Review

Gestational Diabetes Mellitus

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BACKGROUND: Gestational diabetes mellitus, defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes, is becoming more common as the epidemic of obesity and type 2 diabetes continues. Newly proposed diagnostic criteria will, if adopted universally, further increase the prevalence of this condition. Much controversy surrounds the diagnosis and management of gestational diabetes.

CONTENT: This review provides information regarding various approaches to the diagnosis of gestational diabetes and the recommendations of a number of professional organizations. The implications of gestational diabetes for both the mother and the offspring are described. Approaches to self-monitoring of blood glucose concentrations and treatment with diet, oral medications, and insulin injections are covered. Management of glucose metabolism during labor and the postpartum period are discussed, and an approach to determining the timing of delivery and the mode of delivery is outlined.

SUMMARY: This review provides an overview of current controversies as well as current recommendations for gestational diabetes care.

Gestational diabetes mellitus (GDM)[3] is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes (1). This condition is associated with adverse pregnancy outcomes, including fetal macrosomia, stillbirth, neonatal metabolic disturbances, and related problems (2). Offspring of mothers with GDM are at increased risk for diabetes and obesity (3–5). Women with GDM are more likely to develop diabetes in the years following pregnancy (4, 6). There continues to be controversy regarding the degree of risk associated with GDM, the most appropriate diagnostic criteria, the ability of identification and treatment to improve pregnancy outcomes, and the cost vs benefit of such efforts.

Diagnosis

As early as 1882, J. Matthews Duncan observed that diabetes might appear during pregnancy and cease with the end of pregnancy (7). In the 1950s, W.P.U. Jackson reported a high likelihood of previous stillbirth and fetal macrosomia in women with diabetes (8), and in 1957 Elsie Reed Carrington et al. coined the term "gestational diabetes" (9). In the US at that time, the diagnosis of diabetes was made with a 100-g, 3-h oral glucose tolerance test (OGTT) using the US Public Health Service Criteria. In 1964 O'Sullivan and Mahan (10) noted that the OGTT may be altered by pregnancy and reported on the results of 100-g, 3-h OGTTs in 752 pregnant women, most of whom were tested in the second and third trimesters. Potential cutoffs were 1, 2, and 3 SDs above the mean for each of the 4 values. These cutoffs were then retrospectively applied to a second data set of OGTTs in 1013 previous pregnancies in women who subsequently underwent periodic OGTTs in the nonpregnant state. Two or more increased glucose values, rather than a single abnormality, were used as diagnostic criteria to avoid reliance on a single laboratory measurement to make a diagnosis. This pioneering work revealed that the use of 2 SDs above mean values would result in a 1.99% prevalence of gestational diabetes, which was similar to the reported prevalence of diabetes in the nonpregnant population at the time. Furthermore, diabetes would develop in 22.6% of individuals formerly diagnosed with GDM within the ensuing 8 years. The "O'Sullivan" thresholds, both the raw numbers and the easier-to-remember rounded numbers, depicted in Table 1, came into widespread use by the 1970s. These thresholds were based on venous whole blood samples analyzed by the Somogyi–Nelson technique. Because most laboratories had switched to plasma or serum measurements, the National Diabetes Data Group (NDDG) proposed newly derived thresholds in 1979 (11). The already rounded

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[3] Nonstandard abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data Group; C&C, Carpenter and Coustan; ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; HAPO, Hyperglycemia and Adverse Pregnancy Outcome study; NICU, neonatal intensive care unit; IADPSG, International Association of Diabetes In Pregnancy Study Groups; Hb A_{1c}, hemoglobin A_{1c}; IOM, Institute of Medicine; BMI, body mass index; CZI, crystalline zinc insulin; NPH, Neutral Protamine Hagedorn; FDA, US Food and Drug Administration.

Table 1. O'Sullivan criteria for diagnosing gestational diabetes by using the 100-g, 3-h OGTT, along with subsequently derived values.
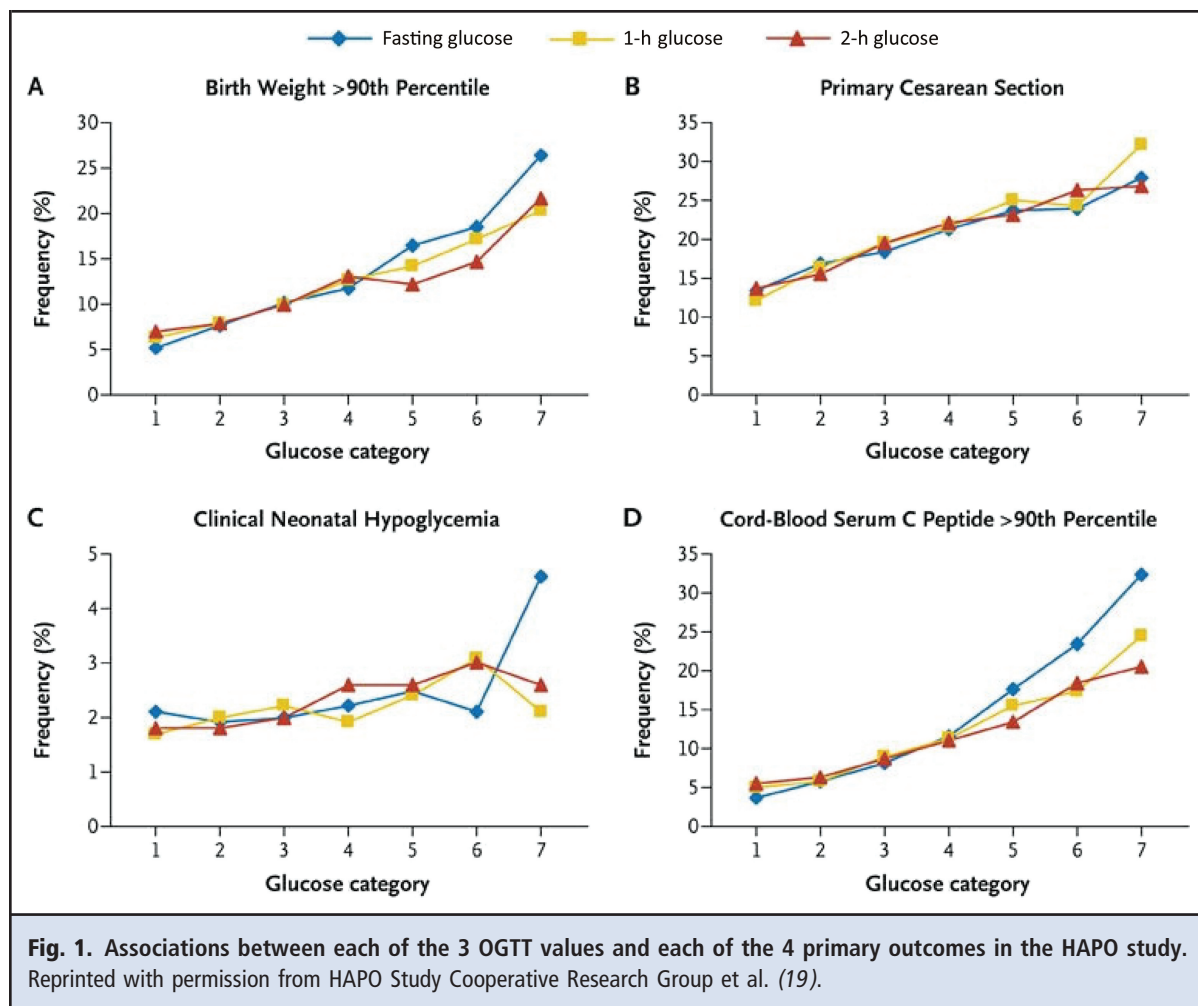
Time of glucose measurement	Threshold glucose values, mg/dL (mmol/L)			
	Original values [O'Sullivan and Mahan (10)], venous whole blood, Somogyi–Nelson method	Rounded O'Sullivan values	NDDG modification [NDDG (11)], plasma	C&C modification [Carpenter and Coustan (12)], plasma, glucose oxidase
Fasting	90 (5.00)	90 (5.00)	105 (5.83)	95 (5.27)
1 h	165 (9.16)	165 (9.16)	190 (10.55)	180 (9.99)
2 h	143 (7.94)	145 (8.05)	165 (9.16)	155 (8.60)
3 h	127 (7.05)	125 (6.94)	145 (8.05)	140 (7.77)

O'Sullivan values were increased by approximately 15% to account for the difference between whole blood glucose and plasma or serum glucose. In 1982 we published a second set of thresholds derived from the O'Sullivan and Mahan raw numbers, but decreased by 5 mg/dL (0.28 mmol/L) because of the universal change in laboratory methods from those used for the Somogyi–Nelson method, which measured approximately 5 mg/dL of reducing substances other than glucose, to more specific enzymatic methods (12). The resulting values were then increased by 14% to account for the change from whole blood to plasma. The 2 sets of thresholds, both derived from the O'Sullivan and Mahan criteria, are generally referred to as "NDDG" and "Carpenter and Coustan" (C&C) criteria. Both were deemed acceptable by the American College of Obstetricians and Gynecologists (ACOG) and are still recommended as reasonable alternatives (13). A head-to-head comparison of the 2 sets of criteria, performed by using the original methodology of O'Sullivan and Mahan vs plasma and glucose oxidase, found that the C&C criteria were within 95% confidence limits of the original values, whereas the NDDG were above the 95% confidence limits at each of the 3 postload times of measurement (14). The American Diabetes Association (ADA) subsequently endorsed the C&C criteria, and these remained their recommended diagnostic thresholds until 2011, when a new set of diagnostic criteria was incorporated into the ADA's recommendations (1).

Because the O'Sullivan criteria, and the thresholds which were derived from them, were validated solely on their ability to predict subsequent diabetes in the mother, it became clear that evidence-based criteria, validated by their prediction of adverse pregnancy outcomes, would be preferable. Furthermore, other diagnostic tests are being used in various parts of the world (15). These include the WHO criteria, which are based on a 75-g, 2-h OGTT with thresholds the same for women during pregnancy as for nonpregnant individuals (16). Gestational diabetes is diagnosed using the nonpregnant criteria for impaired glucose tolerance, a fasting value <126 mg/dL (6.99 mmol/L) plus a 2-h value of 140–199 mg/dL (8.27–11.05 mmol/L). A fasting plasma glucose ≥126 mg/dL or a 2-h value ≥200 mg/dL (≥11.1 mmol/L) is diagnostic for diabetes. The use of different sets of criteria and different glucose loads around the world make it impossible to compare the prevalences of GDM and the results of treatment among various locations. Published prevalence figures vary from 1.7% to 11.7% in countries throughout the world (17), and from 3.4% to 7.2% even among states in the US (18). The 75-g, 2-h OGTT has been accepted for use around the world in nonpregnant individuals, but different glucose challenges used in pregnancy in various centers (e.g., 50, 75, or 100 g) make it nearly impossible to compare studies and results to one another.

For the above reasons the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed to evaluate the relationship between plasma glucose concentrations on the 75-g, 2-h OGTT and various adverse pregnancy outcomes (19). It was hoped that this would inform the development of evidence-based diagnostic criteria, which might then be widely adapted. Blinded OGTTs were administered to over 23 000 pregnant women in the late second and early third trimester in 14 centers in 9 countries around the world. The primary outcomes of macrosomia (birth weight >90th centile), fetal hyperinsulinemia (cord C-peptide >90th centile), clinical neonatal hypoglycemia, and primary cesarean section were all related to each of the 3 plasma glucose measurements (fasting, 1 h, and 2 h) in a continuous fashion, down to the lowest concentrations of glucose, with no inflection points (Fig. 1). Secondary outcomes such as preeclampsia, neonatal body fat (skin-fold thickness), neonatal intensive care unit (NICU) admission, and preterm birth were similarly related. These findings of a direct relationship between GTT values at 24–32 weeks gestation and ultimate out-

Fig. 1. Associations between each of the 3 OGTT values and each of the 4 primary outcomes in the HAPO study. Reprinted with permission from HAPO Study Cooperative Research Group et al. (19).

comes support the Pedersen hypothesis (20) of maternal hyperglycemia causing fetal hyperinsulinemia leading to increased fetal fat deposition and macrosomia. Although the HAPO study did not address the relationship of fasting values ≥105 mg/dL (≥5.83 mmol/L) or 2-h values ≥200 mg/dL (≥11.1 mmol/L) with adverse pregnancy outcomes, numerous other reported studies have demonstrated such an association. The fact that the relationship holds down to the lowest glucose concentrations suggests a basic biologic phenomenon.

Given the lack of an inflection point for any of these relationships, there were no obvious diagnostic cutoffs. The selection of diagnostic criteria would, of necessity, be somewhat arbitrary. The International Association of Diabetes In Pregnancy Study Groups (IADPSG) was called upon to oversee a process in which data were presented to, and input solicited from, a broad range of experts and constituencies from throughout the world (21). Consideration was given to the use of OGTT cutoffs that identified odds ratios of

1.5, 1.75, or 2.0 (compared to median values) for the risk of fetal macrosomia, neonatal adiposity, and fetal hyperinsulinemia (all defined as >90th percentile). Although it would have been desirable to use a single glucose value rather than performing a full OGTT, it was determined that the 3 values of the OGTT each contributed independently to the prediction of adverse outcomes. Consequently the IADPSG recommended the use of the 75-g, 2-h OGTT with cutoffs at an odds ratio of 1.75, as depicted in Table 2. Because much of the world uses the International System of Units (mmol/L), whereas the US employs milligrams per deciliter, the unrounded values were recommended. In addition, rounding up or down to the nearest 5 mg/dL (or 0.5 mmol/L) would have significantly impacted the prevalence of diagnosed GDM.

The IADPSG recommendations, when applied to the HAPO data, would have identified 16.1% of pregnant women as having GDM, and that figure increased to approximately 18% when women who were ex-

Table 2. IADPSG Recommendations.[a]
At first visit, assign diagnosis of preexisting diabetes if any of the following are present:
Fasting plasma glucose ≥126 mg/dL (≥6.99 mmol/L)
Hb A$_{1c}$ ≥6.5% (≥48 mmol/mol)
Random plasma glucose ≥200 mg/dL (≥11.1 mmol/L) (confirmed by FPG or Hb A$_{1c}$)
At first visit, assign diagnosis of gestational diabetes if present:
Fasting plasma glucose ≥92 mg/dL (≥5.11 mmol/L) and <126 mg/dL (<6.99 mmol/L)
At 24–28 weeks gestation, perform 75-g, 2-h OGTT. Assign diagnosis of gestational diabetes if one or more of the following plasma glucose values is met or exceeded:
Fasting 92 mg/dL (5.11 mmol/L)
1 h 180 mg/dL (9.99 mmol/L)
2 h 153 mg/dL (8.49 mmol/L)
[a] Adapted from the International Association of Diabetes and Pregnancy Study Groups Consensus Panel (21).

cluded from the study because of high glucose values were considered (21). This recommendation has been controversial, and arguments for and against can be found in a previous issue of this journal (22, 23). Such a high prevalence of GDM has major implications for healthcare delivery. However, the recommended thresholds for GDM are not dissimilar to the current generally accepted diagnostic criteria for prediabetes (Table 3) in nonpregnant individuals. In view of the current 11.3% prevalence of diabetes in the US adult population (24) and the 35% prevalence of prediabetes (25), the proposed increase in prevalence of GDM does not seem unreasonable. The ADA has endorsed the IADPSG recommendations (1) for diagnosing gesta-

tional diabetes, whereas ACOG has not done so as yet (13).

The IADPSG made further recommendations to enable detection of preexisting diabetes during early pregnancy (21). A fasting plasma glucose ≥126 mg/dL (6.99 mmol/L), random plasma glucose ≥200 mg/dL (11.1 mmol/L), or hemoglobin A$_{1c}$ (Hb A$_{1c}$) ≥6.5% (≥48 mmol/mol) would be the basis for making the diagnosis (Table 2). The ADA has endorsed a similar recommendation (1), although requiring a second, confirmatory test. The ADA permits defining overt diabetes with a random glucose ≥200 mg/dL only for patients who exhibit classic symptoms of hyperglycemia or hyperglycemic crisis. In contrast, a random glucose of ≥200 mg/dL may be used in the presence or absence of such symptoms, but it must be confirmed by an Hb A$_{1c}$ or fasting plasma glucose, according to the IADPSG. The IADPSG suggests either testing all pregnant women, or testing only those with risk factors, at the first prenatal visit, whereas the ADA recommends testing only those with risk factors. Both organizations recommend the 75-g, 2-h OGTT for GDM at 24–28 weeks in those who have not already been diagnosed with diabetes or GDM.

Screening and Testing Strategies

The ACOG recommends universal screening as the most sensitive approach, but there may be pregnant women at low risk who are less likely to benefit from testing. To be considered low risk, women must be younger than 25 years, not be a member of a racial or ethnic group with a high prevalence of diabetes, not be overweight, have no history of abnormal glucose tolerance or adverse pregnancy outcomes, and have no known diabetes in a first-degree relative. The first step

Table 3. Diagnostic criteria for diabetes and prediabetes in nonpregnant individuals.[a]				
	Fasting plasma glucose	2-h plasma glucose on 75-g, 2-h OGTT	Hb A$_{1c}$	Random plasma glucose
Diabetes	≥126 mg/dL[b]	≥200 mg/dL[b]	≥6.5%[b]	≥200 mg/dL[c]
	≥6.99 mmol/L	≥11.1 mmol/L	≥48 mmol/mol	≥11.1 mmol/L
Prediabetes			5.7%–6.4%	
Impaired fasting glucose	100–125 mg/dL	—		
	5.55–6.94 mmol/L			
Impaired glucose tolerance	—	140–199 mg/dL		
		7.77–11.05 mmol/L		
[a] Adapted from ADA (1).				
[b] In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.				
[c] In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.				

in screening for gestational diabetes is a 50-g, 1-h glucose challenge (13) at 24–28 weeks. Values ≥130 mg/dL (≥7.22 mmol/L) or ≥140 mg/dL (≥7.77 mmol/L) are followed up with a 100-g, 3-h OGTT. Two or more increased values are diagnostic for GDM. Either the NDDG or C&C modifications are acceptable (Table 1). The new recommendation from the ADA (1) for diagnosing gestational diabetes is the 75-g, 2-h OGTT, which is not a screening test but rather a diagnostic test.

Implications of Gestational Diabetes

Maternal hyperglycemia, whether from preexisting diabetes or from gestational diabetes, leads to fetal hyperglycemia because glucose is easily transferred across the placenta. The fetal pancreas responds to increased glucose concentrations by producing and releasing more insulin. It is this fetal hyperinsulinemia that leads to most of the fetal problems, collectively known as diabetic fetopathy, seen in diabetic pregnancy (26). Fetal macrosomia is one of the more prominent problems and appears to be related to the growth-promoting activity of fetal insulin. The excessive growth is disproportional and leads to large amounts of subcutaneous fat and broad shoulders, which predispose infants to shoulder dystocia at delivery. Infants of gestational diabetic mothers who are born prematurely are more likely to develop respiratory distress syndrome and other problems of prematurity. Hyperinsulinemic babies are prone to hypoglycemia during the early neonatal period, when they are suddenly isolated from the maternal source of glucose and still have high concentrations of circulating insulin. Other problems encountered by such infants include hypocalcemia, hyperbilirubinemia, and plethora. Such problems may require close monitoring in the NICU. Offspring of gestational diabetic mothers have an increased risk of developing both obesity and diabetes later in life (3–5).

Gestational diabetes also has implications for the mother. Preeclampsia and cesarean sections are both increased in undiagnosed, untreated GDM and may be prevented with diagnosis and treatment (27, 28). Although gestational diabetes is not, of itself, an indication for cesarean section, its complications may be. For example, preeclampsia may necessitate early delivery by induction of labor before the cervix is "ripe," making cesarean section more likely. When the estimate of fetal weight is in the range of 4500 g, the ACOG recommends consideration of primary cesarean section without labor to avoid shoulder dystocia (29). Over the longer term, GDM may be thought of as a provocative test for future diabetes. In landmark studies, O'Sullivan and Mahan found that approximately 50% of women with previous GDM had developed diabetes, primarily

type 2 diabetes, within 20 years of their index pregnancy (6). Other studies have confirmed increased risk, with the magnitude varying according to the prevalence of type 2 diabetes in the population (4, 30, 31).

Medical Management

SELF–GLUCOSE MONITORING
Medical management is aimed at maintaining circulating glucose concentrations in the reference interval for pregnant women. Until self–glucose monitoring became widely available in the late 1970s, women with GDM needed to travel to laboratory sites to have their blood glucose checked. This meant that the day on which glucose tests were conducted was not like an ordinary day, and the results probably did not accurately reflect what was going on in the individual's day-to-day life. As test strips and reflectance meters came on the market, it became possible to incorporate glucose testing into nearly any lifestyle.

Goals for glucose control in diabetic pregnancy were originally based on studies of healthy nondiabetic pregnant women (32). Other studies revealed lower perinatal mortality rates for diabetic pregnancies when mean glucose concentrations were kept in that reference interval (33). The ACOG recommends fasting values below 95 mg/dL (5.27 mmol/L), 1-h postprandial values below 130–140 mg/dL (7.22–7.77 mmol/L), and 2-h postprandial values below 120 mg/dL (6.66 mmol/L) (34). The ADA makes similar recommendations (1). It should be noted that these recommendations are based primarily on limited scientific evidence and expert opinion. Patients with gestational diabetes are usually advised to perform daily self–glucose monitoring after fasting and either 1 h or 2 h after each meal. Although many endocrinologists recommend preprandial glucose testing for nonpregnant individuals, the advantages of postprandial testing in GDM were demonstrated in a randomized trial comparing preprandial glucose testing 3 times daily with fasting and postprandial glucose measurement 3 times daily in women with GDM who required insulin (35). Postprandial testing was associated with lower rates of large-for-gestational-age offspring, fewer cesarean sections, and less neonatal hypoglycemia. It appears that the fetal pancreas is most sensitive to the height of blood glucose excursions, which typically occur after meals.

DIET
Medical nutritional therapy is the initial step in attaining euglycemia in gestational diabetes (36). Patients are counseled by a registered dietitian if one is available, or else by an individual with knowledge and expertise in the field. The diet plan is individualized according to

the patient's weight and height and is based on the nutritional requirements of pregnancy as well as the principles of diet management in diabetes; success is based upon the achievement of blood glucose goals as described above. The diet is also intended to avoid ketosis and to help the mother achieve appropriate weight gain. The Institute of Medicine (IOM) recommendations for pregnancy weight gain, revised in 2009 (37), are based upon prepregnancy body mass index (BMI) (kg/m²). Underweight mothers (BMI <18.5) are advised to gain 28–40 pounds throughout pregnancy, and those of normal weight (BMI 18.5–24.9) should gain 25–35 pounds. Overweight women (BMI 25–29.9) should gain 15–25 pounds, and those who are obese (BMI >30) should gain 11–20 pounds. Women with GDM are advised to avoid concentrated sweets and highly processed foods because of their propensity to cause rapid rises in circulating glucose concentrations. The use of severely calorie-restricted diets for obese patients with GDM is somewhat controversial. Although some studies have demonstrated benefit in reducing macrosomia in the offspring (38), others have suggested risk of causing ketonemia and ketonuria (39) in the mothers, which may be associated with lower mental and motor function of the offspring at the ages of 3 and 7 years (40, 41). The IOM (37) does not recommend weight loss during pregnancy, even for morbidly obese women.

ORAL AGENTS

Oral antidiabetic agents are the second line of treatment of type 2 diabetes and are generally instituted when medical nutrition therapy has failed to provide adequate blood glucose control. There has been great interest in their use during pregnancy because insulin, the generally accepted gold standard, requires subcutaneous injections which can be uncomfortable and off-putting to patients. Two classes of oral agents have been most widely used. Sulfonylureas stimulate insulin production and release in the pancreas; they may cause hypoglycemia and are effective only when the pancreas is capable of producing insulin. Thus they are not used in women with type 1 diabetes. First-generation sulfonylureas were shown to cross the placenta and possibly cause neonatal hypoglycemia. Glyburide, a second-generation sulfonylurea, was found to be similarly effective to insulin in improving Hb A_{1c} concentrations, reducing macrosomia, and preventing neonatal hypoglycemia in a randomized open-label clinical trial involving women with GDM whose levels of glycemia required pharmacologic treatment (42). Results of a number of other reported studies have supported the efficacy of this drug, with additional insulin required in 6% to 25% of patients with GDM (43). Initial publications reported that glyburide did not cross the isolated,

perfused placental cotyledon from the maternal to the fetal circulation (44) and was not found in cord blood (42), but subsequent investigators reported that fetal concentrations at delivery were 70% of maternal concentrations (45), although both concentrations were quite low because of the time elapsed since last dosing before delivery. Adverse fetal and neonatal effects such as neonatal hypoglycemia and macrosomia have not been reported to increase with the use of glyburide during pregnancy, but long-term studies of offspring have not been carried out. Given current concerns regarding in utero programming (46), it is important to inform patients of these remaining questions when sulfonylureas are prescribed.

The other class of drugs which have been widely used in pregnancy are the biguanides, of which metformin is the only available agent. Metformin acts as an insulin sensitizer at the liver and periphery. It does not cause hypoglycemia. A randomized trial comparing metformin to insulin in women with GDM requiring pharmacologic intervention demonstrated that the 2 approaches were similarly effective in preventing adverse pregnancy outcomes (47). As would be expected, women preferred metformin to insulin. However, nearly half of women assigned to metformin treatment required the addition of insulin to achieve adequate glycemic control. Other reported studies have had similar results (43). Metformin crosses the placenta, and fetal concentrations are considerably higher than maternal concentrations (48). Although no increase in adverse outcomes has been reported, long-term studies of the offspring have not been carried out thus far. When metformin is prescribed during pregnancy, patients should be informed that it crosses the placenta to the fetus and that potential benefits or harms are not yet known.

A number of other classes of agents are available to treat diabetes in nonpregnant individuals. Acarbose, an α-glucosidase inhibitor, prevents absorption of sugar from the gastrointestinal tract and has been investigated in at least 2 pilot studies (49, 50). Although it can decrease postprandial glucose excursions, bothersome side effects can include cramping and excessive flatus. Very little is absorbed systemically. Insulin sensitizers such as thiazolidinediones have been reported to cross the placenta and generally not used in pregnancy.

INSULIN

Insulin has long been the gold standard medication when diet and exercise are not sufficient to control circulating glucose concentrations in women with GDM. Insulin derived from the pancreases of pigs and cows was initially used but elicited immune responses, with antiinsulin antibodies, in many patients. Recombinant DNA technology then enabled the production of hu-

	Onset, h	Peak, h	Duration, h
Table 4. Characteristics of various insulin preparations (based on package inserts).			
Rapid-acting analogs			
Insulin lispro (Humalog)	<0.25–0.5	0.5–2.5	3–5
Insulin aspart (Novolog)	<0.25	1–3	3–5
Insulin glulisine (Apidra)	<0.25	0.75–2	3–5
Short-acting			
Regular insulin, CZI, soluble	0.5–1	2–3	5–8
Intermediate-acting			
NPH, isophane	2–4	4–10	10–16
Long-acting analogs			
Insulin glargine (Lantus)	2	Relatively flat	11–24
Insulin detemir (Levemir)	1–2	Relatively flat	Dose dependent
			12 h for 0.2 U/kg
			14 h for 0.4 U/kg
			range 7.6–24 h

man insulin, which was not antigenic. Various vehicles were added to delay absorption of the insulin, resulting in short-acting [e.g., regular, also known as crystalline zinc insulin (CZI)], intermediate-acting [Neutral Protamine Hagedorn (NPH)], and long-acting (ultralente) insulins. Most recently, biosynthetic insulin analogs have been developed, with single amino acid substitutions, changing the absorption characteristics. The commonly available insulins and their onset and duration of action are listed in Table 4. Insulin lispro *(51)* and insulin aspart *(52)* appear not to cross the placenta and are commonly used in pregnancy. They are rapid-acting insulin analogs with a short duration of action, so they can be taken immediately before meals, providing more flexibility in meal timing than was possible with regular insulin, which needed to be taken 20–30 min before eating. NPH insulin is intermediate acting and can be mixed with short-acting insulins so as to cover the immediate meal and the subsequent meal. Longer-acting biosynthetic insulin analogs are available and are used to mimic basal insulin production. These insulin analogs appear to have no peak of action, at least in nonpregnant individuals, and last for over 24 h. Insulin detemir has been used to treat pregnant women with preexisting diabetes and was compared with NPH insulin in a randomized clinical trial *(53)*. Insulin detemir was demonstrated to be noninferior to NPH insulin with respect to Hb A_{1c} concentrations at 36 weeks, and fasting glucose concentrations were lower with detemir at 24 and 36 weeks gestation. Rates of hypoglycemia were similar in both groups. As a result of this study, insulin detemir has been reclassified by the US Food and Drug Administration (FDA) to

FDA Pregnancy Category B. However, data have not yet been published regarding whether insulin detemir crosses the placenta. Insulin glargine, which is FDA Pregnancy Category C, has been shown not to cross the placenta when used at therapeutic doses *(54)*. Meta-analyses have not shown any differences in maternal or fetal outcomes with insulin glargine compared to NPH insulin *(55, 56)*. As a general rule, patients with GDM can be safely and effectively managed with combinations of NPH and short-acting insulin analogs, without the need for long-acting analogs.

Management during Labor and the Puerperium

Diabetic management during labor and delivery is aimed at maintaining maternal euglycemia to avoid neonatal hypoglycemia. The hyperinsulinemic fetus of a diabetic mother, having been exposed to hyperglycemia throughout the pregnancy, exhibits a brisk insulin response to a glucose challenge. If maternal glucose concentrations are increased just before delivery, neonatal hypoglycemia is likely to develop as the newborn adapts to being cut off from the placental supply of glucose. Neonatal hypoglycemia can cause seizures and other problems and so should be avoided. Therefore, at our institution, point-of-care capillary glucose concentrations are checked frequently during labor, with a goal of 70–120 mg/dL (3.89–6.66 mmol/L). Although maternal glucose concentrations in the range of 60 and even 50 mg/dL are generally well tolerated, healthy newborns drop their glucose concentrations approximately in half during the first few hours of life, so it is best for maternal glucose to be no lower than 70 mg/dL

at delivery. Most women with gestational diabetes will not become hyperglycemic during labor, because they are not eating (although they are generally allowed to drink fluids). We often provide an intravenous infusion of 5% dextrose to meet the caloric needs of labor. If maternal glucose concentrations exceed 120 mg/dL a constant intravenous insulin infusion can be administered starting at 1 U/h. This is virtually always needed for gravidas with type 1 diabetes, sometimes needed for those with type 2 diabetes, and rarely necessary for gestational diabetes.

Once delivery has occurred, and the fetal–placental unit is no longer releasing hormones that cause insulin resistance, maternal glucose metabolism generally rapidly returns to normal. Because some women with gestational diabetes actually had undiagnosed preexisting diabetes before their pregnancy, we measure a fasting plasma glucose on the morning after delivery to make sure that no further treatment is needed at that time.

Obstetric Management

TESTS OF FETAL WELL-BEING

Pregnancies complicated by gestational diabetes are at increased risk of stillbirth (2). Although there is no single best evidence-based approach to monitoring fetal well-being in gestational diabetic pregnancies, the ACOG has stated: "Despite the lack of conclusive data, it would seem reasonable that women whose GDM is not well controlled, who require insulin, or who have other risk factors such as hypertension or adverse obstetric history should be managed the same as individuals with preexisting diabetes. The particular antepartum test selected, whether nonstress test, contraction stress test, or biophysical profile, may be chosen according to local practice" (34). In our institution GDM mothers with risk factors noted above begin twice weekly nonstress tests and amniotic fluid indices at between 32 and 36 weeks, depending upon the severity of the risk factors. Those with no risk factors and whose circulating glucose concentrations are within targets, using medical nutrition therapy alone, start weekly testing at 36 weeks.

FETAL GROWTH

The rate of macrosomia in GDM varies, depending upon the diagnostic criteria and the method of treatment. In a randomized trial of identification and treatment of mild forms of GDM, macrosomia (birthweight >4000 g) was present in 21% (27) and 14% (28) of untreated pregnancies, which was about twice the rate in each study in pregnancies in which GDM was identified and treated. Because GDM is associated with fetal macrosomia, and macrosomia in a fetus of a diabetic mother is associated with an increased risk of shoulder dystocia compared to the risk in a similar-weight fetus of a nondiabetic mother, normalization of maternal glucose is the most important means of prevention of this problem. However, such efforts are not always successful, and large babies are sometimes born to mothers whose GDM is well controlled. Therefore periodic ultrasound imaging of the fetus is used to estimate fetal weight and growth trajectory. Caution should be exercised in interpreting ultrasound fetal weight estimations because the range of error is relatively wide. One series of investigations has demonstrated the successful use of ultrasound estimates of fetal growth trajectories to determine which GDM mothers may or may not benefit from insulin treatment with (57) or without (58) increased fasting glucose concentrations.

TIMING OF DELIVERY

There is an increased risk of stillbirth in gestational diabetic pregnancies, particularly when glucose concentrations are not within target ranges and the fetus is presumably hyperinsulinemic. A 2011 workshop jointly sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Society for Maternal-Fetal Medicine recommended that gestational diabetic pregnancies in which glucose concentrations are well controlled, with or without medication, not be delivered electively before 39 weeks (59). When GDM is poorly controlled the timing of delivery is individualized and is generally between 34 and 39 weeks, depending upon the situation. When all of almost 200 000 pregnancies complicated by GDM in California over a 10-year period were analyzed, the stillbirth rate plus infant mortality rate associated with delivery at various gestational ages was compared to determine the risk of early delivery vs waiting 1 more week (60). Such risks were not different between 36 and 38 weeks, but at 39 weeks and beyond the relative risk of expectant management exceeded that of delivery. The absolute differences were small but significant, with the number needed to deliver at 39 weeks (vs 40 weeks) to prevent a single excess death being 1518. Because there is increased perinatal morbidity associated with early term delivery before 39 weeks (61), delivery between 39 and 40 weeks in cases of gestational diabetic pregnancy appears to be a reasonable course. At our institution we recommend induction of labor for undelivered women with well-controlled gestational diabetes at some time between 39 and 40 completed weeks of gestation, depending upon the patient's preference. Delivery is often performed earlier in patients whose GDM is not well controlled.

MODE OF DELIVERY

Gestational diabetes is not an indication for cesarean section. However, cesarean section is more common in GDM than in nondiabetic pregnancies. The absolute rates are dependent upon the criteria used for the diagnosis of GDM and the prevailing cesarean section rates in the particular location. In the randomized trials of identification and treatment of mild gestational diabetes, cesarean sections were performed in 32% of untreated vs 31% of treated (27) and 34% of untreated vs 27% of treated GDM pregnancies (28), which in the latter study was significantly higher. For example, preeclampsia is more likely to occur in gestational diabetic pregnancies than in nondiabetic pregnancies, and its treatment may require early delivery when the cervix is not favorable. Cesarean section may result. Macrosomia is more commonly encountered, by mechanisms outlined above, and failure to progress in labor because of disproportion between fetus and pelvis may necessitate cesarean section. Because the fetus of a diabetic mother tends to have broader shoulders compared to its head, shoulder dystocia is more likely at any given birth weight (62). A decision analysis (63) led to the conclusion that if a policy of elective cesarean section were put in place when the estimated fetal weight is ≥4500 g, then 3695 cesarean sections would be needed to prevent 1 case of permanent Erb palsy in nondiabetic pregnancies, whereas 443 cesarean sections would be needed for diabetic pregnancies. The ACOG suggests offering cesarean section without labor when the estimated fetal weight in a diabetic pregnancy is ≥4500 g (29). Pregnant patients with a history of infant shoulder dystocia in an earlier delivery, whose estimated fetal weight is equal to or greater than that of the previous affected offspring, are also typically offered cesareans. Another possible cause of increased cesarean sections in gestational diabetic pregnancies is the obstetrician's concern about the possibility of shoulder dystocia, even when the fetus is not large. A Canadian study (64) found that when obstetricians were blinded to the diagnosis of mild GDM and patients were not treated, cesarean sections were performed more often than in nondiabetic pregnancies and were associated with macrosomic fetuses. However, when caregivers knew the diagnosis of more severe GDM and treated it accordingly, macrosomia was reduced but cesarean sections were still performed at a greater rate than in the nondiabetic population; these cesarean sections were not confined to the macrosomic fetuses. It could be concluded that the obstetricians were more likely to intervene because of their concerns regarding macrosomia and shoulder dystocia, which were brought about by the caregivers' knowledge of the diagnosis of GDM.

Postpartum Management

Patients with gestational diabetes are prone to developing type 2 diabetes later in life. In one follow-up study (6), nearly 40% of former GDMs had been diagnosed with diabetes within 20 years of their index pregnancy. Diagnostic criteria for GDM are not too dissimilar from those for prediabetes in nonpregnant individuals (Table 3), so it is not too surprising that many women with GDM will have prediabetes after their pregnancy is completed. Some will have diabetes, and it is presumed that they had this condition before pregnancy but it was not diagnosed. In a high-risk Hispanic–American population, 9% of former GDMs had type 2 diabetes when tested at 5–8 weeks postpartum; another 10% had impaired glucose tolerance (65). A systematic review of the literature (66) revealed that the cumulative incidence of type 2 diabetes after GDM increases most rapidly during the first 5 years after delivery, and then appears to level off after 10 years. For these reasons, both the ADA (36) and ACOG (34) recommend that women with GDM undergo a 75-g, 2-h OGTT at approximately the time of their 6-week checkup. Although testing for diabetes can also be performed with a measurement of fasting plasma glucose or Hb A_{1c}, the National Health and Nutrition Examination Survey data from 2005 to 2008 demonstrated that only 31% of adults with impaired fasting glucose [100–125 mg/dL (5.55–6.94 mmol/L)] had impaired glucose tolerance [2-h plasma glucose on a 75-g OGTT, 140–199 mg/dL (7.77–11.05 mmol/L)] and only 58% of adults with impaired glucose tolerance had impaired fasting glucose (67). An Hb A_{1c} above 5.7% was present in only 32% of those with impaired fasting glucose and 32% of those with impaired glucose tolerance. A study of women with previous GDM who were tested between 6 weeks and 36 months postpartum also found that Hb A_{1c} was only moderately sensitive for detecting abnormal glucose tolerance (68). Former GDM mothers are presumably still in the reproductive age and the diagnosis of prediabetes or diabetes would be important information applicable to the preconception care during future pregnancies. The OGTT is the most sensitive way to diagnose prediabetes and diabetes (67, 68). The ADA recommends that women with a history of previous GDM should have lifelong screening for diabetes and prediabetes at least every 3 years (1).

Identification of patients with prediabetes allows interventions to prevent the development of type 2 diabetes. In the Diabetes Prevention Program (69), women with previous GDM and current impaired glucose tolerance, whose fasting plasma glucose was also 95–125 mg/dL (5.27–6.94 mmol/L) and who were randomized to placebo, progressed to type 2 diabetes at a rate of 15% per year. This pro-

gression rate was reduced to 7.4% per year with intensive lifestyle intervention and 7.8% per year with metformin treatment.

Public Health Implications

As the prevalence of gestational diabetes increases, it is appropriate to ask the difficult questions regarding its overall public health impact. An understanding of what resources are required for its diagnosis and treatment and how cost-effective our efforts will be is essential. An analysis of the costs and benefits of diagnosis and treatment of mild gestational diabetes [75-g, 2-h glucose tolerance test value of 140–199 mg/dL (7.77–11.05 mmol/L)] revealed that the incremental direct inpatient and outpatient hospital cost of treating 1 case of mild gestational diabetes was A\$539.85 (Australian dollars), and the additional charges incurred by the patient's family were A\$65.21 (70). For every 100 cases of gestational diabetes that were identified and treated, 2.2 fewer babies experienced serious perinatal complications (defined as death, shoulder dystocia, bone fracture, and nerve palsy), and 1 fewer babies experienced perinatal death. The incremental cost per serious perinatal complication prevented was A\$27 503. There is great concern that the new recommendations from IADPSG/ADA may increase healthcare costs without improving the health of our population (71). A Canadian randomized trial (72) revealed that the per patient direct costs of screening and testing would be greater (Can\$108.38 [Canadian dollars]) with a 1-step approach using the WHO criteria (16) than with 2-step protocols utilizing either the NDDG-recommended (11) 100-g, 3-h OGTT criteria (Can\$91.61) or the Canadian Diabetes Association (73) criteria (Can\$89.03). In this randomized trial the investigators did not test the new IADPSG/ADA criteria (1). The prevalence of

gestational diabetes was similar (3.6%–3.7%) in each of the 3 groups. Assuming that the prevalence of GDM by the new ADA criteria would be in the 16% range, the cost per case of GDM diagnosed would presumably fall from Can\$3010 to Can\$677, and in that sense the ADA 1-step approach would be considerably more cost-effective than either 2-step approach. A decision analysis model (74) was used to compared no screening with the current ACOG approach (13) and the IADPSG/ADA approach (1). Compared to no screening, the IADPSG/ADA strategy was equally as cost-effective as the current ACOG strategy only if treatment included postdelivery care, which reduces the incidence of subsequent diabetes. It is to be expected that more information about public health implications will become available if and when the new criteria are more widely adopted.

Regardless of the criteria used, gestational diabetes is increasing in prevalence around the world in parallel with the increasing prevalence of obesity and type 2 diabetes. All of these trends will no doubt stress the healthcare systems both in the US and abroad. Hopefully, more efficient and more scientifically based approaches to diagnosis and treatment will evolve to keep up with demands. Ultimately, prevention must be the goal.

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