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MEDICAL COMPLICATIONS OF PREGNANCY

DIABETES COMPLICATING PREGNANCY

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Obstetricians use a unique form of classification of diabetes in pregnancy originally proposed by Dr. Priscilla White.[94] The system was designed to estimate the prognosis for pregnancy outcome for women with diabetes who become pregnant. White first described her classification system in a report entitled, "Pregnancy Complicating Diabetes." The prognostic system was based on the observation that women in whom diabetes was diagnosed at an earlier age, was of longer duration, or produced vascular complications had a poorer pregnancy prognosis. From an obstetric point of view, diabetes is thought to complicate pregnancy. A large amount of resources is committed to finding, monitoring, and treating diabetes first diagnosed during and presumably induced by pregnancy. White never included an induced form of diabetes in her original classification system; class A diabetes was, in her scheme, subclinical or chemical diabetes that nonetheless preceded pregnancy.

Few pregnant women have had a pregestational diagnosis of diabetes. Validated observations about high rates of fetal morbidity and mortality in women with diabetes induced speculation that unexplained morbidity and mortality might be attributed to undiagnosed diabetes.[31] Nonetheless, this latter complication of pregnancy has failed to account for a measurable number of pregnancy losses, and, ironically, the undiagnosed but likely overt diabetic has received little attention until recently in comparison with concern about glucose intolerance and its benign consequences in a much larger number of women.

Another irony in diabetes and pregnancy is the persistent use of glucose tolerance testing in pregnancy. O'Sullivan and Mahan[78] evaluated glucose tolerance tests in pregnant women to establish thresholds that were analogous to those used in nonpregnant individuals. Internal medicine specialists subsequently abandoned glucose tolerance testing as inaccurate. Recently, the American Diabetes Association[63] has endorsed not only the unique classification system for diabetes in pregnancy that has been used for decades by obstetricians but also the continued use of oral glucose tolerance tests to screen and diagnose diabetes in pregnancy. Despite arguing that universal screening of pregnant women is not supportable because a diagnosis that cannot be predicted on the basis of risk factors is questionable, the association endorsed lower diagnostic thresholds that will increase the prevalence of the diagnosis with little evidence that this change will improve the care and outcome of pregnancies.

Significant changes have occurred over the last 10 years in the diagnosis and treatment of diabetes that impact on pregnancy occurrence in women with diabetes and that affect pregnant women newly diagnosed with diabetes. The Diabetes Care and Complications Trial[27] has demonstrated that more strict glycemic normalization reduces the frequency and severity of complications of diabetes and may improve pregnancy outcomes if women are in better glycemic control when they conceive. If the recently reported success of pancreatic islet cell transplants results in widespread availability of this therapeutic modality, the problem of poor periconceptual control may be replaced by a need to consider the impact of new immunosuppressive therapies on the pregnancy.[50] Recommendations have changed regarding the diagnosis of diabetes in nonpregnant individuals. The long-standing diagnostic threshold of a fasting glycemic level of 140 mg/dL has been lowered to 126 mg/dL. As a result, the incidence of diabetes will rise, and there is concern that the incidence of diabetes is increasing independently of diagnostic criteria changes owing to an increase in risk factors in the population.[39] The primary risk factor of concern is the current "epidemic of obesity." It is hoped that earlier diagnosis and treatment of diabetes will reduce the incidence and severity of complications of hyperglycemia. Insofar as gestational diabetes is a risk factor for the subsequent development of diabetes in the nonpregnant individual, the importance of the diagnosis in pregnancy would seem to be increased.

DIABETES DIAGNOSED BEFORE PREGNANCY: PREGESTATIONAL DIABETES

White was a diabetologist interested in the outcome of pregnancy in relation to the duration of disease, the age at diagnosis, and the presence of end-organ effects of diabetes. These variables in her analysis were prognostically significant and were incorporated, initially in a more complex form, into the classification system still in widespread use today (Table 1) . Limitations of the system include the fact that the categories are not mutually exclusive (a woman might be classified differently according to different single variables); therefore, descriptive relationships between classification categories and outcomes lack reference to a specific independent variable. Similarly, the lack of correspondence to the classification system used outside of pregnancy by most US internists (e.g., insulin-dependent diabetes mellitus or non–insulin-dependent diabetes mellitus) or to the World Health Organization classification system widely used internationally makes pooling of data difficult. Indeed, because many reports in the US literature have used phraseology such as "insulin dependent" or "insulin requiring" when referring to insulin-treated women, type 1 versus type 2 effects cannot be discerned.

TABLE 1 -- CLASSIFICATION OF DIABETES IN PREGNANCY

Class	Age of onset (year)		Duration of Pregestational Diabetes (year)	Vascular Disease	Therapy
A	Any		Any	None	A-1, diet only
B	>20		<10	None	A-2, insulin
C	10–19	or	10–19	None	Insulin
D	10	or	20	Benign retinopathy	Insulin
F	Any		Any	Nephropathy	Insulin
R	Any		Any	Proliferative retinopathy	Insulin
H	Any		Any	Heart disease	Insulin

Gestational Diabetes Class	Fasting Glucose Level		Postprandial Glucose Level
A-1	<105 mg/dL	and	<120 mg/dL
A-2	≥105 mg/dL	and/or	≥120 mg/dL

The modified White classification also uses nonindependent criteria for assignment, but, in general, these criteria relate to the severity of the disease in terms of duration since diagnosis or the presence of end-organ effects. The likelihood of type 1 disease increases with an earlier age of onset of diagnosis (a synonym for type 1 disease is juvenile onset); therefore, women with class C disease are more likely type 1 if they are of average child-bearing age at the index pregnancy. Women with class D disease (if so classified on the basis of the age of onset or the duration of disease rather than the presence of benign retinopathy) are most likely type 1. Women with type 1 (insulin-dependent or ketosis-prone) diabetes generally have more difficult diabetes to control and more extremes of metabolic abnormalities when compared with women with type 2 diabetes. Women with class C, D, F, H, or R diabetes have an increased risk of poor pregnancy outcome. This risk may relate to type 1 metabolic effects.

Morbidity Associated with Pregestational Diabetes

Morbidity in diabetic women during pregnancy depends for the most part on the condition of the woman and on the degree of glycemic control at the time of conception. A woman on hypoglycemic therapy is as likely as any woman in pregnancy to experience anorexia or hyperemesis, and hypoglycemia can be severe and associated with maternal seizures and brain damage. In early investigations into the relationship between glycemia and fetal malformation, maternal hypoglycemia in the first trimester was related to a better outcome and a lower rate of fetal malformation.[90] In contrast, diabetic ketoacidosis is associated with a probability of fetal loss, and the maternal mortality rate is estimated to be 1%. At greatest risk is the rare undiagnosed woman with first manifestation of diabetes as diabetic ketoacidosis in pregnancy.

Common complications of pregnancy occur more frequently in women with diabetes, including pyelonephritis and vaginitis, and, generally, infection increases the risk of ketoacidosis in insulin-dependent women. An increased risk of pregnancy-induced hypertension pertains to all women with diabetes, and the risk is directly related to the severity of the diabetes. An indicated delivery due to hypertension is one of the contributors to preterm delivery in women with diabetes. Women with proteinuria are likely to experience worsening during pregnancy, but this change is not likely to be sustained after delivery. In general, renal insufficiency is not worsened, and renal insufficiency does not adversely affect the outcome of pregnancy unless it is severe. Retinopathy is not adversely affected by pregnancy, per se, but enthusiasm for rapid normalization of poorly controlled hyperglycemia can ironically result in increased vascular proliferative retinopathy.[19] The same phenomenon occurs in nonpregnant diabetic women with overly aggressive hypoglycemic therapy. Women with microvascular heart disease should be discouraged from conceiving and from continuing pregnancy. The increased cardiovascular demands in pregnancy predictably increase decompensation in a system with limited reserve. The increase in the cesarean delivery related to increased macrosomia and an increased rate and failure of labor induction results in an increase in operative complications. These risks are not often considered preconceptually. Counseling limited to whether pregnancy is feasible may not address appropriate concerns about the long-term prognosis for women already experiencing advanced complications of disease.

The infants of mothers with diabetes mellitus have a rate of malformation that is increased two to three times over the rate for the general population or the background rate.[90] Women with class C, D, F, H, or R diabetes have an increased risk when compared with women in classes A or B,[87] and the degree of hyperglycemia as reflected in early glycosolated hemoglobin is directly related to the risk of malformation of the fetus.[66] [58] [97] This relationship has been validated as causal based on the prevention of malformation by strict glycemic control before or at the time of conception.[32] [66] Initiation of hypoglycemic therapy or normalization of glycemia after the period of organogenesis does not have this protective or preventive effect.[67]

An increased rate of stillbirth is attributed to pregestational diabetes. This observational relationship was established

by a retrospective study of death certificates in which an increase in the prevalence of the diagnosis of diabetes in mothers of stillborns was reported; however, death certificate data have significant potential for bias because the ascertainment of fetal “exposure” to maternal diabetes may be increased in an attempt to identify a cause of the stillbirth. The reason for this increase is uncertain. Although some researchers suspect that macrosomia may be a risk factor for demise, the increased rate of macrosomia in the infants of diabetic mothers is observational rather than causal, or an increased rate of stillbirth in the infants of class A1 diabetics, who experience a similarly increased rate of macrosomia, would also be observed.[33] [59] Hypoglycemia in the early morning hours in insulin-treated women may make the high rate of oxidative metabolism necessary in the otherwise hyperglycemic fetus susceptible to stress, such as that which occurs in early labor with contraction-induced decreases in uterine flow. The possibility that the original observation may not be relevant, at least to contemporary risks, is suggested by the fact that, in most series, corrected perinatal mortality is as good or better than the general population rate.[2] Treatment and management factors may be related to this relationship.

An increase in the incidence of macrosomic neonates (i.e., large for gestational age or heavy for gestational age infants) is observed in women with pregestational diabetes. The Pedersen hypothesis[79] suggests that maternal hyperglycemia results in fetal hyperglycemia and fetal hyperinsulinemia and, as a consequence, fetal macrosomia. Although that hypothesis has been repeatedly validated observationally and experimentally, macrosomia is not a unique consequence of hyperglycemia. The potent risk factor of maternal obesity is prevalent and effective in women with diabetes. Ironically, overinsulinization with uncontrolled caloric intake contributes to this confounded relationship. Although the amount of macrosomia attributable to glycemia in the presence of other risk factors is unknown, hyperglycemia clearly does not account for most of the excess occurrence observed.[15] [95] Even though birth weight reduction is possible with aggressive hypoglycemic treatment,[25] [52] it may not be a salutary goal.

Treatment and Management of Women with Pregestational Diabetes

The observation that the stillbirth rate was increased in women with diabetes led to an early delivery management strategy and the expressed hope that increased screening efforts to diagnose diabetes in pregnancy would result in a decrease in previously unexplained stillbirths. Ironically, the aforementioned potential error in regards to the bias in death certificate data may have been compounded in the observation that a lower than expected prevalence of maternal diabetes was described in another series of stillborns. It was presumed that identification of maternal diabetes would result in better outcome.[31] That expectation had a basis in fact; the corrected perinatal mortality has, in the last 3 decades, generally been better than the rate observed in the general population; however, the specific aspect of contemporary management that has produced this result is uncertain. After more than a decade of intensive efforts to find undiagnosed diabetes in pregnancy, it can be concluded that this etiology does not account for a measurable fraction of unexplained stillbirths.

The initial response to the observed increased risk of fetal death at term was to effect early delivery. That strategy resulted in no improvement in perinatal outcome initially, and mortality due to iatrogenic prematurity was increased. The importance of documenting fetal lung maturity was one of the lessons of this strategy, and the observation that fetal lung maturity was delayed in pregnancies complicated by maternal diabetes was readily accepted as a partial explanation for the poor results of early delivery. Complex endocrinologic explanations were proposed to account for the delayed fetal lung maturity despite the fact that gestational age criteria were not well described in the initial reports. An adjustment was not made for the effect of a high prevalence of large for gestational age birth weights. Targeting delivery at 38 weeks' gestational age results in the delivery of infants who manifest normal maturity for gestational age. If dating criteria are insecure, an lecithin/sphingomyelin (L/S) ratio of 2.0 has the same predictive value for the infants of diabetic mothers as it does for infants of uncomplicated pregnancies.

Just as the effectiveness of delivery at 38 weeks presumes a risk of intrauterine death for these fetuses through term, the efficacy of other strategies to prevent stillbirth in normally developed infants is equally difficult to quantify. Pedersen's[79] observation decades ago that maternal noncompliance was a risk factor for perinatal mortality is likely still germane. Fetal testing programs in the third trimester may only reflect the nonspecific effect of compliance. Fetal loss after normal tests and in pregnancies complicated by maternal diabetes is well documented. Similarly, reports of successful monitoring until 40 weeks without fetal loss are difficult to interpret because the numbers are small enough in these reports to lack power to detect a potentially significant increase in the relative risk of fetal death. An alternative explanation is that the historic attribution of risk compared with the risk in uncomplicated

pregnancies has been overestimated. It is doubtful that a trial will be designed to test the latter possibility.

Various fetal evaluation and testing schemes have been proposed and are widely practiced. Women with pregestational diabetes are repeatedly assessed by sonograms (biometrics for size), biophysical profiles, and electronic fetal heart rate tracings in various combinations and frequencies. These techniques have known limitations. The unpredictable events of cord accident and abruption contribute to an irreducible minimum of 1 to 2 fetal losses per 1000 live births.[24] Although a reported "excess" of three fetal deaths in a group of almost 500 women with diabetes that occurred within 2 days of a normal fetal heart rate tracing is difficult to interpret statistically, it is circuitous to suppose that the finding indicates a need for such testing.[86] Intermittent fetal heart rate monitoring for short periods of time simply has significant predictive limitations.

The success of such schemes is as difficult to quantitate as their failure. At each antepartum visit, the number of assessed but unrecorded or unmeasured variables exceeds the number that are recorded. If a woman has a minimally reactive fetal heart rate tracing and complains of pelvic pressure and decreased fetal movement and her glycemic record indicates a change in levels (up or down) with the same amount of administered insulin, which of the variables was responsible for any subsequent intervention? As subsequently validated for intrapartum fetal heart rate monitoring in the mid 1970s, some other variable may be responsible for the association with better outcome. All methods of assessment of maternal-fetal normalcy are effective on the basis of chance alone. An accurate assessment of the effectiveness of any particular method or single variable to predict rare outcomes is almost impossible. Antepartum assessments are analogous to compliance as an effector of outcome; the specific assessments may be less important than the fact that an assessment was performed.

The relationship between glycemic level and perinatal outcome is undefined, except at extremes. Women with high glycemic levels, especially if associated with ketonemia, experience a high rate of fetal death. With ketoacidosis, the fetal death rate is as high as 50%, and maternal mortality has been estimated to remain at around 1%.[2] Reports of associations between lesser degrees of hyperglycemia and fetal death have often failed to control for malformations, and, if a threshold exists for the association, it is well above the levels targeted for control at the vast majority of centers.

Hypoglycemia can also be associated with fetal loss. Decreasing insulin requirements in the third trimester, although most often the result of decreased caloric intake, can reflect decreased placental production of human placental lactogen (HPL). Before it was acknowledged that 24-hour urine collections were too cumbersome and gave results too late to be of clinical utility, associations between diminished placental function and fetal loss were described. First-trimester hypoglycemia was a good prognostic indicator in Pedersen's observations, and, generally, hypoglycemia has not received much attention as a risk factor. It has been suggested that the timing of some third-trimester losses in the early morning hours might coincide with maternal hypoglycemia.[82] Hypoglycemia in a usually hyperglycemic fetus may confer the greatest risk of demise.

The high rate of macrosomic infants born to women with diabetes has been resistant to hypoglycemic therapy. Although this resistance is attributable, at least in part, to effects other than glycemia (e.g., maternal obesity),[95] the Pedersen hypothesis has been validated repeatedly both clinically and biochemically, and overgrowth of the fetus is a predictable consequence of hyperglycemia. The occurrence of macrosomia even after good third-trimester control prompted many observers to conclude that preprandial monitoring and targeting of glycemic control were perhaps inappropriate and inadequate to prevent hyperglycemic effects on fetal growth. This background is the only way to understand what otherwise would be an unintelligible widespread and immediate acceptance of results from a relatively small study reporting reduced birth weight in insulin-treated women in whom postprandial thresholds were targeted versus preprandial targets.[23] The most relevant information regarding treatment targeting either preprandial or postprandial glycemic levels in regards to the prevention of fetal macrosomia comes from studies in gestational diabetics. The threshold for effective treatment to reduce macrosomia in the fetuses of pregestational diabetic women was described by one group as the "maximum tolerated dose" (to hypoglycemia).[37] Judging the success of therapy based on birth weight distribution may not be valid, as discussed later in the section on gestational diabetes.

The preventability of macrosomia is compounded by increasing obesity in diabetic women.[13] Maternal obesity and excessive weight gain in pregnancy increase the rate of neonatal macrosomia.[57] Large for gestational age rates for pregestational diabetic women range from 20% to 40%. Many insulin-treated women gain an excessive amount of body weight during pregnancy, evidence of overinsulinization.[13] Increasing the amount of administered insulin is not enough to optimize the maternal condition. Caloric restriction for women with class A1 gestational diabetes has been demonstrated to be effective in reducing the expected rate of macrosomia[47] but is acknowledged to be a difficult therapeutic action to apply reliably. Insufficient control of caloric intake can thwart the therapeutic benefits of insulin. Maternal obesity is associated with a macrosomic outcome in pregnancy and is a more prevalent risk factor than diabetes for fetal overweight.[88] Obesity has also been demonstrated to have an independent contribution to macrosomic neonatal outcome within women with diabetes. One half of macrosomia occurrence in gestational diabetics has been estimated to be attributable to hyperglycemia, with an equal proportion attributable to maternal obesity.[15] It is likely that the same proportions apply to insulin-treated diabetic women.[95]

Insulin-treated diabetic women have a persistently high rate of macrosomia, but the consequences of this rate on birth trauma are muted by a high rate of cesarean delivery. Fifty percent to 75% of the infants of insulin-treated diabetic mothers are delivered abdominally, but the numbers of these infants are too few to increase significantly the cesarean rate. Numerous factors contribute to the cesarean rate, and many series have documented the poor clinical ability to select the macrosomic fetus for abdominal delivery discriminatingly.[3] [4] Sonography has been inaccurate in the estimation of fetal weight and in identifying a fetus in excess of a safe threshold.[89] Prophylactic cesarean delivery has been recommended if the estimated fetal weight of an infant of a diabetic mother exceeds 4500 g or if the infant of a nondiabetic mother exceeds 5000 g.[3] This difference in thresholds reflects an increased proportion of large for gestational age neonates in diabetic pregnancies at any level of birth weight, and the predictive and preventive value of the antepartum estimate of fetal weight and weight percentile increases marginally because of this increased prevalence.

DIABETES DIAGNOSED DURING PREGNANCY: GESTATIONAL DIABETES

The current recommendations of the American Diabetes Association[63] and the American College of Obstetricians and Gynecologists (ACOG)[2] are reviewed in the next section to examine the explicit and implicit clinical expectations of applied guidelines. An attempt will be made to resolve some of the contradictions in favor of articulating clinical goals and appraising the expectations from following the recommendations.

Current Recommendations

The most recent recommendations for the evaluation and classification of women with diabetes in pregnancy were developed at the fourth International Conference on Gestational Diabetes in 1998 and subsequently endorsed in the Recommendations for the Diagnosis and Treatment of Diabetes published by the American Diabetes Association in 1999 and 2000 (Table 2) . The most recent ACOG technical bulletin on the subject was published in 1994 and listed similar criteria as optional. These recommendations represent modifications of glucose tolerance testing as applied to pregnant women originally studied and described by O'Sullivan and Mahan.[78]

TABLE 2 - - DETECTION OF GESTATIONAL DIABETES

Screening Test	**Plasma Glucose Level (mg/dL)** *
50-g, 1-hour screen	130–140
	O'Sullivan Criteria (mg/dL) (30) †
Diagnostic 100-g Oral Glucose	

Tolerance Test‡	NDDG Conversion (44)†	Carpenter Conversion (33)†
Fasting	105	95
1 hour	190	180
2 hours	165	140
3 hours	145	155

NDDG = National Diabetes Data Group.

*Result is upper limit of normal.

‡ Diagnosis of gestational diabetes is made when any two values are met or exceeded.

†Data are reported in the references shown in parentheses.

O'Sullivan developed diagnostic criteria for screening and diagnosis of diabetes in pregnancy using glucose tolerance testing. The glycemic response to an oral glucose ingestion was recognized to be higher in pregnancy and fasting glycemia lower in comparison with the nonpregnant state. O'Sullivan developed population-based criteria by studying the test results in nondiabetic women during pregnancy and using statistical criteria for the diagnosis of abnormality. The combination of two of the four 3-hour oral glucose tolerance test results in excess of two standard deviations above the mean in a population of asymptomatic pregnant women was derived in part by reasoning that no more than 2% of such women should be diagnosed with diabetes in pregnancy. The criteria were initially validated by correlation with the diagnosis of diabetes subsequent to the index pregnancy. An increase in fetal death was the first reported perinatal association with the diagnosis of diabetes in pregnancy using these criteria. By the late 1970s and with the knowledge that diabetes complicating pregnancy was associated with an increase in the stillbirth rate, hope was expressed that a large proportion of previously unexplained stillbirths would be attributable to gestational diabetes.[31]

Diabetologists and practitioners of internal medicine were concluding that glucose tolerance testing was unreliable and too inaccurate for testing nonpregnant persons for diabetes. Screening and diagnosis by means of random, fasting, and, occasionally, postprandial glycemic measures were widely practiced and recommended by the 1980s. Despite O'Sullivan's reanalysis attributing increased fetal loss in his series to elevated fasting blood sugar,[78] glucose tolerance testing became widely practiced and accepted in the United States. Corroborating evidence from other investigators affirmed that no increase in fetal loss should be expected in the absence of fasting hyperglycemia.[33] [59]

The National Diabetes Data Group (NDDG) published a translation of O'Sullivan's whole-blood values into venous serum thresholds in 1979,[74] and screening using a 50_g oral glucose load followed by a glycemic measure 1 hour later was adopted widely. A screening result equal to, or in excess of, 140 mg/dL was abnormal and was followed by a 3-hour diagnostic 100-g oral glucose tolerance test. Gestational diabetes was diagnosed if the fasting value was in excess of 105 mg/dL, or if any two of the hourly post-glucola values exceeded thresholds of 190, 165, or 145 mg/dL, respectively. Insulin treatment was recommended for fasting hyperglycemia, and, because of the associated risk of fetal death, early delivery and management otherwise similar to the treatment of pregestational diabetes were widely recommended and practiced.

The first International Conference on Gestational Diabetes was held in 1979 and defined gestational diabetes as diabetes mellitus first diagnosed during pregnancy. This definition has been reaffirmed at three subsequent meetings.[63] The heterogeneity of the degree of glycemic metabolic abnormality included in this one diagnostic category was reduced by the addition of a subcategory of gestational diabetes that defined class A1 as post-glucola hyperglycemia alone and class A2 as fasting hyperglycemia in the 1986 ACOG technical bulletin on diabetes in pregnancy.[5] This distinction seemed directly related to the prognostic significance of fasting hyperglycemia and an important discriminator of risk. Implicit in the subcategorization was the recognition that gestational diabetes as a

diagnostic entity was too broad if a woman with diabetic ketoacidosis at 8 weeks' gestation was not differentiated from a woman with mild glucose intolerance at term. Unfortunately, this improvement in categorization was offset by the inclusion of persistent postprandial hyperglycemia in the same A2 category. Women with a 2-hour postprandial glucose level in excess of 120 mg/dL were also considered eligible for treatment with insulin. The inclusion of the postprandial criteria was based on the observation that nondiabetic women rarely had such a postprandial level. Insisting that women already diagnosed with glucose intolerance not manifest the same was redundant. Including women with persistent glucose intolerance in the group with fasting hyperglycemia introduced a new element of heterogeneity to the diagnosis of gestational diabetes and confounded the relationship between diagnosis, treatment, and prognosis. Subsequent reports on gestational diabetes and outcome often described the proportion of women treated with insulin as it related to outcome but rarely analyzed the impact of the different criteria for insulin treatment eligibility. Even when the criterion of fasting abnormality only was used to define class A2 gestational diabetes, the prognosis differed depending on whether the time of diagnosis was early or late in gestation.[85]

Another signal inclusion in the 1986 ACOG technical bulletin was the description of universal screening of pregnant women for gestational diabetes regardless of risk factors. By 1991, a current opinion article[22] recommended universal screening. The rationalization for this recommendation was that selective screening might miss a considerable portion of women who would be diagnosed if subjected to the screening process, and that identification of women with gestational diabetes was important to prevent associated morbidities. Unfortunately, the recommendation was made without reference to morbidities either associated with the diagnosis or preventable with intervention. As a result, confusion persisted regarding the relationship between the diagnosis and associated morbidities, leading to continued references to the famous criticism that gestational diabetes was still a diagnosis looking for a disease.[59] Descriptive reports detailed the limited sensitivity of the 140 mg/dL cut-off value for screening abnormality, which was estimated to miss as many as 20% of women. Although some reports suggested that selective screening missed only 0.1% of low-risk women with the diagnosis, some estimates were as high as 50% (based on symptoms alone) without universal screening. Despite these problems with testing for gestational diabetes, considerable experience was accumulated using the NDDG testing criteria. Fifteen percent of all women in a given population could be expected to have an abnormal 1-hour screening test, and 15% of those undergoing a 3-hour diagnostic test likewise could be anticipated to have an abnormal result. The expectation was that 2% to 3% of pregnant women would be diagnosed with gestational diabetes, a finding that seemed an indirect validation of the NDDG criteria as a valid modification of the O'Sullivan thresholds.

Problems with the two-step testing scheme using the NDDG criteria included the uncertain relationship to the subsequent development of diabetes in women who tested positive. It was estimated that 20% to 30% of women with gestational diabetes might subsequently be diagnosed with diabetes within 20 years of their index pregnancy. The recurrence of gestational diabetes seemed to occur in, at best, 50% of women in subsequent pregnancies.[74] The persistence of diabetes following the diagnosis of gestational diabetes was not expected, except in the rare case of high levels of fasting hyperglycemia during pregnancy. Even repeated testing of the same individual in the same pregnancy did not produce reliable results. In one report, one third of women tested in consecutive weeks with 3-hour glucose tolerance tests had the alternative diagnosis made on the second test.[16] These observations suggested that the test results and diagnosis were weakly related to underlying disease or attributable outcomes.[59]

Despite the apparent appropriateness of the NDDG criteria, in 1982 Carpenter and Coustan[14] recommended that lower thresholds be adopted for the 50-g oral glucose tolerance screening test and the 3-hour diagnostic results. They reasoned that a conversion error was made by the NDDG in translating O'Sullivan's whole-blood glycemic measures into plasma or serum results, and they estimated that the lower thresholds would increase the diagnosis to 3% of the screened population. Without any other validation, their criteria were listed as alternative findings in the 1986 ACOG technical bulletin. Approximately 25% of the population would have a screening value in excess of 130 mg/dL, and 25% of these individuals, or 6% of the total population, would be diagnosed with gestational diabetes using the Carpenter and Coustan thresholds of 95, 180, 155, and 140 mg/dL for the 100-g, 3-hour glucose tolerance test results. These criteria were recommended to replace the NDDG criteria at the Fourth International Conference on Gestational Diabetes.[63]

Other faults of the testing scheme that have received less attention include the delays inherent in the two-step process and the high rate of noncompliance or incomplete testing. The serum or plasma screening result is not immediately available, and an additional patient visit or call is necessary to report the results and schedule a

diagnostic test if the screening test is abnormal. Patient noncompliance with repeated glucose tolerance testing is reported to be as high as 40% in some series.[61] The time to complete diagnostic testing has characteristically been 4 to 6 weeks from the time of the initial administration of the 50-g glucola screening test. Two percent to 3% of the women expected to receive a diagnosis on the basis of the NDDG criteria are not identified until 30 to 32 weeks' gestational age. Consequently, in most cases, intervention strategies to reduce the morbidities associated with gestational diabetes are not initiated until the middle of the third trimester.[52]

An additional recommendation made at the fourth international conference[63] was that, in addition to performing immediate testing on women with risk factors such as prior gestational diabetes, a random blood sugar measure should be obtained at the time of presentation for prenatal care. Further testing was recommended with a random glucose in excess of 130 mg/dL. The recommendation that all women have a random blood sugar test at the time of their presentation for prenatal care underscored the lack of attention devoted to the detection of a small group of women who might benefit the most from the diagnosis and treatment of diabetes during pregnancy, that is, women with undiagnosed but likely preexisting disease.

Morbidity Associated with Gestational Diabetes

Two of the three major perinatal consequences of maternal diabetes in pregnancy do not pertain to women diagnosed with class A1 gestational diabetes. Women in whom glucose intolerance develops after midpregnancy do not expose the developing embryo to hyperglycemia, and these infants do not have an increase in malformations. They also do not seem to sustain the increase in fetal demise that complicates the pregnancies of women with pregestational, insulin-treated diabetes. Nevertheless, an increase in malformations and stillbirth is observed in women with class A2 gestational diabetes if diagnosed before midpregnancy.[85] This group has perinatal risks similar to women with pregestational diabetes. All groups of women diagnosed with diabetes have an increased rate of large for gestational age or macrosomic neonates. Women with class A1 diabetes share only this manifestation with other diabetic groups.

Large neonatal birth weight is not a morbid condition. More than 90% of large infants are delivered to nondiabetic women,[88] and these infants do not seem to sustain the metabolic abnormalities, such as hypoglycemia, that complicate the course of infants born to women with pregestational or insulin-treated diabetes. The lack of specificity of macrosomic or large for gestational age growth attributable to hyperglycemia is important; the birth of a large infant does not implicate maternal hyperglycemia as the cause. The use of a larger-than-average birth weight as a marker for hyperglycemic effect is inappropriate.[61]

A large for gestational age birth weight increases the risk of shoulder dystocia and birth trauma, and these associations are not unique to pregnancies complicated by maternal diabetes.[15] Some of the ascertainment problems associated with these morbidities are discussed later in this article. The infant of a diabetic mother is at greater risk for shoulder dystocia because the infant is more likely large for gestational age. When compared on the basis of birth weight, these infants appear different; however, this difference disappears if a comparison with nondiabetic infants is made on the basis of birth weight percentile or gestational age–adjusted birth weight. The perinatal morbidities associated with maternal gestational diabetes are attributable only to the risk for a large for gestational age birth weight.

Treatment and Management of Gestational Diabetes

Women with class A2 gestational diabetes can be managed in the same manner as women with pregestational diabetes. If the diagnosis is made early in gestation, an evaluation for effects on fetal development should be made. If the diagnosis is made late on the basis of fasting hyperglycemia, delivery at 38 weeks is a successful strategy to avoid the presumed increase risk of stillbirth originally attributed to gestational diabetes and subsequently ascribed to women with fasting hyperglycemia.[80] The use of postprandial criteria for insulin administration obfuscates estimates of associated risk even if outcomes are reported separately for insulin-treated versus diet-treated women.

Inaccurate means of identifying large for gestational age fetus prenatally has resulted in a widespread increase in the

cesarean delivery rate of women with diabetes. The focus on maternal diabetes is a poor strategy to reduce the population incidence of birth trauma because of a relatively low attributable risk. The frequency of maternal diabetes is too low, no matter how defined, to impact significantly on the incidence of macrosomia-related injury even if all of the cases attributable to diabetes could be removed by the effect of identification and treatment.

Most large for gestational age neonates are born to normoglycemic women, and the most prevalent risk factor for macrosomic outcome is maternal obesity,[88] even among diabetic women.[95] [59] Obesity is relatively immutable as a targetable risk factor, whereas diabetes is treatable. There has been a presumption that, in regards to the effect of gestational diabetes, hyperglycemia is largely manifest in the third trimester, leading to fetal overgrowth during that time. In support of this notion are the sonographic estimated fetal weights in women with gestational diabetes that, in cross-sectional analysis, increase at a rate in excess of average normal or nondiabetic growth. Nonetheless, analysis of sonographic estimates of fetal weight results in identical slopes of weight change estimate over time when large for gestational age infants of diabetic mothers are compared with large for gestational age infants of nondiabetic mothers (Fig. 1) . A comparison within birth weight percentile groups minimizes the effects of an increased prevalence of large for gestational age fetuses within the gestational diabetes group.[56] [57] Large for gestational age infants of nondiabetic mothers are larger than average gestational age counterparts in estimated fetal weight comparisons throughout the second and third trimesters of pregnancy, and large for gestational age infants of diabetic mothers are similarly distributed. This evidence suggests that the diagnosis of gestational diabetes occurs after its reputed effects, that is, excessive fetal growth is not a third-trimester phenomenon. Women with gestational diabetes manifest outcomes and fetal growth in a similar manner as nondiabetic women except for an increased prevalence of large infants. Interventions based on the diagnosis are not preventive against the development of large for gestational fetuses but, if successful, will decrease weight in already large fetuses.[12] [51] [56] [57] Fetal weight or fat loss requires ketosis, and there is concern that prolonged ketosis may be a suboptimal environment for normal brain development. The late initiation of hypoglycemic treatment may not be salutary and, if effective in reducing neonatal birth weight, may have adverse unmeasured consequences on development.

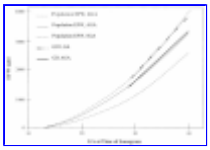

Figure 1. Estimated fetal weight (EFW) versus gestational age (GA) at time of sonogram. Superimposed on the smoothed sonographic estimates of fetal weight in nondiabetic pregnancies according to large for gestational age (LGA), appropriate for gestational age (AGA), or small for gestational age (SGA) birthweight categorizations are similar antepartum mean EFWs for LGA and AGA neonates delivered to women with gestational diabetes.

Fetal overgrowth as a result of diabetes is considered different from large for gestational age size in nondiabetic women. One piece of evidence in support of this theory is the observation that, within any given birth weight strata, the infants of diabetic mothers sustain a disproportionate rate of shoulder dystocia. Even when one ignores the problems of ascertainment of shoulder dystocia (i.e., maneuvers to effect delivery of the shoulders may be resorted to more readily if shoulder dystocia is anticipated because the mother has diabetes), these observations are most likely the result of an increased prevalence of large for gestational age fetuses at any given birth weight. Large for gestational age infants of nondiabetic mothers are at a similar risk for shoulder dystocia.[15]

Similar mechanisms may be involved in fetal growth and fat store deposition in infants delivered to diabetic and nondiabetic mothers.[57] Large infants of nondiabetic mothers have been found to have elevated umbilical cord blood insulin levels.[23] The larger fetal size of infants born to mothers with gestational diabetes could be described as a normal pathologic process. These observations should give pause to an overly focused objective of denying glucose to the fetus. The increased prevalence of large for gestational age infants is correlated with “normal” factors, such as maternal size or, more specifically, maternal obesity, and glycemia seems a less potent and certainly less prevalent effect than maternal weight on fetal growth. Alternatively, fetal overgrowth in nondiabetic women might also be considered pathologic. Because most large for gestational age neonates are delivered to normoglycemic women, investigation into the nonglycemic induction of fetal overgrowth would seem of greater potential benefit than targeting gestational diabetes.

The current recommendations in regards to testing for gestational diabetes suggest that it is important to make the diagnosis because identification should result in favorable preventive or therapeutic intervention; however, many reports have described no such effect.[59] Some investigators have proposed that more aggressive hypoglycemic

therapy is indicated to achieve a therapeutic effect. The largest therapeutic trial[52] of such an approach had numerous flaws, including nonrandom assignment and diagnostic thresholds that identified 10% of screened women as eligible for insulin therapy. With such a large proportion of women that would, in most centers, be considered normal, the relationship of improved outcome to the effects of hypoglycemic therapy was obscured, and the applicability of the study results to other populations was compromised. On an intent-to-treat basis, the outcomes were similar. The decrease in large-for-gestational age infants born to women "effectively" treated was virtually mirrored by an increase in small-for-gestational age infants. The average gestational age at the initiation of therapy was 33 weeks, and the mean age at delivery was less than 40 weeks. A shift in the birth weight distribution as a result of therapy must have caused considerable fetal weight loss over a short period of time. Similar concerns apply to reports describing the selection of women for treatment based on sonographic measures of the fetal abdomen consistent with disproportionate fetal overgrowth.[12] If the success of treatment is measured by normalized birth weight in fetuses already fat, fetal weight loss must have been effected. If the possibility of adverse effects is not considered, such consequences are unlikely to be measured and described.

More recently, a randomized comparison of glyburide with insulin treatment resulted in a comparable rate of macrosomia in the two treatment groups.[50] The administration of glyburide in pregnancy was rationalized because of the inconvenience, cost, and danger related to insulin administration, even though **oral hypoglycemic** agents have typically been avoided because of uncertain risks to the fetus. In all of the women treated, the need for hypoglycemic therapy was unclear. Had there been an untreated control group, would the differences in outcome have been statistically insignificant? More information is needed on the risks and benefits of this therapeutic approach before concluding that it is feasible and effective.

Much attention has been given to a study in which intensive treatment of gestational diabetes targeted postprandial glycemic levels, but all of the subjects had class A2 gestational diabetes and had therapy initiated more than 10 weeks earlier on average than subjects in the aforementioned study.[25] A total of 66 women were randomly allocated to either preprandial or postprandial glycemic monitoring, and a statistically significant decrease in mean birth weight and large for gestational age birth weight was attributed to the postprandial glycemic targeting. The equivalency of preprandial and postprandial targets is doubtful because equal attainment of targeted levels required significantly more insulin in the postprandial group. Although no adverse effects of treatment were reported, there was one small for gestational age infant in the postprandial group. Intense hypoglycemic therapy typically risks hypoglycemia, and, even though no occurrences were reported, it would be imprudent to ignore the possibility. Although the results of this study are widely interpreted as proving benefit of hypoglycemic therapy because of the decrease in large for gestational age neonates and mean birth weight in the postprandially targeted group, there are other important but unanswered questions: Was there any consideration or monitoring for adverse neonatal consequences of reduced weight? What was the pathology averted? What were the health benefits gained? Given the uncertain expectations of benefit from such intervention and acknowledging the possibility of adverse effects on fetal growth, unnecessary diagnosis and therapy with risky actions would seem imprudent. At the author's center, a woman is considered eligible for insulin treatment if repeated fasting blood sugars are in excess of 105 mg/dL. This threshold has been a useful discriminator for years in terms of the risk for fetal death, and management is the same for all insulin-treated women, including increased maternal-fetal surveillance and delivery at early term (38 weeks).[59] [88]

The cesarean delivery of infants of women with gestational diabetes has been considered a therapy and a morbidity. The known relationship between hyperglycemia and fetal growth and the reported increased risk of shoulder dystocia result in an increased rate of cesarean delivery within all groups of women with a diagnosis of diabetes, including gestational diabetes. Although rare, severe shoulder dystocia can result in fetal death, and its occurrence cannot be predicted based on the course of labor. In series detailing the effect of cesarean delivery in women with gestational diabetes, the birth weight of infants delivered abdominally was similar to the weight of infants delivered vaginally.[15] [37] Because the antepartum ability to identify fetuses at risk for shoulder dystocia is so limited, prophylactic cesarean delivery is ineffectual and is considered as a morbidity associated with the diagnosis.

Implementing the lower threshold criteria for gestational diabetes may impact on the cesarean delivery rate. The latter has become a marker of good obstetric practice, at least for third-party payors, such that a high cesarean rate can result in removal of a physician from provider roles. A high cesarean delivery rate in the small number of pregestational diabetic pregnancies will not significantly impact the overall operative delivery rate of a practice;

however, as the number of women diagnosed with gestational diabetes increases to 6% to 10%, the impact can be substantial. A strategy to prevent macrosomia by delivery early at term may seem attractive to reduce the number of infants delivered who weight 4 kg or more. Because the rate and difficulty of shoulder dystocia increase with size of the newborn, this strategy is not entirely irrational; however, most shoulder dystocia occurs in infants weighing less than 4000 g, and the risk factor of large for gestational age is likely already present at these lesser fetal weights.

The inaccuracy of sonography in the prediction of large for gestational age neonates and shoulder dystocia has been acceptable in diabetic prognosticating, in part, because of the low incidence of the diagnosis of diabetes, and prophylactic cesarean delivery has had a low impact on the overall cesarean rate. With an expected increase in the rate of diagnosis, the impact on the cesarean rate will be magnified. Because birth trauma is unexpected and unacceptable, practitioners in the United States are in a difficult circumstance of opposing pressures. Because some reference can be made to sonographic thresholds for predicting macrosomia and large for gestational age or disproportionate abdominal size, consideration of the risk of macrosomic growth and sonographic evaluation and estimation of fetal weight can help in management, even though there are significant limitations. These inaccuracies may be frustrating to clinicians who want to give a more clear recommendation to their patients. A discussion of the low predictive values of fetal weight estimates in regard to birth injury when considering options of management probably best satisfies the responsibility to provide informed consent. At the author's center, when delivery of a large fetus is anticipated, an estimated fetal weight in excess of the 90th percentile is considered as the initial risk factor. If the large for gestational age estimated fetal weight is also associated with abdominal disproportion in relationship to bony measures, the route of delivery is discussed in terms of an increased relative risk but still low absolute risk of traumatic dystocia.

Despite clear recommendations for the postpartum management of women with gestational diabetes, actual practices are difficult to describe. Performance of a 75-g glucose tolerance test is recommended[2] but unavailable at many medical centers. Although some authorities have argued that the general consensus is that this diagnosis is benign, other parties involved in health care may not make similar allowances. Insurance agencies underwrite according to risk, and it is their understanding that women with gestational diabetes are at risk for diabetes later in life. The diagnosis that a clinician might suppose would increase attention to the possibility of future morbidity predictably has the opposite effect; underwriting policies may exclude the future development of diabetes from coverage in women with a history of gestational diabetes. Similarly, many practitioners who undertake obstetric care if Medicaid coverage is obtained will not continue care after delivery. At a minimum, women need to be informed that they may be at risk for the development of diabetes after childbearing and advised to seek evaluation and care if symptoms develop. Periodic evaluation of fasting glycemia is more in accord with primary care practices in the nonpregnant population than the performance of glucose tolerance tests.

SUMMARY

Despite the well-documented relationship between morbidity in pregnancy and pregestational maternal diabetes, the corrected perinatal outcome is, in most series, equal to or better than that of the general reference obstetric population. No single aspect or element of contemporary management is responsible for this improvement; rather, a combination of interventions seems responsible. Targeting delivery early in term, improved compliance, better glycemic control during pregnancy, improved control at conception, improved neonatal care, family planning, and early screening for fetal abnormalities all likely contribute to improved outcome. The currently observed rates of perinatal mortality suggest that an irreducible minimum mortality rate may be reached; however, large disparities in access to care and treatment continue to result in a wide range in rates of morbidity and mortality, a fact that pertains to outcomes in general as well as to pregnancies complicated by diabetes. The identification of women with lesser degrees of hyperglycemia as diabetic by lowering the thresholds for glucose tolerance test abnormality suggests an importance of the diagnosis that is not supported by evidence of either related morbidity or therapeutic benefit. The extrapolation of risk to women with lesser degrees of hyperglycemia seems to have little basis, and the management of women with mild glucose intolerance as if they had overt diabetes is unwarranted. The excess of resources dedicated to the identification and monitoring of an increasing number of women with mild abnormalities of glucose metabolism should prompt a reevaluation of these practices. Perinatal benefits of this expenditure are difficult to document or nonexistent, and there is a predictable increase in iatrogenic morbidities associated with the diagnosis. The exception in the most recent recommendations is the addition of a random glucose measure to screen for the rare women with overt undiagnosed diabetes who presents for prenatal care, because these women are at increased

risk of morbidities related to diabetes.[85]

A curious statement was made in the summary and recommendations of the fourth International Congress on Gestational Diabetes: “There remains a compelling need to develop diagnostic criteria for GDM [gestational diabetes mellitus] that are based on the specific relationships between hyperglycemia and risk of adverse outcome.”[63] If these relationships are undefined, what is the import of the diagnosis? At the author's center, application of the new diagnostic thresholds for the diagnosis of gestational diabetes mellitus has increased the incidence to over 6%. Without a clear expectation of benefit, this increase represents an unsupportable investment of resources. What are the prospects for improving understanding of the relationships between glucose intolerance and pregnancy risks? The direction of new guidelines and recommendations seems to be moving away from resolution of the relationships. The new criteria result in the diagnosis of gestational diabetes in an increasing number of women who were previously normal. It is easier to differentiate women at an extreme of hyperglycemia from normal. Investigations will be even less able to identify attributable effects of glucose intolerance in pregnancy with the inclusion of women with lesser degrees of hyperglycemia.

As evidenced in O'Sullivan's original series, women with fasting hyperglycemia in pregnancy are still presumed to be at increased risk of fetal death. This risk factor remains important in clinical management if insulin treatment, fetal surveillance, and early term delivery can reduce the risk of fetal loss. At the author's center, the relationships among outpatient measures of fasting glycemia, glucose tolerance testing results, and perinatal outcomes are evaluated. Preliminary results suggest that fasting glycemia measured at the time of a 50-g glucose tolerance test is significantly correlated with and as sensitive and predictive of morbidity as the glucose tolerance test diagnosis of gestational diabetes. If these results are confirmed, it will be difficult to rationalize continued glucose tolerance testing.

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