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Pregestational Diabetes Mellitus

Pregestational diabetes mellitus represents one of the most challenging medical complications of pregnancy because of the need for frequent monitoring and adjustment of medications as well as the potential for maternal and fetal complications. This document provides an overview of the current understanding of pregestational diabetes mellitus and suggests management guidelines during pregnancy. Because few well-designed studies have been performed, many of the guidelines are based on expert and consensus opinion. This document has been updated to reflect current data on pregestational diabetes. This Practice Bulletin is updated with summary information to counsel and manage women with pregestational diabetes before and during pregnancy, more recent literature reflecting experience with continuous subcutaneous insulin infusion during pregnancy, an expanded section on the role of oral hypoglycemic agents in pregnancy, and the option of long-acting reversible contraception during the postpartum period.

Background

Definition and Prevalence

An estimated 14.9 million women in the United States have diabetes mellitus (1). The prevalence of diabetes mellitus in women of reproductive age has been reported to be from 3.1% to 6.8%, with pregestational diabetes observed in 1–2% of all pregnancies (2–4). Type 1 pregestational diabetes mellitus is characterized by an autoimmune process that destroys the pancreatic β cells, which leads to onset earlier in life, the need for insulin therapy, and the potential development of vascular, renal, and neuropathic complications. In contrast, type 2 diabetes mellitus, which has become the most common form of pregestational diabetes, is characterized by onset later in life, peripheral insulin resistance, relative insulin deficiency, and obesity. Although 90% of cases of diabetes encountered during pregnancy are gestational diabetes mellitus, more than one half of these women develop type 2 diabetes mellitus later in life. There are racial and ethnic disparities in women with pregestational diabetes. One study found higher rates in black, Native American, and Hispanic women and lower rates in non-Hispanic white and Asian women (4). Interestingly, type 1 and type 2 diabetes have both increased in recent years, and there are variations by race and ethnicity; non-Hispanic white women have had the greatest increase in type 1 diabetes, and Hispanic women have experienced the greatest increase in type 2 diabetes (5). The increasing incidence of type 2 pregestational diabetes mellitus is caused, in part, by increasing obesity in the United States (6, 7). Historically, any time diabetes was diagnosed during pregnancy, it was considered gestational diabetes. However, if diabetes is diagnosed in the first trimester or early second trimester with the standard diagnostic criteria of a hemoglobin A_{1C} (HbA_{1C}) of 6.5% or greater, a fasting plasma glucose of 126 mg/dL or greater, or a 2-hour glucose of 200 mg/dL or greater on a 75-g oral glucose tolerance test, it is considered pregestational diabetes (8). There is little or no guidance regarding the diagnosis of pregestational diabetes in the late second trimester or third trimester.

Management of Diabetes During Pregnancy

Pregnancy is broadly characterized by increased insulin resistance. Because placental-produced hormones increase

through the second trimester and much of the third trimester, insulin resistance is greatest in the third trimester. This physiologic change is similar to the pathophysiology of type 2 diabetes and, thus, can increase insulin requirements and worsen glycemic control in women with either type 1 or type 2 diabetes (9). The increase in insulin resistance is primarily the result of the effects of several placental hormones, including human chorionic somatomammotropin (human placental lactogen), progesterone, prolactin, placental growth hormone, and cortisol. Additionally, tumor necrosis factor α and leptin have been implicated as contributors to the insulin resistant state of pregnancy and resultant maternal hyperglycemia (10, 11). The one exception to this is the late first trimester when relatively higher levels of estrogen may transiently enhance insulin sensitivity and increase the risk of maternal hypoglycemia especially when associated with nausea and vomiting.

Maternal glucose control should be maintained near physiologic levels before and throughout pregnancy to decrease the likelihood of complications of hyperglycemia, including spontaneous abortion, fetal malformation, fetal macrosomia, fetal death, and neonatal morbidity. The management of pregestational diabetes in pregnancy focuses on optimal glucose control, which is achieved using a careful combination of diet, exercise, and medical therapy (12–16). Self-monitoring of blood glucose using fingerstick glucose values recorded in glucose logs are commonly reviewed at least every 1–2 weeks during the first two trimesters and weekly after 24–28 weeks of gestation in order to adapt the treatment regimen to fluctuating insulin needs. In someone with excellent control, this can be individualized.

Similar to the management of gestational diabetes mellitus and diabetes mellitus in nonpregnant individuals, medical nutrition therapy with a carbohydrate-controlled diet is important (17). When possible, having a registered dietitian or certified diabetes educator involved in nutritional counseling is beneficial (18). Because of the physiologic changes that occur during pregnancy, caloric requirements are increased by approximately an additional 300 kcal/day during the second and third trimesters (19). Although the optimal dietary composition for pregnancy is unknown, wholesome food choices (including 40–50% from complex, high-fiber carbohydrates, 15–30% from protein, and 20–35% from primarily unsaturated fats) are commonly advised (20). Generally, the dietary approach to glycemic control is focused on careful carbohydrate counting and allocation of appropriate ratios of carbohydrates to meals and snacks. For example, typical carbohydrate allocation ranges might be 30–45 g at breakfast, 45–60 g at lunch and dinner, and 15-g snacks approximately 2–3 hours after each meal. Carbohydrate counting increases dietary flexibility and insulin dose can be tailored to the planned carbohydrate intake. Rather than simple carbohydrates, complex carbohydrates are recommended because they are digested more slowly and are less likely to produce significant postprandial hyperglycemia (21). It is thought that artificial sweeteners may be safely used in moderate amounts in pregnancy, though there are no large cohort or case–control studies to support this (22). Patients should be encouraged to keep a log of food intake with the specific carbohydrate counts so that this information can be correlated with insulin dosages, exercise, and glucose values.

Most insulin used in the treatment of pregestational diabetes mellitus is biosynthetic human insulin. Insulin requirements will increase throughout pregnancy, most markedly in the period between 28 weeks and 32 weeks of gestation (23). On average, insulin needs increase from a range of 0.7–0.8 units/kg actual body weight/day in the first trimester, to 0.8–1 units/kg/day in the second trimester, to 0.9–1.2 units/kg/day in the third trimester (14, 24). The goal of therapy is to achieve euglycemia in pregnancy without significant hypoglycemia because acute episodes of hypoglycemia can be unsafe. Glycemia goals generally include fasting and premeal glucose values of 95 mg/dL or less and either 1-hour postprandial levels of 140 mg/dL or less or 2-hour postprandial values of 120 mg/dL or less. During the night, glucose levels should not decrease to less than 60 mg/dL. Mean capillary glucose levels should be maintained at an average of 100 mg/dL (25, 26) to minimize fetal risk and complications of pregnancy (27, 28). In the second and third trimesters, an HbA_{1c} less than 6% has the lowest risk of large-for-gestational-age infants (16). Importantly, because of the association of elevated glucose values and congenital anomalies, aggressive approaches to glycemic control early in the first trimester before or during embryogenesis may reduce the risk of fetal anomalies.

Short- or rapid-acting insulin analogues (eg, insulin lispro, insulin aspart) are administered before meals to reduce glucose elevations associated with eating (29, 30) (Table 1). Although regular insulin is considered a short-acting insulin, it is not interchangeable with the rapid-acting insulin analogues. Generally, insulin lispro and insulin aspart should be used preferentially instead of regular insulin because both have a more rapid onset of action, which enables the patient to administer her insulin right before the time of a meal rather than 10–15 minutes or longer before an anticipated meal (31). Although their rapid onset of action improves compliance, patient satisfaction, and glycemic control, insulin lispro or insulin aspart can cause significant hypoglycemia if administered

Table 1. Action Profile of Commonly Used Insulins

Type	Onset of Action	Peak of Action (Hours)	Duration of Action (Hours)
Insulin lispro	1–15 minutes	1–2	4–5
Insulin aspart	1–15 minutes	1–2	4–5
Regular insulin	30–60 minutes	2–4	6–8
Isophane insulin suspension (NPH insulin)	1–3 hours	5–7	13–18
Insulin glargine	1–2 hours	No peak	24
Insulin detemir	1–3 hours	Minimal peak at 8–10 hours	18–26

Abbreviation: NPH, neutral protamine Hagedorn.

Modified from Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstet Gynecol 2003;102:857–68.

inappropriately. However, it appears that, generally, there are fewer hypoglycemic episodes with lispro or aspart than with regular insulin (32). Because of improved outcomes and compliance when used subcutaneously, lispro and aspart insulin generally are preferred over regular insulin (33). A recent European study found a lower rate of congenital anomalies in fetuses when women were treated with insulin analogues, particularly the short acting agents, versus human insulin alone (34).

Longer acting or basal insulins (eg, neutral protamine Hagedorn [NPH], glargine, or detemir) are used to maintain euglycemia between meals and in the fasting state (Table 1). Usually, NPH is given before breakfast with a rapid-acting insulin and before the evening meal or at bedtime (29, 30). Bedtime administration is preferred because an injection given with the evening meal may increase the risks of nocturnal hypoglycemia.

Glargine and detemir are long-acting human insulin analogues produced with recombinant DNA. The absorption of these analogues is delayed, which creates a steady basal insulin state with minimal peak and generally a 24-hour duration (35). A meta-analysis from 331 pregnancies with glargine exposure showed no significant differences in maternal or neonatal outcomes between use of glargine and NPH during pregnancy (36). Detemir received approval from the U.S. Food and Drug Administration for reclassification to pregnancy category B from category C in 2012 based on a randomized trial that compared detemir to NPH in more than 300 pregnant women with type 1 diabetes mellitus. The study showed that detemir was noninferior to NPH in lowering HbA_{1c} and preventing hypoglycemic episodes (37). A retrospective study of singleton pregnancies in women with type 1 diabetes who used either detemir or glargine from the start of the pregnancy showed comparable pregnancy outcomes and safety (38). There are few studies of these agents in pregnant women with type 2 diabetes, but the safety data should be similar, and they can be used when deemed to be clinically indicated. One recent study found lower rates of congenital anomalies in women treated with insulin analogues (34).

Frequent self-monitoring of blood glucose is assumed to be important to achieve euglycemia without significant hypoglycemia during pregnancy. However, no particular approach to blood glucose monitoring has been demonstrated to be superior to any other (39). A common approach is to check capillary glucose levels using a glucose meter in the fasting state, 1 or 2 hours after each meal, and before bed. If insulin dose is based on premeal values, premeal assessment should be integrated as well. Blood glucose meters indicate plasma glucose levels. Fasting glucose levels reflect the action of overnight basal insulin, whereas glucose concentrations before meals indicate daytime basal insulin activity (29). Levels after meals reveal the effect of the meal and recent insulin doses. In selected patients, especially those on insulin pumps, glucose determinations at 2–3 AM may help detect nocturnal hypoglycemia, which can then cause elevated fasting blood glucose values through excessive carbohydrate intake to correct the low glucose level or through the Somogyi effect. Nocturnal hypoglycemia is caused by excessive basal insulin or an inadequate bedtime snack. Nocturnal hyperglycemia may be due to insufficient basal insulin or pump failure.

Increasingly, continuous glucose monitors are used to assess glucose control in individuals with diabetes mellitus. Continuous glucose monitors measure the glucose content of interstitial fluid through a needle

sensor inserted subcutaneously. Occasional fingersticks are still necessary for calibration. A recent trial found that in comparison to offspring of pregnant women randomized to usual care with capillary blood glucose monitoring, the offspring of pregnant women randomized to continuous glucose monitors were less likely to experience neonatal hypoglycemia, be large for gestational age, or be admitted to the neonatal intensive care unit (40). Alternatively, another recent trial of continuous glucose monitoring found no difference in fetal macrosomia but did demonstrate lower rates of preeclampsia in women randomized to continuous glucose monitors (41). Closed loop systems that take the information from a continuous glucose monitor and actually change the insulin dose in an insulin pump are now available and, in one small case series in pregnant women, showed some promise with fewer hypoglycemic episodes (42).

Insulin doses generally are changed in response to a pattern of hyperglycemia or hypoglycemia. Hemoglobin A_{1c} may be used as an integrated measure of glucose but may not fully capture hyperglycemia and hypoglycemia, therefore, it should be used as a secondary measure of glycemic control. Given the alteration in red blood cell turnover and physiologic changes in glucose parameters, HbA_{1c} levels may need to be monitored more frequently in pregnancy than in the nonpregnant population (eg, monthly).

Because of the risk of diabetic ketoacidosis (DKA), women with pregestational diabetes should check urine ketones when their glucose levels exceed 200 mg/dL and immediately report positive test results to their health care teams. Historically, it was thought that women with type 2 diabetes could not develop DKA, but now there is evidence to the contrary, so these women should follow these recommendations just as women with type 1 diabetes do (43, 44). In particular, it appears that African-American women may more commonly present with ketosis-prone type 2 diabetes (45).

Even with meticulous monitoring, hypoglycemia is more frequent in pregnancy than at other times, particularly in women with type 1 pregestational diabetes mellitus. Patients should be questioned to determine if they can recognize when their glucose levels decrease to less than 60 mg/dL. Patients and their families should be taught how to respond quickly and appropriately to hypoglycemia. The best approach is to have glucose tablets available at all times. A drink of fruit juice or milk can be used if immediately available. In general, patients should be instructed to consume 15 g of carbohydrate and then wait 15 minutes for their glucose level to correct before taking in additional glucose (46). Patients should have glucagon on hand for severe hypoglycemia and loss of consciousness. Glucagon administration can be performed by nonmedical personnel, including family members, who should know where glucagon is kept and how to administer it. Patients also should wear a medical bracelet or necklace that indicates they have diabetes (47).

Maternal Morbidity

Pregnancy has been associated with exacerbation of diabetes-related complications, particularly retinopathy and nephropathy (48, 49). Poorly controlled pregestational diabetes mellitus leads to serious end-organ damage that may eventually become life threatening. In turn, preexisting diabetes-related end-organ disease may have deleterious effects on obstetric outcomes.

Diabetic retinopathy is the leading cause of blindness in the United States in individuals aged 24–74 years and is classified as nonproliferative retinopathy (which is characterized by retinal microaneurysms and dot-blot hemorrhages) and proliferative retinopathy (which is marked by neovascularization) (50). It appears that retinopathy commonly progresses in pregnancy. In two studies, retinopathy progression is seen in about one fourth of patients and associated with chronic hypertension (51, 52). In another study, one third of women experienced retinopathy progression that was associated with the rapid institution of strict glycemic control early in pregnancy and hypertensive disorders of pregnancy (53). This is consistent with nonpregnant diabetic individuals who experience progression with improved glycemic control, although the long-term benefits of glycemic control appear to outweigh the harms (54). Proliferative retinopathy is best treated with pan-retinal photocoagulation, ideally before the patient becomes pregnant (55). Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and should be monitored closely throughout pregnancy at the physician's discretion depending on the results of the first trimester examination (56).

Diabetic nephropathy is estimated to be present in 5–10% of diabetic pregnancies (57–59). Most studies have failed to demonstrate permanent deterioration in renal function associated with pregnancy in women with mild-to-moderate diabetic nephropathy (60, 61). However, progression to end stage renal disease has been reported in women with serum creatinine levels exceeding 1.5 mg/dL or severe proteinuria (more than 3 g per 24 hours) at baseline (48, 57). Women with preexisting diabetic nephropathy are at significantly higher risk for several adverse obstetric complications, including hypertensive disorders, uteroplacental insufficiency, and iatrogenic preterm birth because of worsening renal function (59, 62, 63). Before becoming pregnant, a baseline evaluation of renal function by serum creatinine and

assessment of urinary protein excretion (urine protein-to-creatinine ratio or 24-hour protein excretion) are recommended with follow-up measurements at regular intervals throughout pregnancy (64). If a 24-hour collection for creatinine clearance has not been done in the year before pregnancy, it is common for this assessment to be done early in pregnancy to establish a baseline.

Chronic hypertension is observed in approximately 5–10% of pregnant patients with pregestational diabetes mellitus (65). Hypertension, especially in the presence of nephropathy, increases the risk of preeclampsia, uteroplacental insufficiency, and stillbirth (66). At least one study found that tighter control of blood pressures in women with type 1 diabetes may be beneficial (67). Ideally, hypertension should be controlled before pregnancy. In nonpregnant patients, treatment is likely to include an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. Because of their adverse fetal effects, these medications should be discontinued before becoming pregnant and should not be used during pregnancy (68).

Pregestational diabetes is a risk factor for acute myocardial infarction during pregnancy (69, 70). Symptomatic coronary artery disease in women with pregestational diabetes mellitus is most commonly seen in those with long-standing disease, nephropathy, and hypertension (71). Preexisting coronary artery disease may be a contraindication to pregnancy because of the pregnancy-associated hemodynamic changes that may result in myocardial infarction and death (72). It is common to assess women with pregestational diabetes with a baseline electrocardiogram, particularly in those with longstanding diabetes (eg, Class D) or any vascular complications.

Diabetic neuropathy is not well-studied in pregnancy but may manifest as recalcitrant nausea and vomiting secondary to gastroparesis (73). It does not appear that pregnancy increases the risk of diabetic neuropathy, but it can affect the pregnancy (74, 75). Women with gastroparesis secondary to an autonomic neuropathy are at increased risk of hyperemesis and may require total parenteral nutrition during pregnancy (76). Gastroparesis affects the interaction between diet and diabetes management, further complicates the control of diabetes itself, and increases the risk of hypoglycemic episodes. In women with this diagnosis, metoclopramide, a prokinetic agent, can be used in pregnancy.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a life-threatening emergency observed in 5–10% of all pregnancies complicated by pregestational diabetes mellitus (77–79). Because diabetic ketoacidosis is caused by an absolute or relative insulin deficiency, it is most commonly observed in women with type 1 pregestational diabetes mellitus, but it also can be seen in those with type 2 diabetes. Enhanced insulin resistance probably plays a role in the higher incidence of diabetic ketoacidosis observed during pregnancy, as well as the propensity for diabetic ketoacidosis to develop more rapidly and at less severe levels of hyperglycemia and even with normal glucose levels (80). Common risk factors for diabetic ketoacidosis during pregnancy include new onset diabetes; infections, such as influenza and urinary tract infection; poor patient compliance; insulin pump failure; and treatment with β-mimetic tocolytic medications and antenatal corticosteroids (81).

Typical clinical presentation of diabetic ketoacidosis in pregnancy includes abdominal pain, nausea and vomiting, and altered sensorium. Abnormal laboratory findings commonly include a low arterial pH (less than 7.3), a low serum bicarbonate level (less than 15 mEq/L), an elevated anion gap, and positive serum ketones (65). Continuous fetal heart rate monitoring commonly demonstrates minimal variability and may have late decelerations in the setting of contractions. However, this pattern usually resolves as the maternal condition improves, and delivery is rarely indicated.

For laboratory assessment, obtain arterial blood gases to document degree of acidosis present, measure glucose (in addition to hourly capillary blood glucose ketones), and serum ketones electrolyte levels obtained at 1- to 2-hour intervals. Treatment regimens are based on aggressive hydration and intravenous insulin (see Box 1). As opposed to subcutaneous insulin, there appears to be no advantage to the insulin lispro or insulin aspart as compared with regular insulin, which is the most common form of intravenous insulin. Because hypoglycemia and hypokalemia are frequent complications of diabetic ketoacidosis therapy, glucose and potassium concentrations should be monitored closely. Maternal mortality is rare, and many of these cases resolve quickly with appropriate medical management (79). Historically, fetal mortality has ranged from 10% to 35% of cases, but mortality has decreased considerably in recent years (78, 79, 82, 83).

Perinatal Morbidity and Mortality

The perinatal mortality rate in pregnancies complicated by pregestational diabetes mellitus decreased markedly in the twentieth century (84), and one study from the United Kingdom found that it has continued to decrease (85). Overall perinatal outcomes are best when glucose control is achieved before a woman becomes pregnant and in the absence of maternal vascular or hypertensive disease (13, 86, 87). The relationship between maternal end-organ disease and adverse pregnancy outcome was first

Box 1. Management of Diabetic Ketoacidosis During Pregnancy

Intravenous Fluids

Isotonic sodium chloride is used, with total replacement of 4–6 L in the first 12 hr.

- Insert intravenous catheters: Maintain hourly flow sheet for fluids and electrolytes, potassium, insulin, and laboratory results.
- Administer normal saline (0.9% NaCl) at 1–2 L/h for the first hour.
- Infuse normal saline at 250–500 mL/h depending on hydration state (8 hr). If serum sodium is elevated, use half-normal saline (0.45% NaCl).
- When plasma or serum glucose reaches 200 mg/dL, change to 5% dextrose with 0.45% NaCl at 150–250 mL/hr.
- After 8 hr, use half-normal saline at 125 mL/hr.

Potassium

Establish adequate renal function (urine output ~50 mL/hr).

- If serum potassium is <3.3 mEq/L, hold insulin and give 20–30 mEq K^+/h until K^+ is >3.3 mEq/L or is being corrected.
- If serum K^+ is >3.3 mEq/L but <5.3 mEq/L, give 20–30 mEq K^+ in each liter of IV fluid to keep serum K^+ between 4 and 5 mEq/L.
- If serum K^+ is >5.3 mEq/L, do not give K^+ but check serum K^+ every 2 hr.

Insulin

Use regular insulin intravenously.

- Consider a loading dose of 0.1–0.2 units/kg as an IV bolus depending on plasma glucose.
- Begin continuous insulin infusion at 0.1 units/kg/hr.
- If plasma or serum glucose does not fall by 50–70 mg/dL in the first hour, double the insulin infusion every hour until a steady glucose decline is achieved.
- When plasma or serum glucose reaches 200 mg/dL, reduce insulin infusion to 0.05–0.1 U/kg/hr.
- Keep plasma or serum glucose between 100 and 150 mg/dL until resolution of diabetic ketoacidosis.

Bicarbonate

Assess need, and provide based on pH.

- pH >7.0: No HCO_3 is needed.
- pH is 6.9–7.0: Dilute $NaHCO_3$ (50 mmol) in 200 mL H_2O with 10 mEq KCl and infuse over 1 hr. Repeat $NaHCO_3$ administration every 2 hr until pH is 7.0. Monitor serum K^+.
- pH <6.9–7.0: Dilute $NaHCO_3$ (100 mmol) in 400 mL H_2O with 20 mEq KCl and infuse for 2 hr. Repeat $NaHCO_3$ administration every 2 hr until pH is 7.0. Monitor serum K^+.

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described by a study that used a classification system that attempted to predict perinatal risk according to the age at onset of diabetes; duration of diabetes; and the presence of vasculopathy, renal (Class F), proliferative retinal (Class R), and cardiac (Class H) complications (88, 89). This system still appears to be valuable in predicting pregnancy complications, with those who have had diabetes for a longer time having a higher rate of problems (87, 90). Complications also are more significant in the presence of chronic hypertension (90, 91).

Major congenital anomalies are the leading cause of perinatal mortality in pregnancies complicated by pregestational diabetes mellitus, and they occur in 6–12% of infants of women with diabetes (92–94). Studies have linked the increased rate of congenital malformations, as well as spontaneous abortion, to poor prepregnancy glucose control (85, 95, 96). Hyperglycemia during organogenesis (5–8 weeks after the last menstrual period) is thought to play a critical role in abnormal development (97, 98), and in animal models has been shown to affect gene expression (99, 100). There is a concern that the increase in hypoglycemic episodes seen with tighter glycemic control may have a negative effect on the pregnancy, but clinical studies have not demonstrated an

association between hypoglycemic episodes and adverse fetal outcomes (101, 102). Glycosylated hemoglobin levels correlate directly with the frequency of anomalies. In classic studies, a level less than 1% higher than the upper limit of normal, or approximately 5–6%, is associated with a fetal malformation rate close to that observed in normal pregnancies (2–3%). However, an HbA_{1c} concentration near 10% is associated with a fetal anomaly rate of 20–25% (92, 103). More recent studies support these findings with higher rates of all anomalies and cardiac anomalies in women with elevated HbA_{1c} levels (104–106). Complex cardiac defects; central nervous system anomalies, such as anencephaly and spina bifida; and skeletal malformations, including sacral agenesis, are most common (26, 93, 94, 107, 108).

Women with pregestational diabetes mellitus, particularly those who receive scant or late prenatal care (109), more often experience adverse perinatal outcomes (26). Stillbirths are higher in women with diabetes and are associated with higher HbA_{1c} values (110) and with delayed or absent prenatal care (109). Facilitated diffusion of glucose across the placenta leads to transient fetal hyperglycemia. Subsequent stimulation of the fetal pancreatic β cells results in fetal hyperinsulinemia with several fetal and neonatal consequences. Because insulin is a potent growth hormone, excessive fetal growth occurs, particularly in adipose tissue (111). The fetus of a woman with poorly controlled diabetes is at increased risk of fetal death and is more likely to weigh more than 4,000 g with a disproportionate concentration of fat around the shoulders and chest, which more than doubles the risk of shoulder dystocia at vaginal delivery (26). Fetal macrosomia is strongly associated with HbA_{1c} values in the pregnancy (112), and there is a suggestion that elevated postprandial values may be most closely related to the risk of macrosomia (113, 114).

The neonatal consequences of poorly controlled pregestational diabetes mellitus during pregnancy include profound hypoglycemia, a higher rate of respiratory distress syndrome, polycythemia, organomegaly, electrolyte disturbances, and hyperbilirubinemia. Long-term outcomes for offspring of women with type 1 diabetes mellitus include obesity and carbohydrate intolerance (115–118). These long-term effects are likely due to fetal programming and lead to increases in metabolic syndrome and cardiac disease in adult life (119). In one study, there was an association between higher HbA_{1c} in women and lower primary school achievement in their offspring, but the exact causal mechanism of this finding is unclear (120). In a systematic review and meta-analysis of 33 observational studies, pregnant women with type 2 diabetes mellitus were found to have similar rates of congenital malformations, stillbirth, and neonatal mortality, and increased rates of perinatal mortality compared with pregnant women with type 1 diabetes mellitus (83). A recent study also demonstrated an association between pregestational diabetes mellitus in pregnancy and subsequent autism spectrum disorder in these children with adjusted hazard ratios of 2.33 (95% CI, 1.29–4.21) for type 1 diabetes mellitus and 1.39 (95% CI, 1.18–1.62) for type 2 diabetes mellitus (121).

Obstetric Complications

Women with pregestational diabetes mellitus have a greater risk of a wide range of obstetric complications. For these women, the rate of primary cesarean delivery is increased (65, 122); spontaneous preterm labor appears to be more common (123, 124); and for some women—particularly those with poor glycemic control—the increased incidence of polyhydramnios may be a cause of preterm labor (65). Improvements in HbA_{1c} from greater than 7% to 6–7% to less than 6% demonstrate better obstetric outcomes (28).

Preeclampsia is observed in 15–20% of pregnancies complicated by type 1 diabetes mellitus without nephropathy and in approximately 50% with nephropathy (90, 123, 125). Preeclampsia is more likely to occur in women with hypertension and poor glucose control (57, 58, 62, 90, 91).

Clinical Considerations and Recommendations

▶ *Is there a role for prepregnancy counseling?*

Prepregnancy counseling for women with pregestational diabetes mellitus has been reported to be beneficial and cost effective and should be encouraged (2, 126). Because less than one third of women with diabetes mellitus seek prepregnancy counseling (127), any visit to a health care provider should be used as an opportunity to review the aspects of diabetes management during pregnancy and if a pregnancy is not being planned, opportunities for contraception. Prepregnancy counseling should focus on the importance of euglycemic control before pregnancy, as well as the adverse obstetric and maternal outcomes that can result from poorly controlled diabetes. The specific risk of fetal embryopathy related to glycemic control is an important outcome to counsel patients about in order to emphasize the importance of prepregnancy glycemic control (128). Additionally, because the recommended glucose levels are usually lower in pregnancy and glycemic management changes frequently throughout gestation because of the effect of placental hormones, these differences should be discussed with patients who are considering pregnancy. Evaluating for underlying vasculopathy

is generally advised, including a retinal examination by an ophthalmologist, a 24-hour urine collection for protein excretion and creatinine clearance, lipid assessment, and electrocardiography. Because up to 40% of young women with type 1 diabetes mellitus also may have thyroid dysfunction, thyroid function studies should be obtained as well (129). At least 400 micrograms of folic acid should be prescribed to all women contemplating pregnancy (130). This is particularly important in women with diabetes given their increased risk of neural tube defects. Higher doses of folic acid may be beneficial in high-risk patients and doses of 800 micrograms or 1 mg have been prescribed, especially in the presence of other risk factors for neural tube defects. However, there is not specific, prospective evidence that supports this recommendation. Additionally, because pregestational diabetes is considered a high-risk factor for the development of preeclampsia, the American College of Obstetricians and Gynecologists recommends that low-dose aspirin (81 mg/day) prophylaxis should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continued until delivery (131) (Box 2).

▶ *Is there a role for continuous subcutaneous insulin infusion during pregnancy?*

With continuous subcutaneous insulin infusion therapy (the insulin pump), insulin can be delivered in a pattern that closely resembles physiologic insulin secretion (132–134). A rapid-acting insulin, such as insulin lispro, is most appropriate for infusion pumps (135). Usually 50–60% of the total daily dose is administered at a continuous basal rate; boluses before meals and snacks comprise the rest (40–50%) of the total daily dose (134). Patients who use continuous subcutaneous insulin infusion must be highly motivated and compliant. Potential advantages of the insulin pump include a decrease in episodes of severe hypoglycemia, better control of hyperglycemia, and a more flexible lifestyle. Although improved glycemic control had been demonstrated in a systematic review in individuals with type 1 diabetes (136, 137), it was only recently demonstrated in individuals with type 2 diabetes (138, 139). Potential disadvantages include the increased cost of the pump and pump supplies. In addition, adverse events with the insulin pump occur approximately three times per 1 year of use and of these approximately 38% are pump malfunctions (140). If the delivery of insulin is interrupted or impaired by battery failure or infection at the infusion site, DKA may develop rapidly; 9.8% of pump adverse events lead to high ketones or DKA (140, 141). Despite potential advantages and modest evidence that glycemic control may be improved (142, 143), in a recent meta-analysis of five small randomized trials of the insulin

Box 2. Counseling and Management of Women with Pregestational Diabetes Before and During Pregnancy

Prepregnancy visit

- Counsel about potential complications in pregnancy including fetal anomalies, preterm delivery, preeclampsia, fetal macrosomia, mode of delivery, neonatal complications, hyperglycemia, worsening diabetic retinopathy and nephropathy
- Evaluate for baseline complications including hypertension, nephropathy, retinopathy, and cardiovascular disease
- Ensure adequate contraception if not planning pregnancy immediately
- Plan to optimize HbA_{1c} (less than 6.0%)
- Discuss plan to start increased folic acid when attempting to get pregnant

First trimester

- Prenatal labs/tests include HbA_{1c}, TSH, 24-hour urine if no baseline, electrocardiogram
- Evaluation by ophthalmologist, dietitian, possibly endocrinologist, cardiologist or nephrologist
- Regular ongoing assessment of blood glucose values

Second trimester

- Start low-dose aspirin 12–28 weeks of gestation (optimally before 16 weeks of gestation)
- Ultrasonography including a detailed anatomical survey
- Consider fetal echocardiography

Third trimester

- Evaluate fetal growth
- Start low-dose aspirin by 28 weeks of gestation if not started in the second trimester
- Fetal monitoring (nonstress test, nonstress test or amniotic fluid index, biophysical profile)

Delivery

- If estimated fetal weight 4,500 g or greater, consider cesarean delivery
- Without vascular complications and with well-controlled blood glucose levels, deliver at 39 0/7 weeks to 39 6/7 weeks of gestation
- In women with vascular complications or poorly controlled blood glucose, consider delivery at 36 0/7 weeks to 38 6/7 weeks of gestation, and in rare cases, even earlier

Abbreviations: HbA_{1C}, hemoglobin A_{1C}; TSH, thyroid-stimulating hormone.

pump versus injectable insulin, there were no statistically significant differences in outcomes (144). Thus, in women who have euglycemia with multiple dose injectable insulin, they can be maintained on that insulin dosage approach. However, in those women without good control, conversion to a subcutaneous insulin pump before pregnancy may improve glycemic control, particularly in those with type 1 diabetes (136).

▶ *Is there a role for oral hypoglycemic agents in pregnancy?*

Oral hypoglycemic agents are not generally used in patients with type 1 diabetes. Although they are used widely in the treatment of nonpregnant patients with type 2 diabetes, they have not been well studied in the treatment of women with pregestational diabetes during pregnancy. However, although there are little data on women with pregestational diabetes, glyburide (a second-generation sulfonylurea) and metformin (a biguanide) have been used to treat gestational diabetes in the third trimester. Glyburide acts to increase insulin release from the beta cells of the pancreas, and its onset of action is approximately 4 hours and its duration of action is approximately 10 hours. Initial studies of glyburide demonstrated no difference when compared with insulin, but recent meta-analyses have identified some adverse neonatal outcomes in women with gestational diabetes managed on glyburide (145–148). Metformin, a category B drug, has been used as a hypoglycemic agent and a treatment for infertility in polycystic ovary syndrome (149, 150). In a randomized trial of 751 women with gestational diabetes mellitus treated between 20 weeks and 33 weeks of gestation, metformin (alone or with supplemental insulin) was not associated with increased diabetes-related perinatal complications compared with insulin, with no significant differences in glucose control (151). A recent network meta-analysis found that metformin had the greatest probability of reducing complications in women with gestational diabetes compared with glyburide and insulin (152). In a recent cohort study, metformin was associated with congenital anomalies compared with a population with no metformin use (153). However, when the analysis was stratified between those on metformin for diabetes versus other indications, it was only the women with diabetes who had an increased risk of congenital anomalies (odds ratio, −3.95; 95% CI, 1.77–9.41), not the other indications (odds ratio, −0.83; 95% CI, 0.18–2.81). In another recent study of the use of oral agents by women with pregestational diabetes, there was no increase in the risk of miscarriage, anomalies, or stillbirth in women who used oral hypoglycemic medications during pregnancy (154). Similarly, a recent case–control study found no statistically significant increased risk of nongenetic congenital anomalies in women exposed to metformin in the first trimester (155). Despite increasing data on metformin's use in pregnancy, there is limited long-term safety information on the infants of these women. The use of all oral hypoglycemic agents for control of pregestational type 2 diabetes mellitus during pregnancy should be limited and individualized until data regarding the safety and efficacy of these drugs become available. Thus, insulin is the preferred treatment for pregestational diabetes in pregnancy not controlled by diet and exercise. Women with type 2 diabetes who are stable on oral agents before pregnancy and become pregnant should be counseled that insulin is the preferred therapy in pregnancy and that oral antidiabetic medications are not approved by the U.S. FDA for treatment of diabetes during pregnancy because they cross the placenta and lack long-term neonatal safety data. For those women with type 2 diabetes who decline insulin, those who their obstetricians or obstetric care providers believe will be unable to safely administer insulin, or those who cannot afford insulin, metformin (and rarely glyburide) is a reasonable alternative choice in the context of discussing with the patient the limitations of the safety data and a high rate of treatment failure, which requires insulin supplementation (156).

▶ *What fetal assessment is appropriate in women with pregestational diabetes mellitus?*

An ultrasound examination early in gestation can be used not only to demonstrate fetal viability but to accurately date the pregnancy as well (157). Most major anomalies can be detected at 18–20 weeks of gestation by a detailed ultrasound examination that includes a carefully performed assessment of fetal cardiac structures, including the great vessels (158, 159). Echocardiography may be indicated in cases of suspected cardiac defects or when the fetal heart and great vessels cannot be visualized adequately by routine anatomical ultrasonography or in patients at increased risk of cardiac anomalies (eg, elevated HbA_{1C}) (105, 160). Because fetal echocardiography is not routinely available in all settings, some practices may choose to refer for this evaluation only in those with increased risk, whereas other practices will obtain the fetal echo routinely in all women with pregestational diabetes. Neonates delivered to women with pregestational diabetes are at increased risk of macrosomia and, depending on concomitant risk factors, also may be at increased risk of fetal growth restriction (91, 161). Certainly, screening with fundal height measurements is recommended, but it is also common for ultrasonography to be used to assess fetal weight in the third trimester. If abnormal fetal growth is suspected, ultrasound examinations should be used to approximate fetal growth. There is no particular approach that has been demonstrated as superior to another, but

when fetal macrosomia or large for gestational age is of concern, it is common to obtain a fetal growth ultrasound examination before delivery, commonly at 34 0/7 weeks to 38 6/7 weeks of gestation. If there is a concern for fetal growth restriction, additional, earlier ultrasound examinations during the third trimester may be used.

Maternal assessment of fetal movements is a potentially simple method for monitoring fetal well-being. However, most practitioners obtain formal antenatal testing. Antepartum fetal monitoring, including the nonstress test, the biophysical profile, or the modified biophysical profile when performed at appropriate intervals (usually once or twice per week), is a valuable approach and can be used to monitor the pregnancies of women with pregestational diabetes mellitus (162–165). Initiation of testing is appropriate for most women at 32 weeks of gestation. However, testing at earlier gestational ages may be warranted in some pregnancies complicated by additional high-risk conditions. In response to a report of an increased stillbirth rate in patients with a reactive nonstress test within 1 week of delivery, twice weekly testing has been widely adopted (166); however, the optimal timing or frequency of testing has not been ascertained (167) and such testing has not been found to be specifically predictive of impending fetal demise in women with pregestational diabetes. However, if maternal glucose control deteriorates, the fetal condition may deteriorate as well, and increased testing for fetal well-being may be indicated. Doppler velocimetry of the umbilical artery may be useful in monitoring pregnancies with growth restriction (165, 168).

▶ *When, where, and how should delivery occur for women with pregestational diabetes?*

Optimal timing of delivery relies on balancing the risk of fetal death with the risks of preterm birth. Early delivery (36 0/7 weeks to 38 6/7 weeks of gestation, or even earlier) may be indicated in some patients with vasculopathy, nephropathy, poor glucose control, or a prior stillbirth (169, 170). In contrast, women with well-controlled diabetes with no other comorbidities may be managed expectantly to 39 0/7 weeks to 39 6/7 weeks of gestation as long as antenatal testing remains reassuring (171, 172). Expectant management beyond 40 0/7 weeks of gestation generally is not recommended. Delivery of women with pregestational diabetes should occur at institutions with health care providers experienced in caring for such individuals. For example, because such patients may require intravenous insulin drips and their offspring may have neonatal hypoglycemia, it is important that the patients give birth at a hospital that can provide such care.

The planned approach to delivery is often based on estimated fetal weight. Although the diagnosis of fetal macrosomia is imprecise, in order to prevent traumatic birth injury to the fetus, prophylactic cesarean delivery may be considered if the estimated fetal weight is at least 4,500 g in women with diabetes (164, 173). Although an ultrasonography estimate of fetal weight may help in this clinical decision, ultrasonography has not proved to be more accurate than clinical assessment in determining the size of the large fetus (174–176). Induction of labor in pregnant women with fetuses with suspected macrosomia has not been found to reduce birth trauma in diabetic women. Historically, there were thought to be no improvements in outcomes of pregnancies induced prophylactically with large for gestational age infants (177). Recently, in one trial and in meta-analyses that did not include women with pregestational diabetes, induction of labor in the setting of suspected large for gestational age infants was associated with a reduction in birth trauma without increasing the risk of cesarean delivery (178–180). However, before becoming routinely adopted, this practice needs further study, particularly in women with pregestational diabetes. During labor, women with pregestational diabetes generally should undergo continuous intrapartum electronic fetal monitoring and typically are excluded from consideration for intermittent auscultation (181).

Women with diabetes have a higher risk of experiencing a shoulder dystocia than women without diabetes even when controlling for birth weight (182). As such, the health care provider should have heightened awareness for shoulder dystocia in the setting of pregestational diabetes and may wish to consider other clinical factors (eg, estimated fetal weight, prolonged second stage of labor, and indication for intervention) that could modify this risk. When considering an operative vaginal delivery, one should carefully consider the relative maternal and neonatal risks. Judicious use of operative vaginal delivery is reasonable even in the presence of risk factors for shoulder dystocia.

▶ *How should glucose control be managed in the hospital and during labor?*

Health care providers generally hospitalize women with diabetes in pregnancy who have experienced frequent episodes of hyper- or hypoglycemia to improve glycemic control. In women who appear to need further education and a consistent, regimented approach to insulin delivery and diet, the current dosage regimen can be used and rapidly adjusted to improve blood glucose values. For those individuals in whom it is unclear how well the glucose values are controlled or for those whose glucose values are very high (eg, greater than 200 mg/dL), an intravenous infusion of

insulin may be started to ascertain the total daily insulin needs of the patient. Additionally, if corticosteroids are administered to accelerate lung maturation in the setting of an obstetric complication, an increased insulin requirement during the next 5 days should be anticipated, and the patient's glucose levels should be closely monitored (183).

During induction of labor, maternal glycemia can be controlled with an intravenous infusion of short-acting (commonly regular) insulin, an "insulin drip," titrated to maintain hourly readings of blood glucose levels less than 110 mg/dL (13, 25, 184) (Box 3). Avoiding intrapartum maternal hyperglycemia may prevent fetal hyperglycemia and reduce the likelihood of subsequent neonatal hypoglycemia (118). During active labor, blood glucose levels should be checked at regular intervals, generally hourly. Insulin may not be needed in women with type 2 diabetes. However, insulin is always required in those with type 1 diabetes; if patients become hypoglycemic, intravenous dextrose should be given and the insulin infusion rate reduced. Alternatively, patients who are using an insulin pump may, instead, continue their basal infusion during labor, though approaches to having patients use their pumps vary from hospital to hospital.

Box 3. Insulin Management During Labor and Delivery

- Usual dose of intermediate-acting or long-acting insulin is given at bedtime.
- Morning dose of insulin is withheld or reduced based upon the timing of admission or delivery.
- Intravenous infusion of normal saline is begun.
- Once active labor begins or glucose levels decrease to less than 70 mg/dL, the infusion is changed from saline to 5% dextrose and delivered at a rate of 100–150 cc/h (2.5 mg/kg/min) to achieve a glucose level of approximately 100 mg/dL.
- Glucose levels are checked hourly using a bedside meter allowing for adjustment in the insulin or glucose infusion rate.
- Regular (short-acting) insulin is administered by intravenous infusion at a rate of 1.25 units/h if glucose levels exceed 100 mg/dL.

Data from Coustan DR. Delivery: timing, mode, and management. In: Reece EA, Coustan DR, Gabbe SG, editors. Diabetes in women: adolescence, pregnancy, and menopause. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004; *and* Jovanovic L, Peterson CM. Management of the pregnant, insulin-dependent diabetic woman. Diabetes Care 1980;3:63–8.

Insulin requirements decrease rapidly after delivery. One third to one half of the predelivery dose of intermediate or long-acting insulin should be started after delivery as basal insulin. After starting regular food intake, one third to one half of the short or rapid acting insulin dosages can be started as well (25). Similarly, for women on insulin pumps, the continuous basal infusion generally should be reduced by approximately 50% to avoid hypoglycemic episodes.

▶ *Are special postpartum considerations necessary?*

Breastfeeding should be encouraged in women with pregestational diabetes mellitus. An additional 500 kcal/d more than the prepregnancy caloric intake is recommended with breastfeeding. Small snacks before breastfeeding may reduce the risks of hypoglycemia (185). It is common for women with diabetes mellitus to have greater difficulties with lactation than the general population, and there should be a low threshold for consultation with a lactation specialist (186).

For women who do not choose permanent contraception with tubal ligation, long-acting reversible contraception with an intrauterine device or implantable progestin are the most effective forms of contraception and should be recommended (187). The long-acting reversible contraception methods do not appear to affect glycemic control postpartum (188, 189). Limited data suggest no increased complications for intrauterine device use in women with diabetes (190, 191). Other second-line options include low-dose combination oral contraceptives for women without vasculopathy who do not smoke, whereas progestin-only pills can be prescribed for women with vascular disease (192). Barrier methods, although less effective, will not affect glucose control or vasculopathy. Because of their increased mortality risk, sterilization is commonly discussed with women with serious vasculopathy or other end-organ complications and for those who have completed their families.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

▶ Maternal glucose control should be maintained near physiologic levels before and throughout pregnancy

to decrease the likelihood of complications of hyperglycemia, including spontaneous abortion, fetal malformation, fetal macrosomia, fetal death, and neonatal morbidity.

- The dietary approach to glycemic control is focused on careful carbohydrate counting and allocation of appropriate ratios of carbohydrates to meals and snacks.
- Patients and their families should be taught how to respond quickly and appropriately to hypoglycemia.
- Prepregnancy counseling for women with pregestational diabetes mellitus has been reported to be beneficial and cost effective and should be encouraged.
- Because pregestational diabetes is considered a high-risk factor for the development of preeclampsia, the American College of Obstetricians and Gynecologists recommends that low-dose aspirin (81 mg/day) prophylaxis should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continued until delivery.
- The use of all oral hypoglycemic agents for control of pregestational type 2 diabetes mellitus during pregnancy should be limited and individualized until data regarding the safety and efficacy of these drugs become available.
- Insulin is the preferred treatment for pregestational diabetes in pregnancy not controlled by diet and exercise.
- Antepartum fetal monitoring, including the nonstress test, the biophysical profile, or the modified biophysical profile when performed at appropriate intervals (usually once or twice per week), is a valuable approach and can be used to monitor the pregnancies of women with pregestational diabetes mellitus.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Prepregnancy counseling should focus on the importance of euglycemic control before pregnancy, as well as the adverse obstetric and maternal outcomes that can result from poorly controlled diabetes.
- Although the diagnosis of fetal macrosomia is imprecise, in order to prevent traumatic birth injury to the fetus, prophylactic cesarean delivery may be considered if the estimated fetal weight is at least 4,500 g in women with diabetes.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/PregestationalDiabetes.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. These resources may change without notice.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–June 2018. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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