Chapter 35

Gestational Diabetes

Donald R. Coustan, MD

SUMMARY

Gestational diabetes complicates between 1% and 14% of pregnancies in the United States, depending on the screening method employed, the diagnostic criteria used, and the population tested. Most studies report prevalence rates of 2%-5%. Individuals with gestational diabetes may have increased risk for perinatal mortality and morbidity and clearly are at increased risk for the later development of diabetes and perhaps cardiovascular disease. Researchers should conduct appropriately blinded and controlled studies to improve our understanding of the risks associated with undiagnosed gestational diabetes and to determine the most appropriate diagnostic thresholds. It is likely that there is a continuum of metabolically related reproductive morbidity, with most cases of preexisting diabetes near one end and most cases of gestational diabetes near the other. The actual position along the continuum, i.e., the amount of reproductive risk, is probably determined by ambient glucose (or other metabolite) values, rather than by the mechanism (insulin resistance versus insulinopenia) responsible for the carbohydrate intolerance. Thus, it is not helpful to argue whether gestational diabetes does or does not exist. Rather, the degree of disturbance of carbohydrate metabolism that can cause measurable reproductive damage needs to be established.

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INTRODUCTION

Gestational diabetes, defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy"[1], existed as a concept as early as 1946[2] and was invoked to explain high perinatal mortality rates in pregnancies of women who subsequently developed diabetes. Early studies used the same diagnostic criteria for diabetes in pregnancy that were applied in the nonpregnant state. In 1964 O'Sullivan and Mahan[3], recognizing that pregnancy had measurable effects on carbohydrate metabolism, published diagnostic criteria based on the results of 100-g, 3-hour oral glucose tolerance tests (OGTTs) performed at various times during pregnancy on 752 unselected women and validated by their predictive value for subsequent diabetes. This study, a classic among early epidemiologic investigations, determined the testing conditions and criteria used today throughout the United States[4].

Many changes in our understanding and clinical practices regarding gestational diabetes have occurred during the 30 years following O'Sullivan and Mahan's publication. As epidemiologic methodology has become more sophisticated, the early studies have been criticized because of issues of possible confounders, bias in population selection that may limit the generalization of conclusions, and the need for validation based on pregnancy outcome rather than subsequent maternal diabetes[5]. Some epidemiologists have recommended abandoning efforts to detect gestational diabetes until more data become available[5].

Screening for gestational diabetes with a glucose challenge test has been proposed[6]; over the past 20 years its use has become relatively routine[7]. In the interim, it has become apparent that the prevalence of gestational diabetes is not uniform throughout the United States. Various racial and ethnic groups differ in their susceptibility to this condition, just as with insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). Factors such as age, obesity, and family history of diabetes also increase the risk. Such differences may have impeded our understanding of gestational diabetes because they led to major discrepancies among reports, depending on the population studied.

This chapter considers the diagnostic criteria currently in use, various screening paradigms, prevalence, and the implications of gestational diabetes for mother and offspring. It is hoped that in the near future more valid and generalizable data will be available.

DEFINITION AND DIAGNOSTIC CRITERIA

The current definition of gestational diabetes, "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy"[1], was first proposed by the National Diabetes Data Group (NDDG) in 1979[8], although that group used the term "diabetes or impaired glucose tolerance (IGT)" rather than "carbohydrate intolerance of varying severity." The latter term was introduced at the Second International Workshop-Conference on Gestational Diabetes in 1985[9]. The significance of this change is that it acknowledges the uncertainty regarding the most appropriate diagnostic criteria. Currently, the World Health Organization (WHO) does not consider that different diagnostic criteria are appropriate for the pregnant versus the nonpregnant state, preferring instead to use the same definitions of diabetes and IGT for both situations. This approach is consistent with the concept that there should be a single definition for diabetes in all populations, since adjustment of criteria upward or downward to maintain a stable proportion of each population as abnormal does not appear to be biologically appropriate. In general, individuals with diabetes who come from populations with higher prevalence are not less likely to encounter complications than those from low-prevalence populations. However, the use of pregnancy-specific criteria stems from the recognition that pregnancy is a "provocative test" for carbohydrate intolerance, inducing a state of relative insulin resistance. Because the O'Sullivan and Mahan pregnancy criteria have been validated as predictors of subsequent diabetes in a relatively high proportion of women with gestational diabetes, and to a lesser extent have been demonstrated to be associated with increased risk for perinatal morbidity and possibly mortality, they have been assimilated into routine obstetric care in the United States.

The current diagnostic criteria in the United States are based on the values of O'Sullivan and Mahan[2]. They were derived from the results of 100-g, 3-hour OGTTs administered to 752 unselected gravidas, who represented 76% of individuals registering at a prenatal clinic over a 4-month period. The population was evenly divided among white and black women, and 97% of the tests were administered during the second or third trimesters. Data for each of the four venous whole blood glucose values (fasting, 1 hour, 2 hours, and 3 hours) were normally distributed. The predictive value of the derived thresholds (mean plus two standard deviations) for future diabetes was validated by applying them to a second population of 1,013 nonpregnant women who had been tested during a previous pregnancy and followed for up to 8 years. Using the life table method of analysis, O'Sullivan estimated that 29% of those whose values exceeded two standard deviations above the mean would develop diabetes within 7-8 years. It was concluded that the mean plus two standard deviations (rounded to the nearest 5 mg/dl) would be the most appropriate lower limits for diagnosing gestational diabetes (Table 35.1). To avoid reliance on a single laboratory value for diagnosis of gestational diabetes, O'Sullivan and Mahan determined that two of the thresholds should be met or exceeded to make the diagnosis.

Table 35.1
O'Sullivan and Mahan Diagnostic Criteria for Gestational Diabetes Based on Whole Blood Glucose

Time	Raw numbers	Rounded thresholds
Fasting	90 mg/dl	90 mg/dl
1 hour	165 mg/dl	165 mg/dl
2 hours	143 mg/dl	145 mg/dl
3 hours	127 mg/dl	125 mg/dl

If any two threshold values for whole blood glucose after a 100-g oral glucose challenge are met or exceeded, gestational diabetes is diagnosed.

Source: References 3 and 6

Since the original publication of the above thresholds for diagnosing gestational diabetes, a number of changes have occurred in the way glucose is analyzed. The most critical change was the switch from whole blood samples to plasma, or occasionally serum. Plasma or serum glucose levels are, on average, 14% higher than simultaneously measured levels in whole blood[10]. In 1979, the NDDG[8] published conversions of the O'Sullivan and Mahan criteria that were intended to apply to plasma. The resulting values are shown in Table 35.2. Although no explanation was provided, it seems that the NDDG changed the 1-hour whole blood value of O'Sullivan and Mahan from 165 mg/dl to 170 mg/dl. Then, it appears, the NDDG added 14% to each of the whole blood values and rounded off to the nearest 5 mg/dl. These thresholds comprise the most widely used conversion of O'Sullivan and Mahan's criteria and are currently recommended by both the American Diabetes Association (ADA)[1] and the American College of Obstetricians and Gynecologists (ACOG)[11].

Table 35.2
National Diabetes Data Group Conversion of O'Sullivan and Mahan Diagnostic Criteria

Time	Venous blood	Venous plasma
Fasting	90 mg/dl	105 mg/dl
1 hour	170 mg/dl	190 mg/dl
2 hours	145 mg/dl	165 mg/dl
3 hours	125 mg/dl	145 mg/dl

If any two threshold values for glucose after a 100-g oral glucose challenge are met or exceeded, gestational diabetes is diagnosed.

Source: Reference 8

Another change that has occurred since the publication of the O'Sullivan and Mahan criteria has been the switch away from tests, such as the Somogyi-Nelson method, that measure glucose and, to a lesser extent, other reducing substances. Currently available enzymatic methods are more specific for glucose. In whole blood, the Somogyi-Nelson method detects, on average, ~5 mg/dl[12] or more[13] of reducing substances other than glucose compared with enzymatic analyses. For this reason, in 1982 Carpenter and Coustan[14] suggested conversions of the O'Sullivan and Mahan criteria that first subtracted 5 mg/dl from the whole blood glucose values to compensate for the change to specific enzymatic analysis, and then added 14% to convert from whole blood to plasma. The resulting values are shown in Table 35.3.

Because the NDDG[8] and the Carpenter and Coustan[14] conversions of the original O'Sullivan and Mahan criteria[3] are theoretical, the only way to determine which are most appropriate would be to re-create the original methodology (whole blood, Somogyi-Nelson) and run simultaneous samples against the newer plasma, glucose oxidase, or hexokinase methods. When this was carried out[15], it appeared that the NDDG conversions were above the 95% confidence limits for all but the fasting sample, whereas the Carpenter and Coustan conversions were always within the 95% confidence intervals. In one study[16], patients whose glucose tolerance tests were abnormal by the lower, but not the higher, thresholds had a 26% chance to require insulin during pregnancy, versus a 30% chance among those meeting the higher thresholds. These data lead to the conclusion that the conversions recommended by the NDDG significantly overestimate the original O'Sullivan and Mahan values. Nevertheless, the NDDG conversions are most commonly used, and most of the data in this chapter are based on these values.

Table 35.3
Carpenter and Coustan Criteria for Gestational Diabetes

Time	Whole blood, Somogyi-Nelson	Plasma, glucose oxidase
Fasting	90 mg/dl	95 mg/dl
1 hour	165 mg/dl	180 mg/dl
2 hours	143 mg/dl	155 mg/dl
3 hours	127 mg/dl	140 mg/dl

If any two threshold values for glucose after a 100-g oral glucose challenge are met or exceeded, gestational diabetes is diagnosed.

Source: Reference 14

SCREENING FOR GESTATIONAL DIABETES

HISTORIC RISK FACTORS

A number of risk factors have been associated with a greater likelihood of developing gestational diabetes. By and large these are the same factors that predict overt diabetes, and they include advanced maternal age, a family history of diabetes in a first-degree relative, obesity, and glycosuria. In addition, certain outcomes in a previous pregnancy are believed to be predictive, including stillbirth and the birth of a macrosomic baby. The taking of a history can be considered to be a "screening test." Important attributes of any screening test are its sensitivity, i.e., the proportion of individuals with the condition being sought who are correctly identified, and its specificity, the proportion of individuals without the condition who are correctly eliminated from further testing. In studies of screening by means of history taking, sensitivities are reported in the vicinity of 50%[6,17-19], with specificities similarly ~50%. Thus, approximately half of women with gestational diabetes do not have historic risk factors, and approximately half of nondiabetic women do have historic risk factors. In one study in which obesity (prepregnancy weight >150 pounds) and maternal age (≥25 years) were added to the usual risk factors, sensitivity of history-taking was 97%, but specificity was only 24%, meaning that 76% of normal patients had risk factors[20]. Another study, which included maternal age >30 years and obesity >120% of ideal body weight as additional risk factors and a screening test threshold of 140 mg/dl, found a sensitivity of 62% (46/74), but specificity could not be calculated from the data presented[21]. It is thus apparent that using historic risk factors to screen for gestational diabetes is relatively inefficient, since a large proportion of the population has risk factors present and a significant number of those with gestational diabetes do not have such risk factors.

Because the prevalence of gestational diabetes, like that of NIDDM, increases with advancing maternal age, using specific maternal age thresholds at which to pursue universal glucose challenge screening has been advocated by some[11]. Although a number of studies[6,18] found that as many as 80% of women with gestational diabetes are age ≥25 years, the value of an age threshold depends on the characteristics of the population being investigated. For example, in an adolescent pregnancy program all gravidas are age <20 years, while in an infertility program the majority of patients tend to be older. One population-based study[19] of 6,214 pregnancies demonstrated that use of the ACOG[11] recommendations (testing all women age >29 years and younger women if risk factors are present) would detect only 65% of cases of gestational diabetes. Such findings support the ADA's recommendation[1] that all pregnant women should be screened with a glucose challenge test.

GLUCOSE CHALLENGE TEST

In 1973, O'Sullivan et al. suggested the use of a 50-g, 1-hour oral glucose challenge to screen for gestational diabetes[6]. Using venous whole blood samples and the Somogyi-Nelson technology, this group found that a threshold of 130 mg/dl was 79% sensitive and 87% specific for gestational diabetes in a population of 752 gravidas, all of whom also underwent the diagnostic 100-g, 3-hour OGTT. While sensitivity and specificity are the epidemiologic measures usually considered, the clinician is often most interested in positive and negative predictive accuracy. The positive predictive accuracy of a test is the likelihood of the presence of the condition being sought, given a positive screening test. For the O'Sullivan study, the positive predictive accuracy was 14% (15/109). The negative predictive accuracy, or the likelihood of normalcy given a negative screening test, was 99.4% (639/643). This means that 0.6% of individuals with normal screening tests had gestational diabetes. These two attributes of a screening test, unlike sensitivity and specificity, are highly dependent on the prevalence of the condition in the population. If the prevalence of gestational diabetes in O'Sullivan's population had been 10% instead of 2.5%, the negative predictive accuracy would have decreased to 97.5%, meaning that 2.5% of individuals with 1-hour glucose values <130 mg/dl would still have gestational diabetes. The O'Sullivan study is unique because the entire population was tested with both the screening test and the diagnostic test, thus providing complete ascertainment. The 50-g, 1-hour oral glucose challenge proposed by O'Sullivan has been recommended by both the ADA[1] and the ACOG[11], although the latter group recommends this test only for gravidas age ≥30 years and younger women if risk factors are present.

Thresholds

Subsequent research regarding the 50-g, 1-hour glucose challenge test has focused on the most appropriate thresholds and conditions for testing. Because no study, other than that of O'Sullivan et al.[6], has included universal diagnostic testing, sensitivities reported by various studies should be considered as overestimates; there is always the possibility that cases of gestational diabetes existed at lower screening test values in these studies and were undetected. As laboratories changed from whole blood to plasma and adapted enzymatic methods of glucose analysis, it became necessary to extrapolate from O'Sullivan's data[10,12-13] to set screening test thresholds. While the ADA[1] and ACOG[11] recommend a threshold of 140 mg/dl for the 1-hour screen when plasma and enzymatic methods of analysis are used, studies using lower thresholds have demonstrated that 10% of individuals with gestational diabetes manifested screening tests between 130 and 139 mg/dl[19,22].

Conditions of Testing

A number of investigators have explored whether there is any effect on the test if administered to fasting or fed subjects. In one study, normal subjects had a similar screening test result whether they were fasting at the time of glucose challenge or had eaten a mixed-nutrient meal 1 hour earlier[23]. However, women with gestational diabetes showed higher glucose excursions when the test was administered in the fasting rather than in the fed state. Thus it was suggested that administering the screen in the fasting state would allow an increased threshold to be used. Another study also found no difference in the glucose challenge test result for normal subjects, whether administered in the fasting state or at various intervals since the last meal[24]. However, this study purposely excluded women with gestational diabetes, so no conclusion can be drawn regarding its relevance to the screening test, which is, after all, designed to detect gestational diabetes. At present, it seems that the decision on whether to administer the 50-g, 1-hour screening test in the fasting state, or to administer it without regard to the timing of the last meal, rests on the judgment as to whether increased efficiency (i.e., the use of a higher threshold in the fasting state) is more important than the convenience of being able to perform the test at any time of day, without prior scheduling or preparation. This judgment may differ, depending on the circumstances at a particular center.

Composition of Challenge

Researchers have examined the possibility of using a challenge composed of mixed nutrients instead of the traditional pure glucose load. Their rationale was that a mixed meal more closely approximates the way in which people normally ingest nutrients and is more palatable than pure glucose. For example, the use of a plasma glucose determination 1 hour after a standard 600 kcal breakfast was compared with the 50-g challenge in a randomized crossover design in which 50 presumed normal subjects and 20 with known gestational diabetes were tested[25]. At a threshold of 100 mg/dl, sensitivity of the breakfast challenge was 96% and specificity was 74%. Using a threshold of 120 mg/dl at 1 hour after the breakfast would yield a sensitivity of only 75%. This test may be useful, particularly in patients who are unable to tolerate the usual glucose challenge. A 100 mg/dl threshold is recommended.

Timing of the Screening Test

Because of the common recommendation that the glucose challenge be administered at 24-28 weeks gestation, a number of investigators have explored the effect of advancing gestation on screening test function. Hong et al.[26] performed a cross-sectional study of 999 prenatal patients, administering the glucose screening test at the first prenatal visit. There was an increasing likelihood of gestational diabetes as pregnancy progressed, suggesting that the screening test performed early in pregnancy is likely to miss affected individuals (Table 35.4).

Watson et al.[27] performed a longitudinal study of 550 prenatal patients screened at 20, 28, and 34 weeks gestation. There was an average increase in the screening test result of 1.1±1.9 mg/dl per week. Nahum et al.[28] found a significant increase in positive screening test results from the first to the early third trimester in 124 subjects who had serial testing. Gravidas with first trimester screening test results <110 mg/dl were highly unlikely (0/69) to have gestational diabetes when tested in the third trimester. Super et al.[29] found that a threshold of 130 mg/dl in the first trimester provided a sensitivity of 91% for gestational diabetes at any time during pregnancy among a group of 43 high-risk patients, but in this study patients prepared assiduously for the screening test with 3 days of carbohydrate loading and an overnight fast. It is unclear whether similar results could be expected in a population-based study and whether the preparation is an important determinant of the high sensitivity. Benjamin et al.[30] tested 101 high-risk subjects with a 50-g screen in the first trimester and full OGTTs in the second and third trimesters. The first-trimester screening test was 88% sensitive, but the second-trimester OGTTs diagnosed only 25% of the gestational diabetic subjects, the other 75% not becoming positive until the third trimester. Jovanovic and Peterson[31] increased their yield for gestational diabetes by ~50% by retesting, at 33-36 weeks, individuals who were obese, had a positive screen at 27-31 weeks, and were age >33 years. These data suggest that, at least among high-risk individuals, glucose tolerance continues to decrease even in the mid-third trimester. It can be concluded from the foregoing studies that some, but not all, gestational diabetes can be diagnosed as early as the first half of pregnancy. However, early screening, if negative, requires repeat testing in the early third trimester to ensure adequate sensitivity. This retesting will inevitably increase the cost of the screening program. Therefore, evidence of a beneficial effect of early diagnosis of gestational diabetes (i.e., before 24-28 weeks) would be required before universal screening at the first prenatal visit as well as at 24-28 weeks should be recommended. Such evidence is currently lacking. Therefore, it may be most appropriate to reserve early screening for those with a particularly high likelihood of gestational diabetes. Such patients would include, among others, those with gestational diabetes in a previous pregnancy, who appear to have a 50% recurrence risk[32-34].

Table 35.4
Prevalence of Gestational Diabetes According to Gestational Age

Gestation (weeks)	<14	14-23	24-28	>28
Number of subjects	228	354	122	295
GDM prevalence (%)	1.8	2.5	5.7	6.4

National Diabetes Data Group criteria were used to diagnose gestational diabetes.

Source: Reference 26

Reflectance Meters for Screening

Whereas most studies of the screening test for gestational diabetes have used standard laboratory technology, some authors have recommended the use of finger-stick capillary blood samples and reflectance meters, which have the advantages of being inexpensive and convenient to use in the office setting[35-37]. In general, these investigators have studied the accuracy of reflectance meter systems by running parallel samples of capillary blood on meters and venous plasma on standard laboratory instruments. (Accuracy is usually defined as the ability of a test to produce results that are close to the best available measure.) Reflectance meter systems are generally accurate, meaning that their results correlate highly with standard labo-

ratory technology, although it is always necessary to add a "correction factor" to compensate for the fact that these meters tend to systematically over- or underestimate standard laboratory results. The correction factor is specific to each brand and model, and perhaps to each individual meter. However, the studies did not evaluate the precision of the meters[35-37]. Precision refers to the reproducibility, or ability of the test to produce consistent results when performed and interpreted independently under the same conditions. Precision is assessed by repeating the test numerous times on the same samples and it is described by the coefficient of variation, which is the standard deviation of the repeated measures expressed as a percentage of the mean absolute value. The 95% confidence limits are defined as two times the coefficient of variation at a given value. When the precision of various reflectance meters was investigated and compared with standard laboratory technology, the reflectance meters had coefficients of variation between 7% and 10%, whereas the standard laboratory technology ranged from 1%-2%[38]. According to the latter study, if reflectance meters were used for screening and full glucose tolerance testing was desired for 95% of subjects with screening results ≥140 mg/dl (by standard laboratory technology), then 45% of subjects would require glucose tolerance testing, compared with only 16% when standard laboratory methods were used. The ADA does not recommend the use of reflectance meters for screening or diagnostic testing in pregnancy[1].

Variations of the 50-Gram, 1-Hour Screen

Huffman et al.[39] recommended the use of a 2-hour plasma glucose screen after a 50-g load, on the basis of fewer false positive tests. However, in this study patients underwent either the 1-hour or the 2-hour screen, but not both. Gestational diabetes (NDDG criteria) was found in 3.2% of those having the 1-hour screen and 1.9% of those undergoing the 2-hour screen, with the same 130 mg/dl threshold used for both screening tests. Because these figures did not differ statistically, the authors concluded that the yield was similar for the two tests. However, the results could be viewed as showing that 68% more cases were found with the 1-hour screen, and the lack of statistical significance was simply a reflection of inadequate sample size. Sacks et al.[40] have suggested that fasting plasma glucose may be a better screening test than the 1-hour value, because of its higher reproducibility and better performance on a receiver operator characteristic curve. However, these authors only analyzed the data for subjects whose 1-hour screen was ≥135 mg/dl. Thus, the discriminatory value of fasting plasma glucose in the total population could not be evaluated. Further study is clearly necessary before this approach is recommended.

GLYCOSYLATED HEMOGLOBIN AS A SCREENING TEST

One study found the value of glycosylated hemoglobin at 10-15 weeks gestation to be a sensitive and specific predictor of gestational diabetes[41]. However, other investigators have not confirmed that this measure compares favorably with the 50-g, 1-hour oral glucose challenge[42-44]. Measurement of fructosamine or glycosylated serum protein allows estimation of shorter-term glycemia than does glycohemoglobin. Like glycosylated hemoglobin, fructosamine does not appear to have adequate sensitivity or specificity to be a practical screening test for gestational diabetes[45-47].

CURRENT PRACTICE

As noted above, there is not complete agreement among the various professional organizations as to appropriate screening procedures. In 1987, Landon et al.[48] surveyed all board-certified maternal-fetal medicine specialists who were members of the Society of Perinatal Obstetricians, and a random sample of 504 generalist obstetricians, who were members of the ACOG. ACOG members were divided into recent residency graduates (<15 years) and senior practitioners (>15 years). The survey found that 90% of subspecialist respondents, 77% of recent residency graduates, and 76% of more senior practitioners practice universal screening for gestational diabetes. The 50-g 1-hour glucose challenge is used by 95% of specialists and younger generalist obstetricians and 74% of more senior obstetricians. In a 1985 survey of 26 health maintenance organizations serving more than 1.5 million patients, Hughey noted that 65% routinely offered blood glucose screening during pregnancy, most often a 1-hour test[49]. A survey of 228 family practitioners and 188 obstetrician/gynecologists in Indiana found that 72% of family doctors universally screen for gestational diabetes using the 50-g, 1-hour challenge, a significantly lower proportion than the 86% of obstetrician/gynecologists ($p<0.001$)[50].

PREVALENCE OF GESTATIONAL DIABETES

Just as population differences exist with regard to the prevalence of IDDM and NIDDM, various ethnic and racial groups in the United States manifest different proportions affected by gestational diabetes. These

differences confound comparisons between different studies. In turn, estimates of the prevalence of gestational diabetes among different groups are themselves confounded by differences in screening protocols and diagnostic criteria. The only fully accurate method to estimate the prevalence of gestational diabetes within a population is to perform the "gold standard" diagnostic test on all subjects. This approach has not been taken, with the exception of the study of O'Sullivan et al.[6] All other studies selected patients for glucose tolerance testing based on screening criteria, either historic risk factors or a glucose challenge test. Nevertheless, it is useful to view the range of prevalence reported by various investigators (Table 35.5). Each study stated that the prevalence figure was population based, or that descriptor could be inferred from the methods described. As is obvious, there is a wide range of prevalences reported. Some, but clearly not all, of this variability may be ascribed to differences in diagnostic standards or screening methods employed. However, there are unquestionably racial and ethnic differences in the prevalence of gestational diabetes, just as there are for the prevalence of IDDM and NIDDM. Some Native American populations, among whom there is a high rate of NIDDM, are also highly likely to develop gestational diabetes[64], although in one study a rate of 3.2%, similar to that in non-Native American populations, was reported[56]. However, an additional 2% of these Tohono O'odham pregnant women had NIDDM, so that the overall rate of diabetes in pregnancy was 5.2%. Nahum et al.[65] noted the prevalence of gestational diabetes at the Kaiser Foundation Hospital in Los Angeles, CA to be highest among black (7.5%) and Hispanic (6.3%) women, and lower in non-Hispanic whites (4.9%), Asians (4.7%), and Filipinos (3.6%). Dooley et al.[58] similarly have reported relative risks of 2.45 for Hispanic and 1.81 for black women compared with whites. Age and obesity influence the likelihood of gestational diabetes, making comparisons of prevalence among different centers very complex. Some have suggested race-specific screening or diagnostic criteria[65]. However, since the diagnosis of gestational diabetes is presumably sought to decrease perinatal morbidity and mortality, the use of different diagnostic criteria should await data demonstrating differential fetal sensitivity to hyperglycemia in different groups. The criteria for NIDDM are similar around the world, and we generally assume that different groups manifest differing susceptibility to NIDDM. It thus makes little sense to use population-specific criteria for gestational diabetes simply to maintain the prevalence at a similar level across groups.

Table 35.5
Prevalence of Gestational Diabetes in Various Studies

Author	Location	Race of patients	GDM criteria	Number of subjects	Prevalence of GDM (%)
Chen[51]	Brooklyn, NY	?	local	8,288	1.1
Lavin[52]	Akron, OH	?	NDDG[8]	2,077	1.5
Dietrich[53]	Omaha, NE	95% white	NDDG[8]	200	2.0
Coustan[19]	Providence, RI	88% white	NDDG[8]	6,214	2.0
Dacus[21]	Memphis, TN	82% black	NDDG[8]	3,563	2.1
Marquette[54]	Baltimore, MD	84% black	NDDG[8]	1,034	2.3
O'Sullivan[6]	Boston, MA	60% white	O'Sullivan[3]	752	2.5
Merkatz[55]	Cleveland, OH	61% white	local	2,225	3.1
Livingston[56]	Arizona	Tohono O'odham Indian	NDDG[8]	1,853	3.2
Magee[57]	Seattle, WA	mainly white	NDDG[8]	2,019	3.2
			C&C[14]		5.0
Dooley[58]	Chicago, IL	mixed	NDDG[8]	3,744	3.5
			C&C[14]		5.5
Sacks[59]	Los Angeles, CA	?	NDDG[8]	4,116	3.4
Hong[26]	Long Island, NY	61% black	NDDG[8]	999	3.9
			C&C[14]		4.4
Berkowitz[60]	Manhattan, NY	62% Hispanic	C&C[14]	7,762	4.6
Watson[27]	Military	?	NDDG[8]	550	4.9
Murphy[61]	Alaska	Yup'ik Eskimo	NDDG[8]	605	5.8
Amankwah[62]	Springfield, IL	?	local	1,184	6.0
Nahum[28]	Los Angeles, CA	61% white	C&C[14]	1,151	7.1
Mestman[63]	Los Angeles, CA	mainly Hispanic	local	652	8.8
Benjamin[64]	Zuni, NM	Zuni Indian	NDDG[8]	809	14.3

Question mark indicates missing data. GDM, gestational diabetes mellitus; NDDG, National Diabetes Data Group; C&C, Carpenter and Coustan.

Source: References are listed within the table

Another approach to obtaining population data has been the use of birth certificates. Unfortunately, although the 1989 revision of the standard birth certificate includes information about the presence of diabetes in pregnancy, it does not differentiate between gestational diabetes and preexisting diabetes[66]. Since in most populations (other than Native Americans and Hispanics) gestational diabetes is 10 or more times as prevalent as preexisting diabetes, the combined figures from birth certificates should approximate gestational diabetes ascertainment rates. In a study of 3.8 million births in 47 states during 1989[66], the rate of diabetes (established or gestational) was 2.1%. This figure is probably an underestimate, to the extent that universal screening for diabetes was not invariably carried out. Appendix 35.1 shows the percent of U.S. birth certificates in 1991 that listed diabetes in the mother.

IMPLICATIONS FOR PREGNANCY OUTCOME

PERINATAL MORTALITY

Most studies conducted during the past 15 years find no increase in the perinatal mortality rate in pregnancies complicated by gestational diabetes. Indeed, it appears to have been primarily this finding that prompted Hunter and Keirse[5] to recommend abandoning screening programs. All studies showing no increased perinatal mortality, however, included some kind of treatment for gestational diabetes. A broad range of treatments can be considered, from insulin to diet to antepartum testing of fetal well-being to simply diagnosing and identifying the patient as being at some increased risk. This may lead to increased surveillance as subtle as paying more attention to the patient when she notes a change in fetal activity. Another issue that confounds studies with negative results is sample size that is inadequate to identify differences in rare events such as perinatal death. If screening for gestational diabetes were to be abandoned, and if there is truly an increased perinatal mortality risk in cases of undiagnosed gestational diabetes, then potentially preventable perinatal deaths would occur without being noticed. Thus, the most apropos data regarding whether screening is desirable are those collected with the caregivers blinded to the results or in which no specific treatment is offered. Pettitt et al.[67] administered 75-g, 2-hour oral glucose challenges to 811 Pima women in the early third trimester of pregnancy. The results were not used in management. Perinatal mortality was directly proportional to the plasma glucose levels at 2 hours after ingestion of the challenge, rising from 3 per 1,000 at levels <100 mg/dl to 12 per 1,000 at levels of 120-159 mg/dl and 125 per 1,000 when the challenge test result was >200 mg/dl. Although this latter value represented only eight subjects, the association was highly statistically significant. O'Sullivan et al.[68] compared perinatal mortality rates among gravidas whose gestational diabetes was not managed in any special way with that of nondiabetic pregnant women, and found a fourfold increase among the gestational diabetic individuals. Excess perinatal mortality could not be documented in the 53 gestational diabetic individuals age <25 years because there were no perinatal deaths in this small subgroup. Abell and Beischer in Melbourne, Australia[69] also demonstrated an association between relatively mild degrees of hyperglycemia on a glucose tolerance test and increased perinatal mortality. These studies support the likelihood that there is an association between undiagnosed gestational diabetes and perinatal mortality. It is clear that women with preexisting diabetes who become pregnant have a significantly increased risk of perinatal loss, and that such risk is related to the absence of good metabolic control (see Chapter 36). Because gestational diabetes is part of a broad continuum of hyperglycemia, it would seem most productive to focus future investigations on identifying a threshold glucose value for increased perinatal mortality, rather than on endlessly debating the existence of the entity.

PERINATAL MORBIDITY

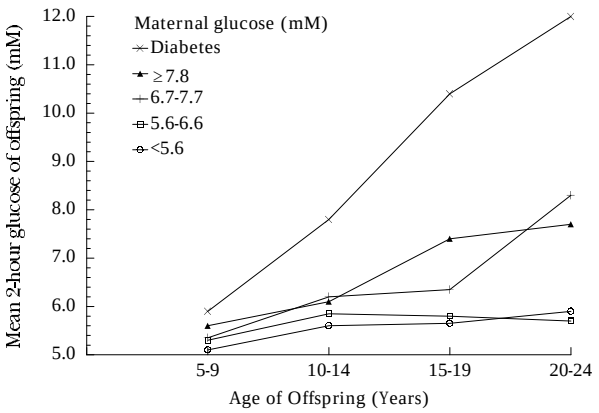
While perinatal mortality is a useful endpoint because death is unequivocal and easy to measure, attention has shifted to perinatal morbidity, which refers to any problem associated with immediate pregnancy outcome. The same problems known to occur in the offspring of women with preexisting diabetes, including neonatal hypoglycemia, plethora, jaundice, and respiratory distress syndrome, may occur in infants of gestational diabetic women. However, the most widely studied "adverse" outcome is macrosomia. Macrosomia is variously defined as birth weight in excess of 8.5 pounds, 9 pounds, 4,000 g, and 4,500 g. Appendix 35.2 shows the proportion of infants weighing >4,000 g at birth in 1991, based on U.S. birth certificate data. "Large for gestational age" is diagnosed when infants are at or above the 90th, 95th, or 97.5th centile for gestational age, and this may be adjusted for variables such as gender and birth order. This lack of uniform standards makes comparing studies difficult. In Pettitt's study of Pima women undergoing a 75-g, 2-hour glucose challenge, there was a direct relationship between the glucose value and the likelihood of macrosomia[67]. In a study of women with normal glucose tolerance tests, Tallarigo

et al.[70] demonstrated a direct relationship between the 2-hour OGTT value and the likelihood of macrosomia. Berkus and Langer[71] found an approximate doubling of the rate of newborns weighing more than the 90th centile among 764 women with one, two, or three abnormal values on their glucose tolerance tests compared with 636 normal control subjects, but the degree of glucose tolerance abnormality was not predictive of macrosomia. The most important variable appeared to be suboptimal diabetic control. Other morbidities, such as neonatal hypoglycemia, have been reported with increased frequency in infants of gestational diabetic mothers[72]. In the population-based study of Magee et al.[57], women with gestational diabetes had a significantly higher likelihood of experiencing any of 33 possible perinatal morbidities, and this was true whether the NDDG criteria[8] or the lower criteria of Carpenter and Coustan[14] were used to make the diagnosis. Many studies relating gestational diabetes to perinatal morbidity have been questioned on the basis of possible confounding variables[5], and the ideal study remains to be performed. It would include a cohort of women with varying degrees of carbohydrate abnormality whose glucose tolerance test results were not known to the caregivers. Data on pregnancy outcome would be collected prospectively for the entire cohort. Until such data become available, it is necessary to use existing, admittedly flawed, data while acknowledging the limitations that exist.

IMPLICATIONS FOR THE OFFSPRING

A good deal of research, over many years, has focused on the fetal and neonatal implications of gestational diabetes and preexisting diabetes. Freinkel[73], in his 1980 Banting lecture to the ADA, suggested that the effects of the metabolic milieu of the diabetic (or gestational diabetic) mother may extend beyond the periods of organogenesis and the immediate neonatal period, and he speculated that "fuel-mediated teratogenesis" may bring about behavioral, metabolic, and anthropometric changes that last a lifetime. Both experimental and clinical evidence are accumulating to support this concept. Van Assche et al.[74] infused streptozotocin into early pregnant Wistar rats, inducing mild hyperglycemia similar to that seen in gestational diabetes. The female offspring developed "gestational diabetes" when pregnant, as did the third generation. Gauguier et al.[75] used glucose infusions in late pregnant rats to produce similar long-term effects on the offspring. In a review of the family history of individuals with gestational diabetes, Martin et al.[76] found that a history of maternal diabetes was three times more likely than paternal diabetes (33% versus 9%), suggesting the possibility of an *in utero* effect of the diabetic mother. This was in contradistinction to pregnant women with preexisting diabetes, in whom no such discrepancy was found (12% diabetic mother versus 7% diabetic father), and to nondiabetic controls. Pettitt et al.[77] have meticulously followed 552 Pima Indian offspring from birth to (in some cases) age 24 years. Subjects were stratified according to their mother's plasma glucose response to a 75-g, 2-hour oral glucose challenge during the third trimester of pregnancy. There was a striking direct relationship between the maternal glucose response and the offspring 2-hour glucose response to a 75-g challenge (Figure 35.1). This relationship held true even when controlled for gender, age, and obesity. During pregnancies occurring in offspring at age 15-24 years, abnormal glucose tolerance was found in 6% of those whose mothers' glucose response was <100 mg/dl, 19% of those with responses of 100-120 mg/dl, 43% of those with 121-139 mg/dl, and 50% of those with ≥140 mg/dl.

Figure 35.1
Mean 2-Hour Glucose in Pima Indian Offspring, by Age and Maternal 2-Hour Glucose During Pregnancy

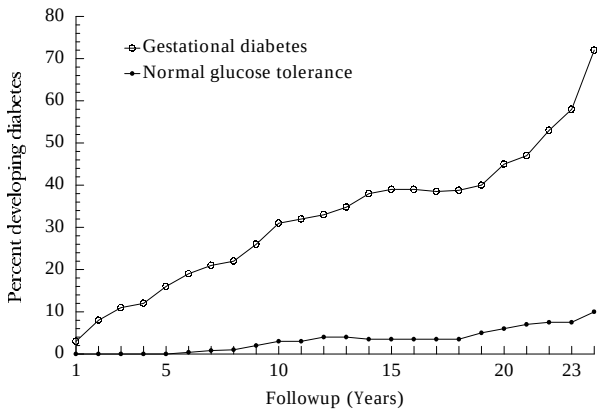


2-hour glucoses are mean values at 2 hours after a 75-g glucose challenge.

Source: Reference 77

In the Pima Indian study[77], there was also a direct relationship between the maternal glucose response during pregnancy and the relative weight of the offspring up to age 14 years, particularly in subjects whose maternal glucose value was ≥140 mg/dl. As offspring grew older, the general tendency toward obesity among Pimas seemed to obscure any effect of maternal glycemia. Silverman et al.[78] followed offspring of mothers with preexisting diabetes and gestational diabetes and found that childhood obesity became particularly common after age 6 years. This group

Figure 35.2
Cumulative Incidence of Diabetes in Women with Normal Glucose Tolerance or Gestational Diabetes During Their Index Pregnancy



United States Public Health Service criteria were used to diagnose diabetes during the followup.

Source: Reference 81

also reported a relationship between second- and third-trimester maternal metabolism and neonatal behavior as well as intellectual performance in childhood[79,80]. Thus, the above evidence lends support to Freinkel's broader vision of global effects of maternal fuel disturbances during pregnancy on long-term outcome.

LONG-TERM IMPLICATIONS FOR THE MOTHER

As mentioned earlier, the O'Sullivan and Mahan criteria were validated for their ability to predict overt diabetes in the nonpregnant state within 7-8 years[3]. In subsequent studies these investigators found that nearly 40% of former gestational diabetic women had developed diabetes by USPHS criteria within 20 years of their pregnancies (Figure 35.2)[81]. Similar findings have been reported from Melbourne, Australia, using a different glucose challenge and different diagnostic criteria for gestational diabetes[82]. In both of these studies there was an increasing prevalence of diabetes with increasing elapsed time since the index pregnancy, indicating that the overt diabetes was probably not present prior to pregnancy in most cases and that the gestational diabetes was at least in part related to the diabetogenic influence of pregnancy. On the other hand, Kjos et al.[83] performed 75-g, 3-hour oral glucose tolerance tests in 246 Hispanic women at 5-8 weeks postpartum after pregnancies complicated by gestational diabetes. Diabetes was found in 9%, with an additional 10% diagnosed as having impaired glucose tolerance. Catalano et al.[84] tested 103 predominantly Caucasian former gestational diabetic patients at ~6 weeks postpartum and found only 3% with diabetes and 4% with impaired glucose tolerance. The differences between the two studies are probably due to population differences in the prevalence of diabetes but may also relate to the lower criteria for gestational diabetes used in the latter study. Another possible confounder is the proximity to pregnancy of postpartum glucose tolerance testing. Lam et al.[85] followed 120 Chinese patients who had met WHO criteria for diabetes or impaired glucose tolerance during pregnancy and who continued to have abnormal tests at 6 weeks postpartum. By 12 months postpartum, only 13% of these subjects still had diabetes or impaired glucose tolerance.

Damm et al.[86] retested 241 women with former gestational diabetes at 2-11 years postpartum, looking for predictive factors for future diabetes. Overt diabetes had developed in 17% and impaired glucose tolerance in another 17%. While there was no relationship between the development of diabetes and the time since index pregnancy, the strongest predictive factors were high fasting glucose during the pregnancy glucose tolerance test, preterm delivery, and an abnormal glucose tolerance test at 2 months postpartum. Coustan et al.[87] carried out a similar study on 350 former gestational diabetic subjects at 0-10 years after pregnancy. Diabetes or impaired glucose tolerance had developed in 6% of those tested at 0-2 years, 13% at 3-4 years, 15% at 5-6 years, and 30% at 7-10 years. Predictive variables included fasting glucose during the pregnancy OGTT, obesity, and time elapsed since the index pregnancy. Logistic regression allowed the construction of an equation to describe the likelihood

Table 35.6
Estimated Percent of Women with Gestational Diabetes Developing NIDDM or IGT After Pregnancy

	% at 2 years after pregnancy			% at 4 years after pregnancy		
Fasting plasma glucose (mg/dl) during pregnancy	BMI before index pregnancy			BMI before index pregnancy		
	15	25	35	15	25	35
100	1.2	2.5	5.5	2.3	8.1	10.6
120	2.5	5.5	11.4	5.1	10.6	20.9
140	5.5	11.4	22.3	10.6	20.9	37.0

Risk of subsequent NIDDM or IGT (impaired glucose tolerance) is calculated from a regression equation based on data from 350 former gestational diabetic women retested at 0-10 years after their index pregnancy with a 75-g 2-hour OGTT, using NDDG criteria.

Source: Reference 87

of subsequent diabetes based on these three variables (Table 35.6). Such studies allow the identification of a high-risk population for future diabetes, possibly enhancing our ability to test various interventions to prevent this problem. This is not a trivial issue, as undiagnosed diabetes is a highly prevalent situation that is associated with significant morbidity[88]. Considerable cost savings could accrue if interventions succeed[89]. Indeed, O'Sullivan found that former gestational diabetic women were at greater risk for hypertension, hyperlipidemia, ECG abnormalities, and mortality[81].

It should be noted that pregnancy appears to function as a provocative test and not as an independent risk factor for future diabetes[90-91]. Thus, there is little reason to believe that the avoidance of pregnancy would decrease the likelihood of developing diabetes.

Dr. Donald R. Coustan is Professor and Chairman, Department of Obstetrics and Gynecology, Brown University School of Medicine, and Obstetrician and Gynecologist in Chief, Women and Infants' Hospital of Rhode Island, Providence, RI.

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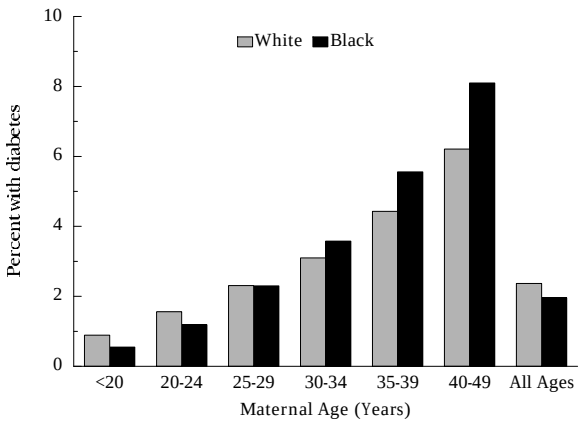
Appendix 35.1

Percent of Birth Certificates Listing Diabetes in the Mother, U.S., 1991

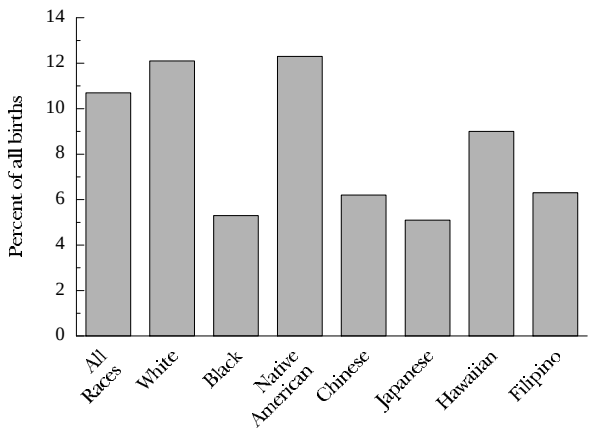


Rates were determined from birth certificates that contained a checkbox for the presence of maternal diabetes (most states and the District of Columbia). The checkboxes do not distinguish among IDDM, NIDDM, and gestational diabetes in the mother. Other limitations of birth certificate data that may have led to an underestimation of diabetes rates are discussed in the text.

Source: Reference 92

Appendix 35.2

Percent of All U.S. Births with Birthweight ≥4,000 Grams, by Race of Mother, 1992



Data from all birth certificates filed in the United States in 1992.

Source: Reference 93