A Consensus Panel of more than 50 individuals representing the member organizations of IADPSG and other groups carried out further review and analysis of HAPO results, held a second face-to-face meeting of panel members, and then published recommendations for the diagnosis and classification of hyperglycemia in pregnancy (67). When IADPSG criteria are used, the diagnosis of gestational diabetes is made if one or more glucose values of the OGTT equals or is greater than threshold concentrations of 92 mg/dL (5.11 mmol/L) fasting, 180 mg/dL (10.00 mmol/L) at 1 hour, or 153 mg/dL (8.49 mmol/L) at 2 hours.

Use of IADPSG criteria yields substantially higher frequencies of gestational diabetes than is the case when two abnormal values and higher thresholds are applied (1,15,16,41). Some groups, including ADA (68), WHO (69), and others (70) have adopted the IADPSG diagnostic recommendations, while others have not (70,71,72). ACOG (71) and a Consensus Panel appointed by the National Institutes of Health (NIH) (72) recommended the continuing use of the longstanding two-step process for detection and diagnosis described above. In 2014, the ADA acknowledged that in the immediate future both O'Sullivan-Mahan-based criteria (1,6,41) and the IADPSG recommendations (67) will be used in the United States (73). The applicable diagnostic thresholds are summarized in Table 4.1 and are also discussed in Chapter 1 *Classification and Diagnosis of Diabetes*.

When the IADPSG thresholds for the diagnosis of gestational diabetes were applied to the HAPO Study data, the unadjusted rates in the 15 participating centers ranged from 9.3% to 25.5% (Table 4.7) (74). Adjusting for maternal age, BMI and height did not eliminate

TABLE 4.8. Crude and Adjusted Frequency of Gestational Diabetes, by HAPO Field Center, 2000–2006

FIELD CENTER*	PARTICIPANTS/ CENTER	PERCENT GDM	
		Crude	Adjusted (95% CI)†
Bellflower, California	1,981	25.5	20.9 (19.1–22.6)
Singapore, Singapore	1,787	25.1	23.6 (21.3–25.9)
Cleveland, Ohio	797	25.0	23.1 (20.0–26.1)
Manchester, United Kingdom	2,376	24.3	22.5 (20.8–24.2)
Bangkok, Thailand	2,499	23.0	22.8 (20.1–25.5)
Chicago, Illinois	753	17.3	17.2 (14.0–20.4)
Belfast, United Kingdom	1,671	17.1	16.9 (14.9–18.8)
Toronto, Canada	2,028	15.5	15.7 (14.0–17.5)
Providence, Rhode Island	757	15.5	14.6 (12.0–17.1)
Newcastle, Australia	668	15.3	13.6 (10.9–16.3)
Hong Kong, China	1,654	14.4	15.6 (13.0–18.1)
Brisbane, Australia	1,444	12.4	13.2 (11.0–15.4)
Barbados, West Indies	2,093	11.9	14.6 (12.8–16.3)
Petah Tiqva, Israel	1,818	10.1	11.9 (10.3–13.6)
Beersheba, Israel	1,631	9.3	10.2 (8.6–11.8)

CI, confidence interval; GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcome Study.
* Centers are listed from highest to lowest unadjusted frequency of gestational diabetes.
† Adjusted using direct standardization across quartiles for age, body mass index, and height.

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center-to-center differences (Table 4.8). The reasons for the differences are not clear and may partially relate to frequencies of obesity and degree of abnormal glucose metabolism in the general populations where HAPO centers were located. Data from the new analysis of the NHANES 1976–1980 and 2007–2010 on glucose tolerance status in women of childbearing age in the United States are summarized in Table 4.6. Comparable data on population characteristics are not available for many countries where HAPO Study centers are located.

Crucial to the definition of new criteria for diagnosis of gestational diabetes is evidence that effective treatment is available. This is especially important if use of the new criteria substantially increases the frequency of the diagnosis. Data from randomized trials using the IADPSG criteria are not yet available. However, the IADPSG thresholds (67) overlap (70) with criteria used in two randomized trials, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) (23) and the Maternal-Fetal Medicine Units (MFMU) Network (24), that showed significant benefit associated with diagnosing and treating mild gestational diabetes. Nonetheless, the 2013 NIH Consensus Development Conference Statement (72) called for studies to "Determine whether the additional women categorized as having diabetes by the IADPSG model, who would be considered normal in the two-step strategy, accrue any benefit from treatment. This question would be best answered by a randomized controlled trial that, ideally, would use clinically important health and patient-centered outcomes." Thus, the goal of globally accepted criteria for the diagnosis of gestational diabetes based on perinatal outcomes (75) remains elusive.

TREATMENT

RANDOMIZED CONTROLLED TRIALS OF MILD GESTATIONAL DIABETES

The results of two randomized controlled trials (23,24) have addressed many of the longstanding controversies about benefits and potential adverse consequences of detection, diagnosis, and treatment of mild gestational diabetes. The ACHOIS (23) and the MFMU Network study (24) performed OGTTs in the second half of pregnancy in women without known diabetes. Women in both studies were then randomized to routine care (providers blinded to OGTT results and diagnosis of gestational diabetes) or to treatment of gestational diabetes (providers aware of diagnosis, stepped care approaches with diet, glucose monitoring, and medications if needed). The studies used different diagnostic tests (75 g vs. 100 g OGTT, respectively) and diagnostic thresholds for gestational diabetes (WHO and Carpenter-Coustan excluding FPG ≥95 mg/dL [≥5.27 mmol/L], respectively) (9,10,41). Means of FPG were the same in the two cohorts (4.8 mmol/L [86.5 mg/dL]), but postload OGTT values were substantially lower in ACHOIS than in MFMU participants. The ACHOIS found a significant reduction of one important primary outcome, serious perinatal complications (composite of death, shoulder dystocia, bone fracture, or nerve palsy; reduced from 4% to 1%, p=0.01) in the treated arm of the trial. That arm also had an increase in admission to the neonatal nursery (71% compared to 61%, p=0.01). The MFMU Network study failed to see a significant difference in its composite endpoint (stillbirth, neonatal death, birth trauma, neonatal jaundice, hypoglycemia, and hyperinsulinemia) between treatment arms. In both randomized controlled trials, treatment resulted in reductions in birthweight, frequency of LGA births, and preeclampsia and gestational hypertension that were small (<10% in absolute magnitude) but significant. A number of systematic reviews concluded that treatment of gestational diabetes can reduce adverse pregnancy outcomes, including reductions in frequencies of LGA, preeclampsia, and shoulder dystocia (25,76,77).

The cost-effectiveness of the IADPSG recommendations for the diagnosis of gestational diabetes has been addressed. Werner *et al.* (78) used data from published reports for their model and concluded that IADPSG recommendations are cost-effective. The results were sensitive to the likelihood of preventing future diabetes in mothers following the index pregnancy. Marseille *et al.* (79) used data from Israel and India and developed a decision-analysis tool to assess cost-effectiveness of gestational diabetes detection and treatment and prevention of type 2 diabetes. Outcome also was sensitive to reduction of type 2 diabetes in both mother and her offspring. Mission *et al.* (80) used data from the HAPO Study (22) and other published literature to model cost-effectiveness of using IADPSG guidelines to test for gestational diabetes. They found that use of the IADPSG guidelines was cost-effective to improve maternal and neonatal outcomes. They speculated that long-term reduction of type 2 diabetes would increase the effectiveness. Duran *et al.* (81) analyzed cost of care for gestational diabetes at their institution immediately before and over the first year during which IADPSG guidelines were followed. Gestational diabetes prevalence increased more than threefold after introduction of IADPSG guidelines, adverse outcomes were less frequent, and cost reduction was demonstrated.

In total, this multitude of findings reveals that diagnosing and treating gestational diabetes can lower the risk of several important perinatal complications, as well as maternal preeclampsia. The relative risk of an adverse outcome can be reduced substantially (50% or more) by treatment. However, the absolute risk reduction is small (10% or less) because most patients do not incur a perinatal risk that can be reduced by detection and treatment. In the absence of a large and clear benefit, debate about the importance of diagnosing and treating gestational diabetes will continue. For example, individuals with a diagnosis of gestational diabetes by IADPSG thresholds (67) have OGTT glucose values that overlap with those of women who participated in the ACHOIS (23) and MFMU (24) randomized controlled trials (70), where small but significant benefits attended diagnosis and treatment of gestational diabetes. The fact remains that the IADPSG criteria are untested in therapeutic trials. Based on that, the 2013 NIH Consensus Development Conference Statement (72) calls for studies to "Determine whether the additional women categorized as having diabetes by the IADPSG model, who would be considered normal in the two-step strategy, accrue any benefit from treatment. This question would be best answered by a randomized controlled trial that, ideally, would use clinically important health and patient-centered outcomes." Thus, the goal of "outcome based, globally accepted criteria for the diagnosis of gestational diabetes" (75) is yet to be reached.

OTHER ADVANCES IN TREATMENT

The majority of pregnancies in women with gestational diabetes are not associated with an adverse perinatal outcome. In addition, the prevalence of gestational diabetes has increased dramatically (Tables 4.2, 4.4, and 4.5) (59,61,63). These observations provide an opportunity to identify a large fraction of low-risk pregnancies that do not need intensive glucose monitoring or treatments beyond lifestyle change for antepartum management of gestational diabetes. In this regard, measurement of fetal abdominal circumference (AC) by ultrasound has been used successfully (82). Women with gestational diabetes by NDDG criteria (1) and FPG <105 mg/dL (<5.83 mmol/L) had fetal ultrasound at 29–33 weeks gestation. At term, all of the excess of LGA infants was observed in pregnancies in which the fetal AC had been >70th percentile at 29–33 weeks and the condition was managed with nutrition alone. Pregnancies with a lower AC and pregnancies with a similarly high AC in which insulin treatment was given had no excess of LGA infants. In another approach, the concentration of FPG, BMI, and other risk factors for macrosomia (maternal height and parity) identified one-third of women with gestational diabetes by IADPSG criteria as low-risk for fetal macrosomia (83).

The low frequency of severe adverse outcomes (5.6 perinatal deaths per 1,000) in the HAPO Study (22) among women whose caregivers were blinded to glucose values (i.e., those with FPG <105 mg/dL and 2-hour value <200 mg/dL [<11.10 mmol/L] on 75 g OGTT) and the similarly low frequency of serious outcomes in women randomized to normal obstetric care in the ACHOIS (23) and MFMU Network (24) trials of mild gestational diabetes suggest that less intensive obstetric care for gestational diabetes may also be feasible for providing acceptable perinatal outcomes.

LONG-TERM IMPLICATIONS OF GESTATIONAL DIABETES

MOTHERS

Development of Diabetes

Since the early work of Wilkerson, O'Sullivan, and others focused on hyperglycemia in pregnancy as a prediabetic state (4,5,6,11,12), much of the interest in long-term maternal health after a diagnosis of gestational diabetes has been on the risk of later progression to type 2 diabetes. However, because of differences in methods of detecting gestational diabetes, diagnostic criteria employed, heterogeneity of populations, and duration of follow-up after the diagnosis of gestational diabetes, results of follow-up studies have been difficult to compare (35). Systematic reviews by Kim *et al.* in 2002 (35) and Bellamy *et al.* in 2009 (84) showed that with adjustment for these confounding differences, there is a very strong risk for development of type 2 diabetes globally, although ethnic and regional differences in risk remain and are not explained. When comparison was limited to studies that followed the NDDG recommendations for detection and diagnosis of gestational diabetes (1),

5-year rates of progression to diabetes after gestational diabetes were between 25% and 50% in most studies and similar among different ethnic groups (35). The impact of gestational diabetes on risk of subsequent type 2 diabetes is also discussed in Chapter 13 *Risk Factors for Type 2 Diabetes*.

The Troglitazone in Prevention of Diabetes (TRIPOD) (85) and Diabetes Prevention Program (DPP) (86) trials showed that the development of diabetes after gestational diabetes can be prevented or delayed by lifestyle intervention or medications that are used to treat diabetes. Reductions in rates of progression to diabetes were 50%–55% in these studies. The potential public health benefits from focusing diabetes prevention efforts in women with previous gestational diabetes have been stressed (87). There are also limitations. For example, the long-term risk of diabetes after having gestational diabetes and potential prevention/delay of diabetes are well documented; however, only half of the women with previous gestational diabetes have early postpartum assessment of glucose tolerance and/or long-term follow-up (88,89). Recommendations have been made for ongoing assessment of glucose tolerance status after initial postpartum evaluation. However, specific paradigms have not been developed that are based on prospectively designed studies. In a simulation modeling study, Kim *et al.* (90) concluded that an OGTT every 3 years was less costly per case of diabetes detected than use of either FPG or A1c performed at the same frequency, because the OGTT identified more cases of diabetes than either the FPG or A1c.

Cardiovascular Disease in Women With Previous Gestational Diabetes

O'Sullivan followed his cohort of women with previous gestational diabetes for up to 16 years (91). At the final examination, women were on average approximately 45 years of age, and those who had progressed to diabetes (decompensated or "chemical") had developed hypertension (blood pressure ≥160/95 mmHg), an abnormal electrocardiogram, or both at significantly greater frequencies than an age-matched control group without gestational diabetes (91). Other data on long-term development of cardiovascular disease (CVD) in women with previous gestational diabetes are very limited. In a study of parous women having first degree relatives with type 2 diabetes, Carr *et al.* (92) found that those with previous gestational diabetes had more CVD and at an earlier age than those without previous gestational diabetes. Carr *et al.* (92) and others (93) also found that women with previous gestational diabetes had more CVD risk factors and features of the metabolic syndrome than those who did not have gestational diabetes. The rate of preeclampsia has been associated with increasing maternal BMI and levels of glycemia (94) and is more frequent in women with gestational diabetes than in those without gestational diabetes. Preeclampsia and gestational hypertension are associated with higher long-term risk of hypertension, but associations with stroke risk and heart disease are uncertain (95). Given these uncertainties, participants at the Fifth International Workshop-Conference on Gestational Diabetes Mellitus recommended that until more specific information is available about CVD risk after gestational diabetes, the indications for CVD risk factor assessment should be those used for the population at large (39).

OFFSPRING

Since the mid-1970s, studies of animal models, human epidemiology, and clinical reports indicate that intrauterine exposure to maternal diabetes or gestational diabetes can place offspring at increased risk for long-term adverse events, including more obesity, higher blood pressure, altered glucose metabolism, and potentially, diabetes (96). From 1980 onward, a series of epidemiologic and clinical reports were based on long-term studies in Pima Indians and at the Northwestern University Diabetes and Pregnancy Center (96).

Some (97,98,99,100,101), but not all (102,103), studies from other populations, suggest that offspring of mothers with type 1 diabetes, type 2 diabetes, and gestational diabetes are at risk for adverse metabolic consequences. In 2005, Krishnaveni *et al.* (97) reported a follow-up study of South Indian children at age 5 years whose mothers had normal glucose tolerance or gestational diabetes during pregnancy. Female offspring of mothers with gestational diabetes had greater adiposity and more impaired glucose tolerance and insulin levels in the OGTT. In contrast, in offspring of fathers with diabetes, OGTT glucose levels and anthropometry did not differ from controls.

From 2002 to 2005, Clausen *et al.* (104) conducted a follow-up study of 597 young adult offspring (approximately 22 years of age) born to women with gestational diabetes or type 1 diabetes and from control mothers (not exposed to intrauterine hyperglycemia). All study participants underwent a 75 g OGTT. Combined rates of type 2 diabetes, impaired fasting glucose, impaired glucose tolerance in offspring were: gestational diabetes 21%, gestational diabetes risk factors but normal maternal OGTT 12%, type 1 diabetes 11%, and controls without gestational diabetes risk factors 4%. Mothers with type 1 diabetes whose offspring had type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance at age 22 years had more hyperglycemia in the third trimester of pregnancy than those whose offspring had normal glucose tolerance.

In 2008, Pettitt *et al.* (98) reported that among participants in the SEARCH for Diabetes in Youth study, age at diagnosis of type 2 diabetes in those exposed to maternal diabetes *in utero* (mean age [standard error] 11.71 years [0.42 years]) was earlier than among those whose mothers developed diabetes after the child's birth (mean age [standard error] 14.07 years [0.27 years]). However, differences in age of diagnosis between subjects who developed type 1 diabetes who had or had not been exposed to *in utero* diabetes were not significant after adjusting for mother's age of diagnosis.

At eight antenatal centers in Scotland, Lindsay *et al.* (99) did an OGTT and anthropometric measurements at a mean age

of 7.4 years on 100 offspring of mothers with type 1 diabetes and 45 offspring of mothers with no history of obstetric or metabolic disease. OGTT glucose values did not differ between groups. Waist circumference, sum of skinfolds (five sites), BMI and BMI standard deviation scores, and frequencies of overweight (22% vs. 0%, p<0.001) and obesity (12% vs. 6.7%, p<0.001) were all greater in the offspring of mothers with type 1 diabetes.

Hummel *et al.* (102) used height and weight measurements at physician visits at ages 2, 5, and 8 years to estimate prevalence of overweight in a large cohort of children in Germany whose mother or father had type 1 diabetes. The investigators did not find maternal type 1 diabetes to be an independent risk factor for overweight in childhood.

Data from a longitudinal study conducted with Pima Indians in Arizona suggest that risks of obesity and glucose intolerance in offspring up to age 25 years increase continuously as a function of maternal glucose levels from 75 g OGTTs during the third trimester (105). Importantly, breastfeeding has been associated with lower risks of obesity in offspring of diabetic mothers (106,107,108,109) and, in one report, in offspring of mothers with gestational diabetes (110), suggesting at least one approach to mitigating the long-term impact to the offspring.

To date, treatment of maternal hyperglycemia during pregnancy has not been shown to alter the development of adiposity in offspring past the perinatal period (111,112). However, the duration of follow-up has been relatively short: 4–5 years for ACHOIS offspring (111) and a mean (standard deviation) of 7.0 years (1.3 years) and 7.2 years (1.4 years) in the case of the treated and untreated MFMU Network cohorts, respectively (112).

Pettitt *et al.* (113) examined 1,185 offspring of the Belfast Northern Ireland center of the HAPO observational study cohort at age 2 years. They found little association between maternal glucose during pregnancy and obesity in the offspring (BMI Z score) at this young age. As of 2012, a follow-up study of mothers and children at age 8–12 years is underway at 10 of the original 15 centers of the HAPO Study (22). It is anticipated that this HAPO Follow-Up Study (114) will provide important additional information about associations between intrauterine metabolic exposure and long-term adiposity and metabolism of offspring.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
AC . . . . . abdominal circumference
ACHOIS . . . . . Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG. . . . . America College of Obstetricians and Gynecologists
ADA . . . . . American Diabetes Association
BMI . . . . . body mass index
CVD . . . . . cardiovascular disease
FPG . . . . . fasting plasma glucose
GCT . . . . . glucose challenge test
HAPO. . . . . Hyperglycemia and Adverse Pregnancy Outcome Study
IADPSG . . . . . International Association of Diabetes and Pregnancy Study Groups
KPCO. . . . . Kaiser Permanente Colorado
KPSC . . . . . Kaiser Permanente Southern California
LGA . . . . . large for gestational age
MFMU . . . . . Maternal-Fetal Medicine Units
NDDG . . . . . National Diabetes Data Group
NHANES . . . . . National Health and Nutrition Examination Survey
NIH . . . . . National Institutes of Health
OGTT . . . . . oral glucose tolerance test
USPSTF . . . . . U.S. Preventive Services Task Force
WHO . . . . . World Health Organization

CONVERSIONS

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Metzger and Buchanan reported no conflicts of interest.

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