Diabetes and Pregnancy

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Keywords Preexisting diabetes · Gestational diabetes mellitus · Congenital anomaly · Insulin resistance · Insulin sensitivity · Normoglycemia

Key Points

- Diabetes is the most common complication affecting pregnancy
- While the macronutrient intake for women with diabetes may be different from the pregnant woman without diabetes, there is no difference in the micronutrient intake
- According to the Dietary Reference Intakes, the minimum carbohydrate intake for pregnant women with diabetes is 175 grams according to the Dietary Reference Intakes (DRI)
- Insulin is the preferred method of pharmacological therapy, if necessary, to promote optimal glucose control in pregnancy
- Either the one-step or two-step method can be used to diagnose diabetes in pregnancy
- Recent research has shown various meal plans, besides restricting the total amount of carbohydrates, may have a positive effect on maternal blood glucose levels

Introduction

Diabetes mellitus affects 29.1 million or 9.3% of the United States population, with 21 million diagnosed cases and 8.1 million undiagnosed (27.8% of people with diabetes are undiagnosed) [1]. It affects approximately 240,000 pregnancies a year, making diabetes the most common complication affecting pregnancy [2].

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The prevalence of gestational diabetes is 9.2%, which accounts for almost 90% of the cases of diabetes in pregnancy [3]. Although perinatal morbidity and mortality have decreased in the last 80 years, the prevalence of fetal complications associated with diabetes continues to be higher than in normal pregnancies. With intensive management and optimal glycemic control, prior to and throughout pregnancy, women with diabetes can reduce their risk of perinatal complications.

Historical Background

Before 1921, women with diabetes were advised to avoid pregnancy or, if conception occurred, to abort because of adverse perinatal outcomes. If the pregnancies advanced to the stage of fetal viability, the infants were often stillborn or were born with major malformations. Before the discovery of insulin in 1921, medical nutrition therapy was the primary method of management for pregnant women with diabetes, however diets were often severely restricted or nutritionally unbalanced. These dietary approaches varied from high carbohydrate-low protein, high protein-high fat, or restricted calories to brief periods of starvation [4, 5]. Alcohol was often included because of its calming effect on the mother [6].

Although insulin revolutionized diabetes management, medical nutrition therapy remained virtually unchanged in the early years after its discovery. In 1937, Priscilla White, a physician at the Joslin Diabetes Center in Boston, MA, developed a new meal plan which consisted of 30 kcal/kg body weight, 1 g protein/kg actual body weight, and 180–250 g carbohydrate with the remainder as fat [7]. Other researchers used similar meal plans to achieve maternal blood glucose control [8, 9].

During the 1950s to 1960s, health care providers were concerned with the risk of macrosomia and hypertension in pregnancy. Weight gain and sodium were restricted to less than 15 lb. (6.8 kg) and 2000 mg, respectively, in all pregnant women. After the publication of *Maternal Nutrition and the Course of Pregnancy* in 1970 [10], weight gain recommendations were increased to 22–30 lbs. (10–13.6 kg) and sodium restriction was eliminated. A comprehensive literature review found no evidence to support the restriction of weight or sodium in pregnancy. However, weight gain and sodium restrictions for pregnant women with diabetes continued until 1970, when the American Diabetes Association recommended the same regimen for pregnant women with diabetes as the non-diabetes pregnant population [11]. Today, pregnant women with and without diabetes follow the same weight gain guidelines.

Preexisting Diabetes

Pathophysiology of Normal Pregnancy

During pregnancy, the fetus receives nutrients across the placenta, including glucose, amino acids, and fatty acids, either via active transport or facilitated diffusion. Maternal glycogen storage and endogenous glucose production increase in the first

trimester. Pregnancy hormones (human placental lactogen and cortisol), estrogen, progesterone, and the constant fetal demand for glucose lower fasting maternal blood glucose levels [12, 13]. This will result in the need for additional calories. In the second trimester, fasting and postprandial glucose levels rise in response to the extra glucose required for fetal growth. Elevated hormonal levels increase insulin resistance, resulting in the production and secretion of additional insulin by the beta cells as glucose is transported across the placenta. Insulin resistance peaks by the latter part of the third trimester, characterized by a three-fold increase in insulin production and secretion. After delivery, insulin production returns to pre-pregnancy levels.

Other hormones thought to affect insulin resistance include leptin, insulin-like growth factors, relaxin, and adiponectin [14, 15]. Maternal insulin does not cross the placental barrier unless bound to insulin immunoglobulins. Fat is deposited and stored primarily in early pregnancy, then mobilized in the third trimester as fetal energy demands increase. Free fatty acids have been shown to contribute to insulin resistance in late pregnancy [16].

Type 1 Diabetes

Women with type 1 diabetes will experience elevated blood glucose levels as the lack of insulin and the rise in free fatty acids lead to the formation of ketones and beta-hydroxybutyrate. There is a risk of diabetic ketoacidosis in the absence or lack of insulin. However, women with type 1 diabetes in optimal glycemic control may experience increased insulin sensitivity and decreased insulin requirements in the first trimester. During the second and third trimesters, elevated hormonal levels increase insulin resistance and extra insulin is necessary to maintain normal maternal glycemic levels and decrease fetal complications.

Type 2 Diabetes

Type 2 diabetes is associated with impaired insulin secretion, insulin resistance, and pancreatic beta cell dysfunction. If the fetus is exposed to excessive maternal glucose, the fetal pancreas is stimulated to secrete additional insulin, which may result in macrosomic growth. Elevated maternal glycemic levels during organogenesis may increase the risk of fetal complications, including congenital anomalies. Exogenous insulin may be necessary to maintain normoglycemia with increasing insulin deficiency and insulin resistance.

Complications Associated with Preexisting Diabetes

Complications associated with diabetes can adversely affect both the woman and fetus. The rate of complications in the fetus is correlated with maternal glycemic control and the trimester of pregnancy.

Fetal

Congenital malformations and spontaneous abortions are associated with maternal hyperglycemia in the first 12 weeks of gestation. The central nervous system, heart, lungs, gastrointestinal tract, kidneys, urinary tract, skeleton, and placenta are all vulnerable to adverse effects (Table 1) [17–19]. The frequency and severity of complications decrease if maternal normoglycemia is maintained throughout pregnancy.

Second and third trimester fetal complications include macrosomia, neonatal hypoglycemia, neonatal hypocalcemia, hyperbilirubinemia, polycythemia, respiratory distress syndrome, preterm delivery, and fetal demise. With the exception of fetal demise, other complications are more closely associated with infant morbidity than mortality.

Table 1 Congenital anomalies associated with preexisting diabetes and pregnancy

Central nervous system
• Neural tube defects (e.g., anencephaly, spina bifida, hydrocephalus)
• Microcephaly
• Dandy-Walker complex
Cardiovascular
• Coarctation
• Transportation of great vessels
• Truncus arteriosus
• Aortic stenosis
• Situs inversus
Gastrointestinal
• Duodenal atresia
• Anorectal atresia
• Gastroschisis
• Anal agenesis
Genitourinary
• Renal agenesis
• Hydronephrosis
• Cystic kidneys
• Anal/rectal atresia
• Ureter duplex
Skeletal
• Caudal regression syndrome

Adapted from Gabrielli S, Pilu G, Reese EA. Prenatal diagnosis and management of congenital malformations in pregnancies complicated by diabetes. In: Reece EA, Coustan DR, Gabbe SG, eds. Diabetes in Women: Adolescence, Pregnancy and Menopause. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004:299–319; and Coustan DR. Prepregnancy counseling and management of women with preexisting diabetes or previous gestational diabetes. In: Coustan DR. ed. Medical Management of Pregnancy Complicated by Diabetes. 5th ed. Alexandria, VA: American Diabetes Association; 2013

Macrosomia, which is fetal growth greater than 4000 g regardless of gestational age, is the most common complication associated with diabetes and pregnancy [20]. Macrosomia is thought to occur if maternal glycemic levels are elevated in the third trimester. Pedersen hypothesized that maternal hyperglycemia leads to fetal hyperglycemia, which stimulates the fetal pancreas to produce excessive insulin and results in excess growth [21]. Macrosomic infants have disproportionately large fetal trunks in relation to their head size, thereby increasing the risk of difficult delivery, shoulder dystocia, brachial plexus palsy, or facial nerve injury.

Neonatal hypoglycemia is another complication associated with diabetes and pregnancy. The American Academy of Pediatrics has developed a guide to screen and manage neonatal hypoglycemia [22]. There is currently no evidence-based guideline to define the exact level of hypoglycemia that could result in brain injury to the neonate. The protocol depends on the age of the infant and whether the infant is asymptomatic or symptomatic for hypoglycemia. If the infant is asymptomatic, the initial feeding is within 1 h of birth and the glucose level is screened after 30 min. If the initial screen is <25 mg/dL (1.39 mmol/L), the infant is re-fed and checked in 1 h. If the result is <25 mg/dL (1.39 mmol/L) after the second feeding, intravenous glucose is given. The target glucose screen is ≥45 mg/dL (2.5 mmol/L) prior to routine feeds. Respiratory distress syndrome is caused by a deficiency of surfactant, necessary for fetal lung maturity. Neonatal hypocalcemia is serum calcium <7 mg/dL (0.38 mmol/L) in the premature infant with a birth weight <1500 g, and <8 mg/dL (0.4 mmol/L) in the term infant, or the premature infant whose birth weight is >1500 g. The definition of hypocalcemia depends upon gestational age and birth weight.

Hyperbilirubinemia occurs when the serum bilirubin level of the neonate >13 mg/dL (0.72 mmol/L). Polycythemia, which is a hematocrit >65% at delivery, could lead to perinatal asphyxia. The risk of these conditions decreases if optimal glycemic control is maintained throughout the pregnancy.

Advances in diabetes research and management have led to decreased risks of fetal demise in infants born to women with preexisting diabetes, though it remains higher than in the non-diabetes pregnant population. Maternal vascular complications, poor blood glucose control, and inadequate or no prenatal care are associated with higher rates of fetal demise than in women with diabetes prior to pregnancy.

Maternal

Preexisting conditions that can complicate the pregnancy in women with type 1 or type 2 diabetes include nephropathy, neuropathy, retinopathy, hypertension, and diabetic ketoacidosis. Diabetic nephropathy is associated with other complications, including preeclampsia, anemia, intrauterine growth restriction, fetal demise, and preterm delivery [23, 24]. If maternal glycemic levels are in optimal control before conception, the severity of complications and further renal deterioration during and after the pregnancy are reduced. Pregnancy itself is not a risk factor for the development or progression of diabetic neuropathy. Gastroparesis, a condition in which the stomach's ability to empty its contents is delayed or impaired, occurs more often in

type 1 diabetes. Women with gastroparesis may experience nausea, vomiting, abdominal discomfort, and difficulty in controlling their glycemic levels. Few studies have been published on gastroparesis and pregnancy. One case report noted severe and intractable vomiting in two women with gastroparesis, resulting in fetal demise in one of the pregnancies [25]. In another case report, one woman with an implantable gastric neurostimulator and on continuous subcutaneous infusion delivered vaginally at 38 weeks gestation with no complications [26].

The effect of pregnancy on diabetic retinopathy depends on the severity of the condition, or whether proteinuria or hypertension is present. In most cases, background retinopathy regresses after delivery. Proliferative retinopathy may progress if the condition was untreated prior to pregnancy [27]. Laser photocoagulation is indicated in the pregnant woman with high-risk proliferative diabetic neuropathy [23]. Obesity is a risk factor for hypertension, and is primarily associated with type 2 diabetes [28]. Diabetic ketoacidosis occurs more rapidly in pregnancy than in the non-pregnant state because of increased insulin resistance and accelerated starvation ketosis. Factors that precipitate diabetic ketoacidosis include hyperemesis, gastroparesis, insulin pump failure, and certain medications, such as steroids [23, 29].

Complications that may develop during pregnancy include hypertensive disorders, polyhydramnios, preterm delivery, and cesarean section. Poor blood glucose control in early pregnancy is associated with the development of preeclampsia and pregnancy-induced hypertension [29]. Although the etiology of polyhydramnios (excessive amniotic fluid) is not well understood, it is associated with suboptimal blood glucose control. Macrosomia may warrant preterm or cesarean delivery.

Medical Nutrition Therapy

There are no specific dietary guidelines for pregnant women with preexisting diabetes [30]. Current guidelines for nutrition recommendations in pregnant women without diabetes may be used for pregnant women with preexisting type 1 diabetes and type 2 diabetes [23]. Individualizing the meal plan is key to providing adequate calories and nutrients in pregnancy. The meal plan works concurrently with insulin therapy to achieve target blood glucose levels. The goals of medical nutrition therapy for pregnancy and diabetes are: (1) to provide adequate nutrients for maternal–fetal nutrition, (2) to provide sufficient calories for appropriate weight gain, and (3) to achieve and maintain optimal glycemic control.

Weight Gain

Weight gain guidelines are based on the 2009 Institute of Medicine's publication, *Weight Gain During Pregnancy: Reexamining the Guidelines*, according to the women's pre-pregnancy body mass index (Table 2) [31]. The pre-pregnancy body mass index and the amount of weight gained during pregnancy are two factors that

Table 2 Institute of medicine weight gain in pregnancy guidelines

Pre-pregnancy BMI	Recommended weight gain	Rate of gain/week (2nd and 3rd trimesters	Recommended total weight gain (twin gestation)
Underweight (<18.6)	28–40 lb. (12.7–18.2 kg	1 ½ lb. (0.7 kg)	
Normal weight (18.6–24.9)	25–35 lb. (11.2–15.9 kg)	1 lb. (0.5 kg)	37–54 lb. (16.8–24.4 kg)
Overweight (25.0–29.9)	15–25 lb. (6.8–11.3 kg)	2/3 lb. (0.3 kg)	31–50 lb. (14.1–22.7 kg)
Obese (>30.0)	11–20 lb. (4.5–9.0 kg)	1/2 lb. (0.25 kg)	25–42 lb. (11.3–19.1 kg)

Adapted from National Academy of Sciences. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academy Press; 2009

affect perinatal outcome. Weight gain below the Institute of Medicine's guidelines is associated with low birth weight and small-for-gestational age infants. Excessive weight gain may lead to macrosomia, cesarean section, and postpartum weight retention. Overweight women with diabetes may need to gain minimum weight to decrease the risk of macrosomia.

Energy Requirements

The estimated energy requirements (EER) during pregnancy are based on the 2002 Dietary Reference Intakes [32]. The estimated energy requirements for pregnancy is:

- First trimester: adult EER for women (no calorie increase)
- Second trimester: adult EER for women+160 kcal (8 kcal/weeks × 20 weeks) +180 kcal
- Third trimester: adult EER for women+272 kcal (8 kcal/weeks × 34 weeks) +180 kcal

The estimated energy requirement for adult women is based on age, height, weight, and physical activity level. The 8 kcal per week is the estimated change in the total energy expenditure in pregnancy; while the 180 kcal is the mean energy deposition during pregnancy. A comprehensive nutrition history/questionnaire, food and blood glucose records, and regular monitoring of weight are used to develop individualized meal plans. Fluctuating blood glucose levels may necessitate frequent adjustments in the meal plan.

Macronutrients

The requirement for protein is 71 g/day or 1.1 g/kg/day for women over 18 years of age [32]. High-fat diets are not recommended, and saturated fats are limited to less than 10% of total calories from fat.

The Dietary Reference Intake for carbohydrates in pregnancy is a minimum of 175 g/day to ensure sufficient glucose for fetal brain growth and development, which is estimated to be 33 g/day [32]. While there is no carbohydrate restriction for women with preexisting diabetes, adjustments may be necessary to maintain normoglycemia.

Micronutrients

There is no difference in the Dietary Reference Intakes for micronutrients for pregnant women with and without diabetes (Table 3) [33–36].

High-Intensity Sweeteners

Six high-intensity sweeteners are approved for use in pregnancy when used within the Acceptable Daily Intakes: saccharin, aspartame, acesulfame potassium, sucralose, neotame, and advantame [37, 38].

Meal Planning Approaches

Various meal planning approaches are used in diabetes management. A woman who follows a meal plan prior to conception may need only minor adjustments to account for fetal growth. Women with no previous medical nutrition therapy will need more intensive self-management education. The appropriate meal planning tool selected depends on the woman's ability and motivation to follow the meal plan [39]. Meal planning tools include menus, My Plate, or Choose Your Food [40]. Carbohydrate counting is used more often today as clients learn the importance of amounts and food sources of carbohydrates, label reading, and food records. Pattern management, calculating insulin-to-carbohydrate ratios, and correction factors are advanced self-management skills used with meal planning [39].

Medications

Exogenous insulin therapy is used for women with preexisting diabetes, however a few recent studies have used metformin in the management of pregnant women with type 2 diabetes [40–42].

Rapid-acting insulin analogs (lispro and aspart) are frequently used in pregnancy [43, 44]. Glargine, detemir, and degludec are long-acting peakless insulin analogs. No clinical studies have been conducted on the use of degludec in pregnancy. Injectable therapies that have not been safely demonstrated in pregnancy include amylin analogs (pramlintide), incretin mimetics (GLP-1, DPP-4), and

Table 3 Dietary reference intakes (DRIs) (over non-pregnant requirements) for protein in pregnnant and lactation

Nutrient	Pregnant woman	Lactating woman
Protein (g)	+25	+25
Vitamin A (mcg)		
14–18 years	750	1200
19–50 years	770	770
Vitamin D (mcg)	5	5
Vitamin K (mcg)		
14–18 years	75	75
19–50 years	90	90
Vitamin C (mg)		
14–18 years	80	115
19–50 years	85	120
Thiamin (mg)	1.4	1.4
Riboflavin (mg)	1.4	1.6
Niacin (mg NE)	18	17
Vitamin B_6 (mg)	1.9	2.0
Folate (mcg FE)	600	500
Vitamin B_{12} (mcg)	2.6	2.8
Calcium (mg)		
14–18 years	1300	1300
19–50 years	1000	1000
Phosphorus (mg)		
14–18 years	1250	1250
19–50 years	700	700
Magnesium (mg)		
14–18 years	400	360
19–50 years	360	320
Iron (mg)		
14–18 years	27	10
19–50 years	27	9
Zinc (mg)		
14–18 years	12	13
19–50 years	11	12
Iodine (mcg)	220	290
Selenium (mcg)	60	70

Adapted from Institute of Medicine. Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press; 2002; and Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press; 2001; and Food and Nutrition Board, Institute of Medicine. DRI Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: The National Academies Press; 1998; and Food and Nutrition Board. Institute of Medicine. DRI Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: The National Academies Press; 2001

sodium-glucose cotransporters 2 inhibitors (SGLTZ). Since 2015, the FDA no longer uses a lettering system to categorize drugs used in pregnancy. Medications used in pregnancy and lactation are now grouped into three categories: pregnancy, lactation, and males and females of reproductive potential.

Multiple daily injections of rapid-acting insulin or short-acting insulin with an intermediate-acting are the most frequently used insulin regimens in pregnancy. Women on a fixed dose of insulin before conception are often switched to multiple daily injections because of frequent insulin adjustments.

A common insulin regimen is rapid-acting or short-acting insulin before breakfast and dinner or before each meal, and intermediate-acting before breakfast and at bedtime. Intermediate-acting insulin is not injected before dinner because of possible nocturnal hypoglycemia.

Insulin requirements change during pregnancy as fetal growth continues and insulin resistance increases. First trimester insulin regimen varies, but is usually 0.7–0.8 units/kg actual body weight/day; second trimester: 0.8–1 unit/kg actual body weight/day. This dose of insulin is increased to 0.9–1.2 units/kg actual body weight/day in the third trimester [25, 30]. The requirements for obese women may be higher (e.g., 1.5–2 units/kg actual body weight/day).

Insulin injection devices include syringes, pens, and continuous subcutaneous insulin infusion (insulin pump therapy). Pump therapy requires rapid-acting insulin, with 50–60% of the dose as basal for continuous insulin, and 40–50% as boluses before meals and snacks. Advantages to the insulin pump are flexibility with lifestyle and meal times, and improved glucose control. The disadvantages include cost, risk of interruption in insulin delivery, and infection at the infusion site [45–48].

Self-Management Tools

Medical nutrition therapy and insulin therapy are only two of the components for successful self-management. Food records will assist the registered dietitian to adjust the meal plan, when necessary. Other self-management tools include sick day rules, self-monitoring of blood glucose and ketones, and physical activity.

Sick Day Rules

Hypoglycemia is a concern if a pregnant woman with diabetes is ill and unable to consume adequate calories. All pregnant women with preexisting diabetes must become aware of hypoglycemia symptoms, which include sweating, blurred vision, nervousness, anxiety, headache, weakness, or in severe cases, seizures or unconsciousness. The treatment for hypoglycemia depends on the severity of the symptoms. Mild to moderate symptoms are treated with 15 g of carbohydrate if the blood glucose level is <70 mg/dL (3.9 mmol/L). This is repeated 15 min later if the blood

glucose level remains <70 mg/dL (3.9 mmol/L). If severe hypoglycemia occurs, either glucagon or intravenous glucose is used [49].

Self-Monitoring

Monitoring provides a necessary tool for adjusting food, medication, and physical activity in diabetes management. Women with preexisting diabetes should monitor their blood glucose levels before and after meals using a glucose meter. Blood glucose goals for diabetes and pregnancy are [50]:

- Fasting: ≤ 95 mg/dL (5.3 mmol/L
- 1-h postprandial: ≤ 140 mg/dL (7.8 mmol/L)
- 2-h postprandial: ≤ 120 mg/dL 6.7 mmol/L)

Urine ketone monitoring is recommended in pregnant women with type 1 diabetes who are at risk for diabetic ketoacidosis at lower blood glucose levels than when not pregnant [50]. Glycosylated hemoglobin (A1C), while not a self-monitoring tool, is useful in measuring blood glucose levels to determine metabolic control and treatment. A1C levels are monitored more frequently in pregnancy because of the more rapid turnover of red blood cells [50].

Physical Activity

There is no empirical evidence demonstrating a beneficial effect of physical activity on glycemic control in women with preexisting diabetes. Unless contraindicated, women who were physically active before pregnancy are encouraged to continue; however, high-intensity or prolonged exercise longer than 45 min could lead to hypoglycemia. Contraindications to exercising with diabetes in pregnancy include poorly controlled type 1 diabetes, and glycemic levels <100 mg/dL (5.6 mmol/L) or >250 mg/dL (13.9 mmol/L) [51].

Postpartum

Insulin requirements usually decrease after delivery. It is not uncommon for the woman with type 1 diabetes to forego insulin for the first 1–2 days after delivery. Insulin adjustments are necessary to prevent hypoglycemia.

There are no contraindications to lactation and diabetes; women should be encouraged to breastfeed. The meal plan is adjusted to include additional snacks and to avoid hypoglycemia, which may be more frequent during lactation. Women with type 2 diabetes who choose to breastfeed may be switched from insulin therapy to an oral antidiabetes agent. Glipizide, glyburide, metformin, and acarbose are considered compatible with breastfeeding [24].

Family planning is an important topic to be discussed with the woman with preexisting diabetes. The use of contraceptive agents will depend on whether cardiovascular diseases are present [52]. Contraceptive agents that contain estrogen should not be prescribed to women with diabetes-related complications, such as retinopathy, nephropathy, or neuropathy, or who are hypertensive. Women with hyperlipidemia or hypertension are recommended to use progestin-only oral contraceptive agents because of their non-effect on liver globulins and possible clotting factors. Intrauterine devices and barrier methods were not found to affect blood glucose levels.

Preconceptional Counseling

Preconception counseling is essential for all women with diabetes in their childbearing years. Women with preexisting diabetes should delay pregnancy until their glycosylated hemoglobin (A1C) levels are <6.5% to decrease the risk of fetal congenital anomalies [50]. Preconceptional care includes a complete physical examination to identify and treat any preexisting diabetes-related or other medical condition, an assessment of her nutritional status, and self-management education, including psychosocial assessment. A discussion of finances is also important because of the additional expense of more frequent testing or diabetes supplies.

Although all women with preexisting diabetes should receive preconceptional counseling, such is not often the case [53, 54]. An observational study from France found that women with type 2 diabetes had a three-fold higher rate of infants born with malformations than women in the general population. Only four of the 87 women in the study received preconception care [55]. Another study conducted in Northern Ireland found a lack of awareness of the risks associated with diabetes in pregnancy and the role of preconception care. One reason for this higher prevalence of complications could be misconception that type 2 diabetes is not as severe as type 1 diabetes [56].

Gestational Diabetes Mellitus

It is estimated that 90% of cases of diabetes in pregnancy are gestational diabetes [3]. Women who are diagnosed with diabetes in their first trimester are classified as having type 2 diabetes. Gestational diabetes is diabetes diagnosed in the second and third trimester of pregnancy, that is clearly not preexisting type 1 or type 2 diabetes [57].

Pathophysiology

The exact mechanism of gestational diabetes is not fully understood, however, it is associated with insulin resistance and decreased insulin secretion. Fasting blood glucose levels are elevated as insulin deficiency and resistance increase. Delayed

insulin response, insulin resistance, and placental hormonal antagonism are responsible for postprandial glucose excursions. Human placental lactogen and cortisol block insulin receptors. This creates a deficiency in circulating insulin production, and glucose intolerance [58].

Complications

Maternal risks associated with gestational diabetes include hypertension, higher rates of cesarean sections, and preterm deliveries [50]. Macrosomia is the most common complication in gestational diabetes. Other complications include neonatal hypoglycemia, neonatal hypocalcemia, neonatal hyperbilirubinemia, and polycythemia. The risk for respiratory distress syndrome decreases if delivery occurs at term.

Risk Factors for Gestational Diabetes

Considerable controversy exists in the screening and diagnosis of gestational diabetes. The American Diabetes Association (ADA) recommends testing for undiagnosed type 2 diabetes at the first prenatal visit if a woman has risk factors associated with type 2 diabetes. The risk factors are found in the American Diabetes Association's 2017 Standards of Medical Care in Diabetes [57]. All pregnant women not previously diagnosed with diabetes should be tested for gestational diabetes at 24–28 weeks' gestation.

The American College of Obstetricians and Gynecologists (ACOG) recommends all pregnant patients be screened for GDM, whether by the patient's medical history, clinical risk factors, or laboratory screening test results, to determine their blood glucose levels. However, this recommendation was given a Level B grade because it is based on limited or inconclusive scientific evidence [59].

Screening and Diagnosis of Gestational Diabetes

In the United States, two methods are used to diagnose gestational diabetes: the one-step and the two-step method [57]. The one-step approach uses a 75 g glucose solution as the oral glucose tolerance test and the blood is drawn at fasting, 1 and 2 h. This method is based on the recommendations from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [60]. The IADPSG derived their recommendations from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large multinational cohort study of 25,000 pregnant women, which demonstrated the risk of adverse outcomes in the fetus, neonate, and mother were at lower glycemic levels than what were considered normal for pregnancy [61]. In 2011, ADA adopted the IADPSG's recommendations.

The two-step method is based on the Carpenter-Coustan criteria for screening and diagnosing GDM. In the first step, a Glucose Challenge Test (GCT) is administered using a 50 g glucose solution and the plasma glucose level is checked in 1 h. The second step, the Oral Glucose Tolerance Test (OGTT), is performed if the result of the 1-h test is ≥130 mg/dL to 140 mg/dL (7.2 to 8.1 mmol/L), depending on the threshold used. The OGTT follows 3 days of unrestricted carbohydrate intake (at least 150 g/day) and unlimited physical activity. The woman fasts for at least 8 h the night before the test. Blood is drawn for a fasting glucose level, followed by 100 g of glucose solution given orally and again at 1, 2, and 3 h. The oral glucose tolerance test is discontinued if the fasting glucose is ≥126 mg/dL (7.0 mmol/L) or a random glucose is ≥200 mg/dL (11.1 mmol/L). Gestational diabetes is diagnosed if at least two of the values exceed the Carpenter and Coustan criteria of:

- Fasting: ≤ 95 mg/dL (5.3 mmol/L)
- 1-h: ≤ 180 mg/dL (10.0 mmol/L)
- 2-h: ≤ 155 mg/dL (8.6 mmol/L)
- 3-h: ≤ 140 mg/dL (7.8 mmol/L)

In 2013, the National Institutes of Health convened a consensus development panel on diagnosing criteria for GDM. The panel examined the research related to the current diagnostic criteria and recommended the two-step approach because of the lack of intervention studies on the one-step approach to diagnosing GDM [62]. As a result, ACOG has continued to use the two-step strategy.

Management of Gestational Diabetes

The treatment for GDM begins with medical nutrition therapy, physical activity, weight management depending on the pregestational weight, and self-monitoring of blood glucose. The goal of management is to optimize blood glucose levels, thereby decreasing the risk of perinatal complications. A 2005 study showed a reduction in perinatal complications in women with GDM who received medical nutrition therapy, self-monitored their blood glucose levels, and used insulin therapy when necessary, compared to women who received routine care [63].

Medical Nutrition Therapy

The primary goals of medical nutrition therapy in GDM is to achieve and maintain normal blood glucose levels as safely as possible, while at the same time providing adequate calories and nutrients for maternal and fetal health [64]. Carbohydrates are the main contributors of postprandial glucose excursions in gestational diabetes, and for many years were restricted to approximately 40–45% of total calories [64–66]. However, newer research has indicated that the type and amount of carbohydrate may impact maternal blood glucose levels without negatively affecting

perinatal outcomes. This includes higher carbohydrate [67], low glycemic index [68, 69, 70], and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern [71]. Iranian women with GDM who followed the DASH dietary pattern, in which the carbohydrate amount exceeded 65% of the total calories, had infants with lower birth weight, head circumference, and ponderal index compared to those born to women on a control diet [71].

The Institute of Medicine's guidelines are used to determine the appropriate weight gain for women with gestational diabetes [32]. The estimated energy requirements are the same for pregnant women without diabetes. Monitoring weight gain and reviewing blood glucose, food, and if necessary, ketone records, are other useful tools to determine diet adequacy.

There is insufficient evidence to increase the protein requirement for women with gestational diabetes, although the intake may be higher than the Dietary Reference Intake in pregnancy if the carbohydrate intake is decreased. The amount of fat has not been shown to affect pregnancy outcome, however, there is limited evidence to suggest that monounsaturated fats may lower diastolic blood pressure and improve insulin sensitivity [72].

Self-Management Tools

Self-management is important for improving perinatal outcome in gestational diabetes. Self-management tools include self-monitoring of blood glucose, physical activity, and pharmacological therapy, when necessary.

Self-Monitoring of Blood Glucose

While limited research has indicated that post-meal blood glucose monitoring yields better outcomes (decreased fetal macrosomia and large-for-gestational age infants), there are no established optimal testing times in gestational diabetes [73]. The general consensus is to self-monitor blood glucose levels four times a day [50, 59].

Ketone Monitoring

Neither the American Diabetes Association's Standards of Medical Care nor the American College of Obstetricians and Gynecologists' Practice Bulletin has recommended ketone testing in women with gestational diabetes. One study is frequently cited as a rationale for recommending ketone testing in gestational diabetes because of the correlation between ketonemia and decreased intelligence scores in the offspring of women with diabetes [74]. It may be advantageous for women with gestational diabetes to monitor for urinary ketones if there is weight loss or inadequate weight gain or energy intake.

Physical Activity

Physical activity may have a positive effect in gestational diabetes by lowering blood glucose levels [75]. Low-impact aerobics such as walking, stair climbing, or swimming are acceptable. The activity should be performed after meals to improve glycemic levels. Pregnant women with any medical or obstetric complications should be evaluated by an obstetrical care provider before recommending any physical activity during pregnancy [75].

Pharmacological Therapy

If normoglycemia cannot be maintained with medical nutrition therapy alone, pharmacological therapy is added. However, there is no consensus among clinicians when pharmacologic therapy should be instituted. The Academy of Nutrition and Dietetics nutrition practice guideline recommends initiating pharmacological therapy if targeted blood glucose levels are not reached after 2 weeks of medical nutrition therapy [65]. Ultrasound measurement of the fetal abdominal circumference to determine macrosomic growth is also used to determine if and when to initiate insulin therapy [76].

Insulin is the first-line therapy used in the management of gestational diabetes, when indicated, because it does not cross the placenta. The types of insulin recommended in gestational diabetes are the same as for pregnant women with preexisting diabetes.

The use of oral antidiabetes agents in the management of gestational diabetes has increased in recent years. A randomized trial in 2000 which compared glyburide to insulin reported no difference in the incidence of maternal or fetal complications [77]. In this study, glyburide was not detected in the cord serum. However, a more recent study has shown glyburide crosses the placenta in varying amounts [78]. A retrospective cohort study showed that infants born to women with gestational diabetes and treated with glyburide were at increased risk for neonatal intensive care admission, respiratory distress, hypoglycemia, birth injury, and large-for-gestational age than those treated with insulin [79]. Metformin is another oral agent used in the management of gestational diabetes [80]. In a systematic review and meta-analysis that compared glibenclamide, metformin, and insulin in the treatment of gestational diabetes, glibenclamide was found to be inferior to insulin and metformin. The authors recommended that glibenclamide not be used if insulin or metformin is available [81].

Postpartum

Women with gestational diabetes are at increased risk for developing type 2 diabetes after pregnancy, and should be screened 6–12 weeks postpartum [50, 59]. The American Diabetes Association recommends a 75 g, 2-h oral glucose tolerance test to identify women with possible undiagnosed diabetes before conception, impaired glucose tolerance, or risk for future diabetes [50]. If the oral glucose tolerance test

is normal, the woman should be reassessed every 1–3 years depending on her other risk factors, which include family history, pre-pregnancy BMI, and the necessity of pharmacologic therapy during pregnancy [50].

Breastfeeding, unless contraindicated, is recommended for women with gestational diabetes [50]. Lactation may improve glucose control, mobilize fat stores, promote weight loss, and protect against future risk of developing type 2 diabetes and metabolic syndrome [82, 83]. A gradual weight loss of 1–2 kg per month is encouraged.

Women with previous histories of gestational diabetes are also at risk of developing gestational diabetes in recurring pregnancies. The Diabetes Prevention Program has shown that women with a history of gestational diabetes or prediabetes prevented or delayed the progression to diabetes with metformin or intensive lifestyle intervention [84]. In a 10-year follow-up study, women in the lifestyle intervention and metformin groups reduced the progression to type 2 diabetes by 35% and 40%, respectively [85]. Women should be encouraged to adopt healthy lifestyles to lessen their risk of developing type 2 diabetes or gestational diabetes in subsequent pregnancies. Lifestyle modifications include achieving and maintaining normal body weight, healthy eating habits, and consistent physical activity [65].

Conclusion

Advances in diabetes management have greatly improved pregnancy outcomes. For the woman with preexisting diabetes, optimal maternal blood glucose control must begin prior to conception and continue throughout the pregnancy. All women with type 1 diabetes and type 2 diabetes of childbearing age should be referred for preconceptional care to incorporate self-management strategies that can decrease perinatal morbidity and mortality. Self-management care includes medical nutrition therapy, self-monitoring of blood glucose, and if necessary, ketone testing, insulin therapy, and physical activity.

Medical nutrition therapy is a key component in the management of gestational diabetes. An individualized meal plan should be designed to provide adequate energy and nutrients for maternal and fetal health and promote appropriate weight gain based on pre-pregnancy body mass index. Food, blood glucose and, if necessary, ketone records, are used to adjust the meal plan. After delivery, lifestyle modifications are necessary to reduce the long-term risk of developing type 2 diabetes. These modifications should focus on diet, physical activity, and achieving and maintaining a healthy weight.

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