Diabetes and Pregnancy

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Faculty

Susan Semb, MSN, CDCES, is a retired RN who received her Master's degree in nursing from the University of San Diego. Her nursing experience includes direct patient care, case management, staff development, program development, and health education. She spent the majority of her nursing career working as a diabetes educator in the health education department of a major health maintenance organization. Ms. Semb has also authored other continuing education courses for nurses published by NetCE and contributed to nursing books and other publications. In her retirement, Ms. Semb enjoys travel, line dancing, and pursuing an interest in antiques and vintage items.

Faculty Disclosure

Contributing faculty, Susan Semb, MSN, CDCES, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

Margo A. Halm, RN, PhD, ACNS-BC

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses in inpatient and outpatient practice areas that include women's health, family medicine, and diabetes/endocrinology, and health education specialists, public health professionals, and nurse educators.

Accreditations & Approvals

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Course Objective

The purpose of this course is to provide nurses with practical information and evidence-based recommendations on all aspects of pregnancy complicated by diabetes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the pathophysiology, risk factors, screening, and treatment of type 1 diabetes, type 2 diabetes, gestational diabetes, and prediabetes.
2. Explain how metabolic changes during normal gestation increase the risk for elevated blood glucose.
3. List maternal and fetal risks of hyperglycemia during pregnancy.
4. Identify future risks to the offspring of mothers who had diabetes during pregnancy.
5. Describe principles of preconception counseling in women with pre-existing diabetes.
6. Summarize the management of pregnancy in women with pre-existing type 1 or type 2 diabetes.
7. Review studies and findings that provide a rationale for the treatment of gestational diabetes.
8. Define recommended blood glucose targets and frequency of blood glucose monitoring in gestational diabetes.
9. Describe goals and guidelines for the nutritional management of gestational diabetes.
10. Identify the safety and efficacy of oral diabetic agents and insulin for use in gestational diabetes.
11. Discuss interventions to prevent the development of gestational diabetes.
12. Describe the obstetrical management of pregnancy complicated by diabetes.
13. Describe maternal postpartum care for pregnancy complicated by diabetes.
14. Discuss the care of the neonate born to the mother with diabetes.
15. Identify important aspects of psychosocial care and follow-up for the woman with diabetes during pregnancy.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Diabetes is a common condition, encountered in nearly every area of health care, and caring for patients with diabetes can be both challenging and rewarding. When a patient with diabetes becomes pregnant, or plans to become pregnant, the demands and opportunities to care for her proliferate. While family planning and preconception care are of utmost importance to women with pre-existing diabetes, blood glucose management is critical throughout the gestational period of all pregnancies complicated by diabetes.

While some patients have type 1 or type 2 diabetes present before pregnancy, others have diabetes with first onset during pregnancy. Known as gestational diabetes mellitus (GDM), this complicates the pregnancy and increases the mother's risk for developing type 2 diabetes in the coming years. For these women, having diabetes is a new, and sometimes temporary, experience, but the risks of poor management are immense. In either type of situation, specialized knowledge is necessary to properly care for patients who have these two common medical conditions—pregnancy and diabetes—simultaneously.

This course will explore all aspects of caring for women with pregnancy complicated by diabetes, including pre-existing diabetes and diabetes with first onset during gestation. This course will describe the causes of the different types of diabetes and their effects on the health of the pregnant woman and her child, both before and after birth. It will explain the physiologic changes of gestation that cause elevated blood glucose and the risks this presents to the mother and fetus. Furthermore, this course will include important aspects of medical and nursing management during all phases of pregnancy complicated by diabetes, from prenatal care to postpartum management and long-term follow-up.

SCOPE OF THE PROBLEM

One need not look far to find evidence that diabetes is a problem of profound significance in the United States and throughout the world. Both medical and popular literature abound with stories and statistics that herald the alarming increase in diabetes and obesity over the past two decades. According to the Centers for Disease Control and Prevention (CDC), 34.1 million adults in the United States have diabetes, whether diagnosed or undiagnosed. This represents 13% of the population. For women in particular, 16.2 million of those older than 18 years of age have diabetes, comprising 12% of the adult female population in the United States [1].

Diabetes is now considered an epidemic, and its toll on the individual and society is enormous. The government estimates that the total direct and indirect economic cost of diabetes is $327 billion per year [1]. As a leading cause of blindness, kidney failure, lower extremity amputation, and cardiovascular disease (CVD), diabetes presents a liability to available resources and the quality of life of the individuals and families that it affects [2].

The causes of diabetes and the reasons for its increasing rates are multifactorial. Well-known risk factors for diabetes include age, genetic predisposition, and lifestyle choices that contribute to overweight or obesity. Studies suggest that the intrauterine environment of a mother with elevated blood glucose may predispose the fetus to metabolic syndrome, obesity, and diabetes in later life.

Diabetes during pregnancy is associated with numerous adverse effects on both the mother and child throughout gestation and into the postpartum period. In pregnant women with pre-existing type 1 diabetes, major birth defects occur in 5% to 10% of pregnancies and spontaneous abortion occurs in 15% to 20% of cases. Pregnant women with diabetes are more likely to have hypertension and pre-eclampsia, while the infant has a higher risk for congenital anomalies and birth injury. Women

who have had GDM have a 35% to 60% chance of developing diabetes in the 10 to 20 years after pregnancy [2]. Their children may also have a higher risk of developing type 2 diabetes in their lifetimes.

At a 2011 meeting of the American Diabetes Association (ADA), GDM was described as a "major public health issue that has both short-term and long-term implications for the mother and her offspring" [3]. In response to research showing that even mildly elevated blood glucose during pregnancy can result in adverse outcomes for the infant, experts now recommend stricter criteria for finding and treating hyperglycemia in pregnancy. While rates of GDM now range from 2% to 10% of pregnancies, the new diagnostic criteria would significantly increase the proportion of women diagnosed with GDM [2]. It is estimated that using these new diagnostic criteria, 18% of all pregnancies will be affected, representing an increase of 20% to 40% [2]. An increased appreciation for the dangers of elevated blood glucose during pregnancy, along with new criteria for case-finding, requires more vigilant care on the part of healthcare providers along with a significant increase in resources needed to treat it.

DIABETES DISEASE PROCESS: A REVIEW

Diabetes is a disorder in how the body utilizes and converts its main fuel source into energy. When the body does not properly regulate this fuel, blood glucose levels rise. If high blood glucose levels are sustained over time, abnormalities in the structure of blood vessels and nerves can result. This leads to organ and tissue damage and can have serious consequences in many body systems, including the eyes, kidneys, and nerves. Other pathologic processes and additional risk factors are strongly related to the development of CVD, which is the leading cause of death in people with diabetes.

NORMAL GLUCOSE METABOLISM

Glucose is available to the body from two main sources: ingested food and the body's production of glucose by the liver. Although some tissues and organs can derive energy from other sources, the brain and central nervous system rely almost entirely upon glucose. Because the brain cannot store or synthesize glucose, it depends on a continuous supply of glucose from the circulation and extracts its energy supply on a minute-by-minute basis.

The Role of the Pancreas

The pancreas supplies two hormones necessary for glucose metabolism: insulin and glucagon. Insulin allows glucose to enter the cells, where it can be utilized for energy. Glucagon has an action opposite that of insulin.

When glucose is ingested, usually by consuming carbohydrate foods, it is absorbed through the intestinal walls and enters the bloodstream, then traveling to the body's cells. Rising blood glucose levels stimulate the production of insulin from the pancreas. When released into the blood, insulin attaches to insulin receptors on cell walls and facilitates the entry of glucose into the cells. Thus, blood glucose is lowered and remains between 60 and 120 mg/dL [4].

Following the immediate postprandial period, unused glucose is stored in muscle and liver tissue as glycogen. The release of this stored energy is regulated by glucagon. Glucagon normally serves as the body's major defense against hypoglycemia. Its role is to maintain blood glucose levels between meals and during the fasting state. When blood glucose levels are high, such as after eating, the secretion of glucagon by the pancreas is inhibited.

The Role of the Liver

The liver plays two roles in the regulation of blood glucose. One is the storage and release of glucose that originated from the diet; the other is the synthesis of its glucose supply (gluconeogenesis). When blood glucose levels are low, the liver releases some of its stored or synthesized glucose, and blood levels rise. Conversely, when blood glucose levels are high, the liver stops producing and releasing glucose.

The Role of Muscle Tissue

As the primary target organ for the action of insulin, skeletal muscle tissue contains the majority of insulin receptor sites. When insulin binds with receptor sites on the skeletal muscle, this allows for the entry of glucose into the cells. When muscle tissue has fewer available receptor sites than are needed by the cells for glucose entry, a condition called insulin resistance occurs. Insulin resistance plays a major role in the development of type 2 diabetes and GDM.

The Gut Hormones

Research has illuminated the important role that incretin hormones play in glucose regulation. Two incretin hormones mediate these actions; they are known as glucagon-like peptide (GLP)-1 and gastric inhibitory peptide (GIP).

Incretins are digestive hormones released from the small intestine after eating in response to the post-prandial rise in blood glucose. The incretins help lower blood glucose in two ways: by stimulating insulin release and by decreasing glucagon production from the pancreas.

Many of the more recent therapies developed for the treatment of type 2 diabetes have been incretin-based. One class of medication, the incretin mimetic, mimics the action of the incretin hormones GLP-1 and GIP, leading to an increase in insulin secretion from the pancreas. An additional beneficial effect of these medications is delayed gastric emptying, which increases satiety and promotes weight loss.

Incretin enhancers, also known as dipeptidyl peptidase (DPP)-4 inhibitors or gliptins, interfere with an enzyme that rapidly inactivates the incretin hormones. By inhibiting DPP-4, these agents prolong active incretin levels, allowing for increased insulin action following the post-prandial rise in blood glucose.

PATHOPHYSIOLOGY OF DIABETES

Any one (or a combination) of three major abnormalities of metabolism can be responsible for inducing the diabetes disease process:

- Abnormal insulin secretion by the pancreas
- Insulin resistance
- Inappropriate glucose production by the liver

Absent or insufficient insulin production by the pancreas is one cause of hyperglycemia. Because the role of insulin is to facilitate the passage of glucose into the cells, its absence or deficiency causes unused glucose to remain in the blood.

Insulin resistance is the second major pathologic process in diabetes. This refers to impairment in the body's ability to utilize insulin. With insulin resistance, circulating blood levels of insulin may be high, but receptor sites are either ineffective or not available.

The third major metabolic abnormality in diabetes is related to glucose production by the liver. As an organ that can make or store glycogen, the liver plays a major role in the regulation of blood glucose levels. Insulin resistance of receptor sites on the liver can prevent it from receiving the signals it needs to stop releasing glucose when blood levels are sufficient.

DIAGNOSIS AND CLASSIFICATION OF DIABETES

Diabetes encompasses a relatively large and somewhat diverse group of metabolic diseases. The ADA has identified four different clinical classes of diabetes based on etiology: type 1, type 2, gestational, and other types. In addition, the ADA has defined categories of increased risk for diabetes, collectively known as "prediabetes." Many of the types of diabetes identified by the ADA are not commonly encountered in nursing practice and are related to rare genetic and immune-mediated syndromes; these fall into the "other types" class. The common pathologic factors that categorize all these diseases as diabetes relate to abnormal insulin production, impaired insulin utilization, or both [5].

PREDIABETES

When blood glucose levels are higher than normal but not high enough to be diagnosed as type 2 diabetes, the condition is referred to as prediabetes. Prediabetes is identified as a category for increased risk for diabetes and CVD. Laboratory findings that indicate prediabetes include [5]:

- Fasting plasma glucose 100–125 mg/dL
- Two-hour postprandial glucose tolerance test 140–199 mg/dL
- Glycosylated hemoglobin (A1C) 5.7% to 6.4%

According to the CDC, 88 million adults in the United States have prediabetes [1]. Identifying patients with prediabetes is vital to delaying or preventing the onset of type 2 diabetes, and research has shown that lifestyle management can prevent the progression of diabetes. When people with prediabetes follow a healthy diet and engage in 150 minutes of moderate-intensity exercise per week, leading to a 5% to 7% loss of body weight, they can reduce their risk of progressing to diabetes by roughly 58% [6].

TYPE 1 DIABETES

Formerly known as juvenile-onset diabetes, type 1 diabetes usually has its onset in people younger than 30 years of age. It is most often seen in people with a lean body type, although it can occur in people who are older and overweight. Type 1 diabetes results when a person's pancreas cannot produce any of its insulin for use by the body. If the individual with type 1 diabetes does not receive insulin from an outside source, he or she is likely to develop a life-threatening condition known as ketoacidosis. Patients with type 1 diabetes require insulin from an exogenous source to stay alive.

Advances are being made in islet cell transplantation for the treatment or cure of type 1 diabetes. For this procedure, donor cells are harvested from cadavers; for an average-sized person, two donor organs are usually required to reap approximately 1 million islets. Because the islets are very fragile, transplant occurs immediately after harvesting. A relatively simple procedure, islet cell transplant involves ultrasound placement of a catheter into the recipient's liver through which the islet cells are injected. After a time, the cells attach to blood vessels and begin releasing insulin. A major risk of islet cell transplantation is that anti-rejection drugs are needed to keep the transplanted cells functioning, and these drugs can have significant side effects. It is also not known how long the islet cells survive after transplant. Because there is an extreme shortage of available donor cells, islet cell transplants are not commonly done [7].

Pancreas transplantation is another approach being explored in the search for a cure for type 1 diabetes. Whole pancreas transplants from cadaver donors or partial pancreas transplants from living relative donors may be used. Compared to islet cell transplantation, whole or partial organ transplantation is a complicated procedure with all the inherent risks of major surgery. Many times, a partial pancreas transplant occurs in conjunction with a kidney transplant using the same living relative donor. In addition to the risks of major surgery, organ transplant requires the lifelong use of immunosuppressant drugs. Even with these drugs, about half of transplanted pancreases are rejected [8].

TYPE 2 DIABETES

In the past, type 2 diabetes was called adult-onset diabetes, but with the increasing incidence among children and adolescents, classification based on age of onset is no longer accurate. Type 2 diabetes is by far the most common type of diabetes, accounting for 90% to 95% of all cases [1]. It usually begins in people older than 30 years of age, most commonly in those older than 55 years of age. However, as mentioned, it can occur at younger ages as well. Regardless of age at onset, type 2 diabetes is more likely to develop in those who are overweight and sedentary.

In individuals with type 2 diabetes, the pancreas is able to produce at least some of its own insulin for the body to use. However, the insulin that is produced is either insufficient for the needs of the body or is poorly utilized by the tissues, as with insulin resistance. The need for an outside insulin source is variable in people with type 2 diabetes. Individual cases may be treated with diet and exercise therapies, oral medications, insulin, or any combination of these. The patient with type 2 diabetes usually produces enough endogenous insulin to prevent ketoacidosis from occurring. However, these patients may require insulin to keep blood glucose levels under control for the prevention of other acute and chronic complications.

GESTATIONAL DIABETES

As discussed, GDM refers to diabetes that develops during pregnancy and complicates approximately 2% to 10% of all pregnancies [144]. It occurs more frequently among American Indian, Asian American, Hispanic/Latina, and Pacific Islander populations. Other risk factors for GDM include age older than 25 years, overweight/obesity, and personal history of GDM or a family history of diabetes [9; 144].

Women with GDM are at higher risk for hypertensive disorders of pregnancy and cesarean delivery. Fetal complications of GDM may include neural tube defects, perinatal death, large body size (macrosomia), lower Apgar scores, and childhood obesity. Although most women with GDM will have normal glucose levels within six weeks postpartum, 35% to 60% will go on to develop type 2 diabetes in the next 10 to 20 years [144]. Therefore, regular blood glucose testing is recommended for these women during and after pregnancy. Maintaining a healthy body weight and engaging in regular physical activity may help prevent the onset of type 2 diabetes in this population.

Treatment of GDM includes close surveillance of the mother and fetus due to the increased risks inherent in this type of pregnancy. Maternal fasting and postprandial blood glucose levels are usually checked several times per day. Nutritional management, along with regular physical activity, is considered the first-line therapy. If this alone does not achieve target glucose levels, insulin therapy or treatment with selected oral agents is indicated. Having GDM does not present any contraindications to breastfeeding. In fact, breastfeeding increases insulin sensitivity in the mother and can protect both mother and infant against diabetes.

SECONDARY DIABETES

Diabetes can occur secondary to a variety of medical conditions, including diseases and tumors that affect the liver or pancreas. Secondary diabetes may also occur in susceptible people who take medications that can impair glucose metabolism. Commonly used medications that can induce diabetes include corticosteroids, thyroid preparations, thiazide diuretics, and phenytoin, among others. Secondary diabetes usually resolves when the underlying cause is eliminated.

Patients with secondary diabetes should receive education on the treatment of the primary condition as well as diabetes, but focusing on the primary condition by the patient and healthcare providers may fragment diabetes education. Although secondary diabetes is generally expected to resolve, the patient will always be at risk for recurrence.

CRITERIA FOR THE DIAGNOSIS OF DIABETES

According to the ADA, the criteria for the diagnosis of diabetes are [5]:

- A1C ≥6.5%, OR
- Fasting plasma glucose ≥126 mg/dL, OR
- Two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, OR
- Random plasma glucose ≥200 mg/dL in a patient exhibiting classic symptoms of hyperglycemia

GLUCOSE METABOLISM DURING PREGNANCY

Pregnancy is a time of hormonal fluctuation, altering a woman's metabolism of carbohydrates, fats, and protein. Placental hormones that help the fetus develop naturally cause some insulin resistance in the mother. Normally, these changes in pregnancy result in a mild increase in maternal glucose levels, which provides the fetus with a continuous, increased supply of glucose for its growth. Most of the time, the mother's body can overcome excessive glycemia by increasing insulin production. In a healthy pregnancy, the mother's insulin secretion doubles by the third trimester [4; 10; 11; 12].

The growing fetal-placental unit has multiple effects on the maternal hormonal balance:

- It metabolizes the mother's hormones.
- It makes hormones of its own.
- It affects maternal fuel utilization.
- It produces placental hormones, growth factors, and cytokines that increase maternal insulin resistance.

FIRST TRIMESTER

Early in pregnancy, estrogen and progesterone stimulate insulin secretion from the beta cells of the mother's pancreas. This results in decreased maternal glycemia in early gestation. Mothers with pre-existing type 1 diabetes typically require lower doses of insulin during this time [4; 10; 11; 12].

SECOND TRIMESTER

In the second trimester, the "diabetogenic" stress of pregnancy begins. Hormones such as human placental lactogen and cortisol cause increased insulin resistance, raising the mother's daily insulin requirement. Women with pre-existing diabetes who use insulin may need to increase their dosage by as much as twice that needed before pregnancy beginning in the second trimester.

THIRD TRIMESTER

In late pregnancy, anabolic hormones responsible for fetal growth and development increase dramatically. Insulin-opposing hormones, such as human placental lactogen, prolactin, estrogen, and progesterone, cause an even greater degree of resistance. As a result, maternal basal insulin levels are high and eating produces two to three times more insulin output than in the prepregnancy state. However, insulin sensitivity decreases by as much as 50% of that seen in the first trimester. Most cases of GDM occur early in the third trimester because of these metabolic changes.

AFTER DELIVERY

The placental hormones that cause insulin resistance and hyperglycemia rapidly clear from the circulation after the delivery of the placenta. In more than 90% of women with GDM, blood glucose levels return to normal in the immediate postpartum period [144].

GLUCOSE METABOLISM IN PREGNANCY COMPLICATED BY DIABETES

As discussed, the hormonal changes of pregnancy result in a state of maternal insulin resistance. Pregnant women who have type 2 diabetes or GDM experience two forms of insulin resistance. The first is insulin resistance related to late pregnancy, brought about by anabolic hormones that support fetal growth and development. The second form of insulin resistance is the chronic form that is present before the pregnancy, exacerbated by the hormonal changes of pregnancy. Thus, women with pre-existing insulin resistance are not able to overcome the underlying condition in addition to the insulin resistance brought on by normal gestational physiology, resulting in pronounced glucose intolerance [13].

For women with pre-existing type 2 diabetes, the increase in insulin sensitivity immediately following birth affects the required dosage of insulin or antidiabetic medications. In the immediate postpartum period, the insulin dosage needed to control blood

glucose may only be half as much as was required before the pregnancy due to the sudden drop in placental hormones and the reduction in maternal growth hormone following delivery. As time goes on, the insulin needs of the woman with type 2 diabetes return to prepregnancy levels.

Occasionally, type 1 diabetes is diagnosed during pregnancy. This is due to maternal insulin deficiency that is identified during pregnancy as opposed to insulin resistance. Type 1 diabetes may be suspected in a woman with a normal body mass index and no family history of type 2 diabetes when hyperglycemia develops during pregnancy. Women diagnosed with type 1 diabetes will require insulin injections during and following the pregnancy.

RISKS OF DIABETES IN PREGNANCY

Maternal diabetes during pregnancy can have both short- and long-term effects on the mother and/or the child. This section will examine the hazards of hyperglycemia as they affect:

- The pregnant woman, during gestation and later in life
- The embryo and fetus
- The neonate
- The offspring later in life

MATERNAL RISKS

Diabetes during pregnancy is associated with an increased risk for several obstetrical and long-term complications for the mother. Maternal complications of diabetes during pregnancy include:

- Preterm labor and delivery
- Cesarean delivery
- Spontaneous abortion and stillbirth
- Hypertension and pre-eclampsia
- Increased risk for infection
- Periodontal disease
- Increased risk for future development of type 2 diabetes
- Increased risk for CVD later in life

Preterm Labor and Delivery

Maternal diabetes during pregnancy increases the risk of preterm labor [14]. Some of this risk may be due to increased uterine volume caused by macrosomia and/or polyhydramnios, which are associated with GDM. Maternal hypertension and urinary tract infections are also associated with GDM and increase the risk of preterm labor. Women with preexisting diabetes who have vascular symptoms also have a higher risk for preterm labor.

Polyhydramnios occurs in about 18% of patients with GDM and is diagnosed when the amniotic fluid volume is greater than 2,000 mL. The excess amniotic fluid can distend the amniotic sac and cause premature rupture of the membranes. Fetal hyperglycemia that leads to increased fetal diuresis is the most likely cause of polyhydramnios. Therapeutic amniocentesis can relieve the pressure of polyhydramnios and prevent premature rupture of the membranes, but it is associated with risks as well [15].

When the delivery of a preterm infant is imminent, mothers often receive corticosteroids, such as betamethasone and dexamethasone, to enhance fetal lung maturity before birth. This acceleration is intended to prevent respiratory distress syndrome and related complications following premature birth. But because these medications lead to hyperglycemia in women with diabetes, patients will require vigilant glucose monitoring and intensified insulin dosing while receiving corticosteroids [16].

Spontaneous Abortion and Stillbirth

Pregnant women with poorly controlled blood glucose have a 30% to 60% increased risk for spontaneous abortion [15]. Hyperglycemia of the fetus causes fetal hypoxia and acidosis, conditions that precede stillbirth.

Hypertension and Pre-Eclampsia

Whether it is pre-existing or of gestational onset, maternal hypertension affects the arteries that supply blood to the placenta. Low blood flow to the placenta is associated with preterm delivery and a low-birth-weight infant.

The terms pre-eclampsia, toxemia, and pregnancy-induced hypertension signify high blood pressure with proteinuria after the 20th week of pregnancy. For prompt detection of hypertension and pre-eclampsia, each prenatal visit should include a check of blood pressure and urinary protein. Edema, particularly in the legs, hands, and face, is a common symptom.

Pre-eclampsia is a serious complication of pregnancy and can cause:

- Placental abruption
- Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome
- Liver failure
- Kidney failure
- Seizures

Placental abruption is the premature separation of the placenta from the uterus before the baby is born. It can damage the placenta, cause heavy uterine bleeding or hemorrhage, and present a life-threatening situation for both mother and child.

HELLP syndrome is a severe form of pre-eclampsia occurring in approximately 5% to 12% of cases [17]. It can lead to liver hemorrhage, disseminated intravascular coagulation, pulmonary edema, kidney failure, and placental abruption. HELLP syndrome may develop after giving birth in women who had pre-eclampsia.

Eclampsia is diagnosed when pre-eclampsia progresses to cause maternal seizures. Left untreated, eclampsia can lead to coma, brain damage, and death for both mother and fetus. Eclampsia is the second leading cause of maternal death in the United States [18].

Treatment of Pre-Eclampsia

The only cure for pre-eclampsia is delivery. When gestational age is less than 37 weeks and the mother has mild pre-eclampsia, the condition can often be managed at home until the fetus reaches term. To halt the progression of pre-eclampsia, patients may undergo labor induction or a cesarean delivery at 37 weeks' gestation. In more severe cases, it may not be possible to consider gestational age before inducing labor or performing a cesarean.

To prolong gestation and prevent adverse outcomes to the pregnancy, the management and treatment of pre-eclampsia may include:

- Bed rest
- Blood pressure monitoring
- Antihypertensive medication
- Liver, kidney, and blood coagulation studies
- Fetal monitoring
- Corticosteroids
- Anticonvulsive medications

Bed rest may help lower blood pressure and increase blood flow to the placenta, allowing the fetus time to mature. The degree of hypertension and the maternal and fetal risk factors determine how strict bed rest must be. Strict bed rest at home requires the woman to lie in bed, sitting and standing only when necessary. Less stringent bed rest may allow the woman to sit on the couch or in bed while limiting most other physical activities. Severe cases of pre-eclampsia may warrant hospitalization for bed rest.

Corticosteroids may be necessary to reduce inflammation and treat HELLP syndrome. These medications can temporarily improve maternal liver and platelet functioning to prolong the pregnancy, typically up to 34 weeks' gestation. In general, these medications have a low-risk, high-benefit safety profile when used during pregnancy [19]. However, as discussed, steroids can cause a loss of glycemic control in patients with diabetes. Therefore, pregnant women with diabetes who require treatment with corticosteroids will require additional monitoring and appropriate insulin/medication dosage adjustment.

Increased Risk for Infection

Pregnant women with diabetes are at significant risk for infection involving virtually any organ system. Vaginitis, especially monilial infections, is common. This further increases the risk of urinary tract infection and pyelonephritis, which can lead to preterm labor. After delivery, bacterial and fungal breast infections may interfere with successful breastfeeding.

Periodontal Disease

Periodontal disease is a bacteria-induced inflammatory condition of the tissues surrounding the teeth. Destruction of the supporting structures of the teeth, such as the periodontal ligament, bone, and other tissues, results from this chronic inflammation. Insulin resistance, vascular changes, and an imbalance of the body's microscopic flora are all part of the pathophysiology of diabetes that may exacerbate the inflammation of periodontitis. This is compounded during pregnancy, which itself can increase gingival inflammation.

Periodontal disease is a complication of poorly controlled type 1 and type 2 diabetes, but it may also increase the risk of developing diabetes. One study revealed a higher prevalence of periodontal disease in women with GDM as compared to nondiabetic pregnant women [20]. In this study, the researchers concluded that the chronic inflammation of periodontal infection appears to induce insulin resistance and lead to GDM [20].

Increased Risk for Development of Type 2 Diabetes

Physiologically, GDM develops in the background of pre-existing maternal insulin resistance. Progressive worsening of beta-cell function in the presence of insulin resistance can lead to type 2 diabetes in the postpartum years. The incidence of progression of GDM to type 2 diabetes has increased over the past 30 years. Experts have identified societal lifestyle changes that have resulted in the higher body weight of women as a leading factor in this trend [3]. The future risk for type 2 diabetes will be discussed later in detail, including possible preventative measures.

Increased Risk for Development of Heart Disease

In addition to an increased risk for type 2 diabetes, women with a history of GDM have an elevated risk of developing CVD and hypertension later in life [21; 22; 23; 24]. Being overweight with a history of GDM or pre-eclampsia further increases this risk.

The American Heart Association recommends that healthcare providers ask female patients about their history of GDM in the routine assessment of cardiovascular risk. They also recommend referring women with complicated pregnancies to primary care or cardiology for close monitoring of cardiovascular risk factors [24].

RISKS TO FETUS AND INFANT

Glucose is a teratogen, and maternal hyperglycemia can directly affect yolk sac development. Furthermore, abnormal energy metabolism can adversely affect organ development in the embryo. These problems can lead to congenital malformations of the skeleton, central nervous system, heart, gastrointestinal tract, and kidneys. Congenital anomalies are directly associated with the mother's glycemic control in the three months prior to conception and the first two months of pregnancy [15].

Maternal hyperglycemia can also affect the growth of the fetus in the second and third trimesters of pregnancy, causing macrosomia and excess adiposity. A large gestational age (LGA) infant is at risk for complications of birth in addition to problems that may extend into later life.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Obstetricians and Gynecologists asserts that control of maternal hyperglycemia reduces the risk of macrosomia; therefore, maternal glucose management is recommended for pregnancies complicated by diabetes.

(https://journals.lww.com/greenjournal/Fulltext/2020/01000/Macrosomia__ACOG_Practice_Bulletin,_Number_216.50.aspx. Last accessed June 12, 2023.)

Level of Evidence: A (Good and consistent scientific evidence)

Possible fetal and infant complications of maternal diabetes include:

- Congenital defects
- Macrosomia
- Respiratory distress syndrome
- Hypoglycemia
- Polycythemia (or erythremia) and hyperbilirubinemia
- Hypocalcemia and hypomagnesemia
- Intrauterine growth restriction
- Risk for metabolic syndrome, obesity, and diabetes later in life

Congenital Anomalies

Major congenital malformations are the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes. Congenital anomalies are three to five times more likely in the offspring of mothers with pre-existing diabetes. Nearly 1 in 13 neonates born to mothers with pre-existing diabetes have one or more congenital anomalies. Infants of mothers with a history of poor preconception care and prepregnancy nephropathy have an especially high risk for congenital anomalies [25; 26].

Fetal organogenesis is usually complete six weeks after conception. Therefore, mothers should undergo A1C testing as soon as pregnancy is detected to help determine their glycemic control in those early weeks. The fetal organs commonly affected by maternal hyperglycemia are the heart, adrenal gland, thymus, spleen, and liver. Maternal hyperglycemia can also lead to malformation of the neural tube and the skeleton. Anal/rectal atresia, renal agenesis malformation, and ureter duplex may develop in some cases [12; 16].

Possible anomalies of the heart include asymmetric septal hypertrophy, transposition of the great vessels, ventricular septal defects, and/or cardiomyopathy. Approximately 30% of infants of mothers with diabetes present with one or more of these cardiac conditions [27].

Central nervous system defects are 16 times more common in infants born to mothers with diabetes. These include anencephaly, spina bifida, and caudal dysplasia. Even in the absence of severe anomalies, infants often display signs of neurologic development delay, such as immature sucking patterns [28].

Macrosomia

Fetal macrosomia, or LGA, refers to a birth weight of greater than 4,000 grams (or 8 pounds, 13 ounces) or greater than 90% for gestational age after correcting for neonatal sex and ethnicity [29]. While macrosomia occurs in about 10% of pregnancies overall, it occurs in 27% to 62% of infants born to mothers with diabetes [30].

Maternal hyperglycemia sets in motion a course of events that results in fetal macrosomia. When a mother has mild hyperglycemia, excessive glucose crosses the placenta and causes fetal hyperglycemia. This stimulates the fetal pancreatic production of insulin, which increases fetal growth and fat deposition. Potential complications of macrosomia include:

- Fetal death
- Fetal hypertonic cardiomyopathy
- Birth injuries
- Neonatal hypoglycemia, polycythemia (or erythremia), and hyperbilirubinemia

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Obstetricians and Gynecologists, women with gestational diabetes should be counseled regarding the option of scheduled cesarean delivery when the estimated fetal weight is 4,500 g or more.

(https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/02/gestational-diabetes-mellitus. Last accessed June 12, 2023.)

Level of Evidence: C (Consensus and expert opinion)

Birth Injuries

Possible birth trauma injuries in cases of macrosomia include shoulder dystocia, brachial plexus trauma, facial nerve injuries, and asphyxia. Shoulder dystocia is potentially catastrophic. While it occurs in fewer than 3% of all vaginal deliveries, 22% of infants weighing greater than 4,500 grams experience shoulder dystocia [31]. Shoulder dystocia occurs during birth when the infant's head is delivered, but the shoulder is unable to completely pass through the birth canal due to a discrepancy between the size of the fetal shoulders and the size of the pelvic inlet. Obstruction may affect one or both shoulders. Infants delivered after shoulder dystocia may experience brachial plexus injury, hypoxia, and even death. In addition to macrosomia, maternal obesity is also a risk factor for shoulder dystocia [31].

Maternal glycemia during the second trimester of pregnancy is the best predictor of large fetal size. Intensified glycemic control at this time can help prevent having an LGA infant in high-risk mothers. Furthermore, postprandial glucose level, rather than fasting, is most strongly associated with excess birth weight. Prenatal healthcare providers can predict macrosomia and estimate birth weight using clinical assessment techniques and tools, including measurements of fundal height and uterine palpation. In high-risk cases, ultrasound can also help predict birth weight [10; 31].

Respiratory Distress Syndrome

Respiratory distress syndrome, or hyaline membrane disease, is a serious neonatal complication associated with premature birth. It occurs with greater frequency and at later gestational age in infants of mothers with diabetes. Severe complications of respiratory distress syndrome, such as septicemia, patent ductus arteriosus, pulmonary hemorrhage, apnea, bradycardia, and failure to thrive, can cause significant morbidities [16; 32].

Neonatal Hypoglycemia

As noted, when exposed to hyperglycemia in utero, the fetal pancreas responds by producing excess amounts of insulin to help lower fetal blood glucose. After birth, when the umbilical cord is severed, the neonate no longer receives excessive glucose from its mother. While the neonate continues to produce insulin and is affected by prenatal insulin stores, hypoglycemia can result soon after birth.

Maternal hypoglycemia during pregnancy presents minimal risk to the fetus if the mother resolves her low blood glucose appropriately. When maternal blood glucose is low, the embryo or fetus can draw from glucose stores in the uterine lining or placenta as needed, thus preventing hypoglycemia in utero. When severe maternal hypoglycemia results in ketosis, the outcome may involve problems in the postnatal neurologic development of the offspring [15].

Polycythemia (Erythremia), Hyperbilirubinemia, and Electrolyte Abnormalities

Polycythemia, also known as erythremia, can result from intrauterine hyperglycemia causing fetal hypoxia and leading to an increase in erythropoiesis. While polycythemia infers an elevation in the total blood cell mass, the problem associated with infants born to mothers with diabetes involves an elevation of only the red cell mass, not the white blood cells or platelets. Hence, erythremia may be a more precise term to describe the condition [16]. A neonate with erythremia has a ruddy appearance and sluggish capillary refill and may experience respiratory distress.

Hyperbilirubinemia often appears concurrently with erythremia. The elevated red cell mass of erythremia increases the volume of bilirubin presented to the neonate's liver, which may be unable to process the excess load [28].

Infants born to mothers with diabetes are also at risk for electrolyte abnormalities, such as hypocalcemia and hypomagnesemia. These abnormalities, as well as the care of neonates with problems related to hyperglycemia, will be discussed in more detail in a later section of this course.

Intrauterine Growth Restriction

Although it is not as common as macrosomia, intrauterine growth restriction (IUGR) can result when the mother has diabetic vascular disease. Inadequate fetal nutrition is a major cause of IUGR and, in some cases, can be attributable to parental periconceptional and prenatal lifestyle, including maternal nutrition and diabetes. IURG limits a fetus's ability to achieve its genetic growth potential. IUGR can also be a result of nutritional deficiency due to placental insufficiency, which can be caused by preexisting vascular disease and/or diabetes [15; 151].

RISK TO OFFSPRING LATER IN LIFE

The effects of GDM on the health of the mother and her offspring are significant. The effects of GDM can extend beyond the prenatal and perinatal periods and cause health problems long after gestation and birth [3]. Exposure to diabetes in utero can herald several problems in offspring, such as:

- Obesity
- Metabolic syndrome
- Insulin resistance
- Prediabetes
- Type 2 diabetes
- CVD
- Cognitive disability

Numerous studies have demonstrated an association between elevated maternal glucose during pregnancy with obesity and diabetes later in the life of the offspring. Hyperglycemia in pregnant women is associated with increased risk of obesity in their children at 5 to 7 years of age, even in neonates of normal birth weight [33]. Fetal exposure to maternal blood glucose concentrations of more than 130 mg/dL is associated with an increased risk for childhood overweight/obesity at 3 years of age, with higher blood glucose levels correlating to greater risk to offspring [34].

The cause of these problems may be influenced by genetic factors. Influences in the postnatal environment, such as family lifestyle, socioeconomic conditions, and cultural factors, may also play a role in the development of future health problems. Despite this, there is a lower risk when maternal glucose intolerance is resolved in the second half of pregnancy. This indicates that hyperglycemia in utero does play a role in the development of significant health problems in the years to come [3; 35].

The Fetal Origins Theory

The fetal origins theory hypothesizes that developmental overnutrition and metabolic programming play important roles in the early development of disease. This theory provides an explanation of why exposure to hyperglycemia in the womb would predispose offspring to excess adiposity and metabolic disease later in life [36].

Overnutrition is defined as "the delivery of nutrients in excess of the needs required for normal growth" [37]. Developmental overnutrition describes a sequence of events, triggered by maternal hyperglycemia, that program the offspring to lifelong adiposity and increased risk for diabetes [35]. Metabolic programming is defined as "the phenomenon whereby a nutritional stress/stimulus applied during critical periods of early development permanently alters an organism's physiology and metabolism, the consequences of which are often observed much later in life" [37].

Research indicates that metabolic factors in utero can predispose an individual to abnormalities of metabolism later in life, including unhealthy blood glucose levels, fatty acids, triglycerides, inflammatory cytokines, insulin, growth factors, and other hormones. Metabolic programming appears to be a critical factor in the development of obesity and its comorbidities [37]. In the United States, obesity in children tends to begin early in life. At as early as 3 years of age, obese children have elevated levels of inflammatory biomarkers that predict heart disease later in life.

Insulin resistance noted in LGA newborns suggests that metabolic abnormalities may occur before birth [37]. This early derangement of metabolism appears to increase the risk for being overweight and having metabolic syndrome in youth and young adulthood [3; 35]. When metabolic syndrome occurs in youth, it predicts a higher risk for adult metabolic syndrome, diabetes, CVD, nonalcoholic fatty liver disease, polycystic ovary syndrome, and adiposity.

The Pima tribe of Arizona has the highest prevalence of diabetes in the world, with a rate of 50%, and studying this group has allowed for great increases in the understanding of the biologic origins of diabetes. For example, the strongest single risk factor for obesity in Pima children is exposure to maternal diabetes while in utero. Pima children born to mothers with diabetes have 10 times the risk of becoming obese during childhood and adolescence and for developing impaired glucose tolerance as adolescents compared to those born to mothers without diabetes. One study found that 45% of offspring of mothers with diabetes in this population developed type 2 diabetes by 24 years of age [37].

Cognitive Function in Later Life

As a teratogen, hyperglycemia can affect the growth and development of the fetal brain. Children exposed to hyperglycemia in utero have increased risks for learning disabilities, lower intelligence quotient (IQ), and motor impairments [15]. Children born to mothers with GDM appear to have twice the risk for cognitive deficits compared to offspring of mothers without diabetes [3]. Other evidence suggests that maternal metabolic conditions, such as diabetes, hypertension, and obesity, increase the risk for neurodevelopmental problems in children, including autism, developmental delay, and impairments in expressive language [38].

PRECONCEPTION CARE FOR WOMEN WITH DIABETES

The proactive management of diabetes is necessary to prevent adverse pregnancy outcomes in women of childbearing age who have pre-existing type 1 or type 2 diabetes. Ideally, preconception care takes place over the continuum of the woman's childbearing years rather than being addressed as an isolated event. Studies have consistently concluded that careful preconception care can prevent or reduce the risk for congenital malformations and spontaneous abortion. Unfortunately, many women with diabetes do not receive preconception care. Approximately 60% of pregnancies among women with diabetes are unplanned [25; 39]. In addition, about one-third of women of childbearing age who have diabetes have not been diagnosed [39].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Endocrine Society recommends that preconception counseling be provided to all women with diabetes who are considering pregnancy.

(https://academic.oup.com/jcem/article/98/11/4227/2834745. Last accessed June 12, 2023.)

Strength of Recommendation/Level of Evidence: 1|++OO (Strong recommendation based on low-quality evidence)

As discussed, diabetes during pregnancy is associated with a high risk for negative outcomes, and this is markedly true when the pregnancy or the diabetes is poorly managed. The risk of spontaneous abortion is as high as double that of the general population, and the risk for congenital malformation is two to five times greater. This risk increases proportionally with maternal glycemia during the first 6 to 8 weeks' gestation. Improved pregnancy outcomes are possible for women with pre-existing diabetes when blood glucose is well controlled and other existing comorbidities are well-managed prior to conception and throughout the pregnancy [16; 25].

According to the ADA, the goals of preconception care are to [40]:

- Provide preconception counseling that addresses the importance of glycemic control as close to normal as is safely possible (ideally A1C <6.5%) to reduce the risk of congenital anomalies.
- Discuss family planning and prescribe effective contraception until the woman is prepared and ready to become pregnant.
- Identify, evaluate, and treat complications of diabetes, including retinopathy, nephropathy, neuropathy, and CVD.

As Coustan states, "A planned pregnancy is the major objective of preconception counseling" [16]. Because organogenesis is mostly complete within eight weeks of the last menstrual period, blood glucose control in early pregnancy, while the woman may be unaware she is pregnant, is of vital importance [40; 41]. Preconception counseling in young women with diabetes should begin at puberty as part of routine diabetic care and should continue throughout reproductive life until menopause or permanent sterilization occurs. Patients should fully understand the rationale behind careful preconception care and glycemic management as it pertains to the course of pregnancy and the well-being of themselves and their infants. Patient teaching should include education about the risks of malformations associated with maternal hyperglycemia and instruction to maintain sexual abstinence or always use effective contraception unless blood glucose levels are well controlled and pregnancy is desired. Women wishing to delay pregnancy require general information about the risks of pregnancy, along with the importance of pregnancy planning and preconception care. In addition, women of childbearing age should be aware of the effects of medications they may be taking for diabetes or its complications, as a number of these are contraindicated in pregnancy [40].

PREPREGNANCY EVALUATION

A preconception history will review [10; 16]:

- History of diabetes, including type, age of onset, and past and present treatments
- Presence of diabetic, cardiovascular, gastrointestinal, or thyroid complications
- Comorbidities, such as hypertension, dyslipidemia, albuminuria, peripheral vascular disease, or neuropathy
- Current medications
- Prior pregnancies and obstetrical history
- Lifestyle behaviors, such as diet, exercise, and tobacco, alcohol, or drug-use habits
- Self-monitoring of blood glucose
- History of hypoglycemia and hypoglycemia awareness
- Previous diabetes education
- Psychologic status
- Social situation and support system

One study published in 2020 used a computer algorithm to review more than 2,000 parameters among 450,000 national electronic health records of pregnant women between 2010 and 2017 [105]. Researchers then narrowed down to nine parameters that were sufficient to accurately identify women at high risk of developing gestational diabetes. Among these parameters were age, BMI, family history of diabetes, and glucose test results during previous pregnancies (if applicable). This algorithm was applied to an additional 140,000 pregnancy records, with evidence that the algorithm consisting of nine parameters helped to accurately identify women who developed gestational diabetes. While more research is required, this study suggests the potential for better prepregnancy screening to identify those at high and low risk of developing gestational diabetes [105].

GLYCEMIC CONTROL

The patient's recent glycemic control should be evaluated prior to pregnancy. In a 2016 position statement, the ADA recommended that women have an A1C of less than 6.5%, or as close to normal as possible, before attempting conception [40]. Hemoglobin A1c (HgbA1c) levels should be assessed monthly in those who are planning pregnancy. Maintaining hemoglobin A1c levels closer to a target of 6.5% is likely to reduce the risk of congenital malformations [157]. The recommended preconceptual blood glucose targets are ≤90 mg/dL fasting, ≤130–140 mg/dL one hour postprandial, and ≤120 mg/dL two hours postprandial [40]. However, these strict targets pose a very real risk for severe hypoglycemia. Therefore, it is vital to educate patients and their support person(s) on the prevention, signs, symptoms, and treatment of hypoglycemia. It is also advisable to provide glucagon and education regarding how to use it. Monitoring blood ketone levels is also recommended for those who are hyperglycemic or feeling unwell, especially those with type 1 diabetes [157].

MEDICATIONS

Healthcare providers should carefully evaluate patients' medications prior to conception. Medications that may be contraindicated in pregnancy include statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and some oral antidiabetic agents [40].

Antihypertensives

Many people with diabetes use ACE inhibitors (e.g., lisinopril, fosinopril) or ARBs (e.g., losartan) to control hypertension and offset their risk for renal disease. The use of ACE inhibitors during pregnancy is associated with neonatal renal failure and spontaneous abortion [16]. Pregnant women should not take ARBs, as they may cause fetal malformations [40].

The ADA's recommendation for nonpregnant patients with diabetes is to maintain blood pressure at less than 130 mm Hg systolic and less than 80 mm Hg diastolic [40]. To maintain healthy blood pressure levels during pregnancy, a change in medications may be necessary. Methyldopa, labetalol, diltiazem, clonidine, and prazosin are considered safe for use in pregnant women with known hypertension [16; 40]. Other antihypertensives considered safe for use in pregnancy include calcium channel blockers, such as nifedipine [15; 42]. Providers should engage in patient-centered discussions with women considering pregnancy when making treatment planning decisions [157].

Statins

Lipid-lowering agents, such as statins, decrease the risk for cardiovascular and cerebrovascular events in patients with diabetes. Women should stop taking these medications a few months before conception, as they present an absolute contraindication to pregnancy. Women of childbearing age should be advised to use contraceptives while taking statin medications [42]. Because dyslipidemia is a chronic condition with slowly accumulating effects, discontinuing statins during pregnancy does not appear to have a long-term adverse effect on the health of the mother [15].

Antidiabetic Medications

Regarding oral medications used to treat diabetes, the ADA states that most oral agents cross the placenta and all lack long-term safety data [40]. Insulin is the principal therapy for pre-existing diabetes in pregnancy; preconception care often involves the discontinuation of oral hypoglycemic agents and the initiation of insulin [40]. Starting insulin prior to pregnancy not only provides the opportunity for glycemic control but also allows the patient to become familiar with and get comfortable using insulin. Intensive insulin therapy, with three to four injections per day, or the use of an insulin pump may be required in order to achieve the blood glucose targets recommended for preconception care [16; 42].

While the ADA advises discontinuation of all oral diabetes medications before conception, this may not be possible for all patients. Glyburide and metformin are the most common choices for use during pregnancy. The use of glyburide in general poses an increased risk of hypoglycemia compared with other oral antidiabetic agents; in maternal use, glyburide may also have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin [40;152]. Hypoglycemia can be life-threatening, and it is crucial to address if it occurs in any patient. Glimepiride and acarbose are also relatively safe, with studies showing no evidence of risk in humans. While these medications are not thought to be teratogenic, they do not provide the opportunity for intensive blood glucose control that insulin does [43; 44].

Folic Acid

Women with diabetes who are contemplating pregnancy should initiate prophylactic folic acid supplementation prior to conception. Research has concluded that lack of folic acid supplementation around the time of conception may double the risk of congenital heart defects in offspring born to women with diabetes [45].

PHYSICAL EXAM AND LABORATORY EVALUATION

For preconception care, the following evaluations are indicated:

- Obstetric/gynecologic exam
- Blood pressure measurement
- Dilated eye exam performed by an ophthalmologist
- Orthostatic heart rate and blood pressure responses
- Thyroid palpation
- Auscultation for carotid and femoral bruits
- Assessment of Achilles reflexes
- Vibratory sensation and monofilament assessment of feet

Hypertension must be treated promptly in women considering pregnancy in order to avoid the onset of pre-eclampsia [16]. Women who have had diabetes for more than 10 years or who have hypertension are at additional risk during pregnancy and may require a more thorough cardiac evaluation, including electrocardiogram and other tests to rule out underlying ischemic disease [16].

A good neurologic assessment can help identify the presence of neuropathy, a common complication of pre-existing diabetes. Measurements of orthostatic heart rate and blood pressure can detect autonomic neuropathy, while sensory and reflex testing of the lower extremities assesses for peripheral neuropathies.

In addition, all preconception patients with diabetes should have the following laboratory tests [16]:

- A1C to determine level of glycemic control
- Lipid profile to further evaluate metabolic control
- Creatinine clearance and microalbuminuria to assess renal function
- Free T4, thyroid stimulating hormone, and antibody testing for detection of thyroid disease

PRECONCEPTION STATUS OF CHRONIC COMPLICATIONS OF DIABETES

In addition to improving the chances for successful pregnancy, preconception care can also prevent health problems in the mother, as some chronic complications of diabetes can worsen during pregnancy. For women planning to conceive, the ADA recommends evaluation and treatment of retinopathy, nephropathy, neuropathy, and CVD prior to conception [46].

Certain medical complications related to diabetes are potential contraindications to pregnancy, as they present high risk to both the mother and child, including [16]:

- Ischemic heart disease
- Untreated active proliferative retinopathy
- Renal insufficiency

Ischemic heart disease and renal insufficiency present significant risk, including death, to both mother and fetus. Therefore, permanent sterilization may be considered for women with these conditions [16].

Retinopathy

If retinopathy is present, the risk of progression during pregnancy is double that during the non-pregnant state. Risk factors for progression include elevated A1C, longer duration of diabetes, and hypertension [16]. If retinopathy is not present before pregnancy, the risk of it developing during pregnancy is low [42].

As such, a dilated retinal exam by an ophthalmologist is an important part of preconception care. If a patient has preproliferative retinopathy or macular edema, she should have laser photocoagulation to stabilize her retinal status before pregnancy [41]. In women with proliferative or severe non-proliferative retinopathy, the ADA recommends slowly lowering the blood glucose levels to near-normal over a six-month period before pregnancy is attempted [25].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Endocrine Society, all women with diabetes who are seeking pregnancy have a detailed ocular assessment by a suitably trained and qualified eye care professional in advance of withdrawing contraceptive measures or otherwise trying to conceive.

(https://academic.oup.com/jcem/article/98/11/4227/2834745. Last accessed June 12, 2023.)

Strength of Recommendation/Level of Evidence: 1|++++ (Strong recommendation based on high-quality evidence)

Nephropathy

As mentioned, renal insufficiency presents significant risks to both mother and child and may contraindicate pregnancy. Nephropathy increases the risk for hypertension and may lead to debilitating lower extremity edema during pregnancy [16]. Assessment of diabetic nephropathy includes serum creatinine, glomerular filtration rate, and screening for albuminuria [42].

Neuropathy

Pregnancy does not increase the risk for the development of most neuropathies, with the exception of gastroparesis. Gastroparesis is an autonomic neuropathy that reduces the ability of the stomach to empty its contents. Pregnancy can present a risk for the development of transient and possibly severe gastroparesis in a woman with pre-existing diabetes. One etiology suspected to underlie worsening gastroparesis in pregnancy is an increase in intragastric pressure [153]. Signs and symptoms include nausea, vomiting, abdominal pain and bloating, diarrhea, and weight loss. Gastroparesis during pregnancy can be difficult to manage and is associated with poor perinatal outcomes and morbidity. In cases of severe gastroparesis, pregnancy may be contraindicated [16].

Cardiovascular Disease

In addition to routine cardiovascular assessment, the preconception evaluation should include additional tests for women at high risk. Risk factors include advanced age, longer duration of diabetes, hypertension, positive cardiovascular history, and symptoms. These patients should have electrocardiogram or echocardiography studies to rule out ischemic heart disease. As noted, ischemic heart disease poses significant risks to both mother and child and is a contraindication to pregnancy [16].

Other Comorbidities

Patients with type 1 diabetes should be screened for vitamin B12 deficiency and celiac disease as part of the preconception evaluation, as these conditions frequently co-occur. In addition, pregnancy and diabetes alone present a risk for thyroid disorder. Therefore, all women of reproductive age require evaluation for hypothyroidism.

THE PRECONCEPTION CARE TEAM

If the results of the healthcare evaluation indicate that it is safe to proceed with pregnancy, the goal of the prepregnancy management plan is to achieve normal blood glucose levels prior to conception and to maintain them throughout pregnancy.

Having a healthy pregnancy with positive outcomes requires commitment on the part of the woman with pre-existing diabetes. She will need to intensify her diabetes management daily and devote a significant amount of time to her medical care. She may incur substantial costs associated with a complicated pregnancy, including frequent medical visits, specialty consultations, and special tests to determine the fetus's well-being. In addition, she faces a greater likelihood of hospitalization during her pregnancy [16].

While it can have many challenges, pregnancy can also provide an opportunity for patients to learn diabetes self-management skills that may provide lifelong benefits. The desire to have a healthy baby is often a motivating force toward good self-care, and patients may be more receptive to making behavior changes at this time.

A multi-disciplinary team approach provides the most comprehensive patient care. As with any diabetes care team, the patient is an integral part and maintains an active role in her care [10]. Other members of the preconception care team are:

- Diabetes educator
- Registered dietitian
- Obstetrician
- Primary care provider
- Endocrinologist
- Nephrologist (in cases of proteinuria)
- Ophthalmologist (for dilated eye exam and treatment of retinopathy, if indicated)
- Cardiologist (for patients with coronary artery disease)
- Neurologist (for patients with neuropathy or autonomic dysfunction, such as gastroparesis)

From adolescence to adulthood, every contact with women with diabetes should include discussion on the benefits of preconception glucose monitoring and glucose control. Recording these discussions and plans can ease transitions. Providing a supportive environment and encouraging partners or other family members to be involved is beneficial [157].

CONTRACEPTION AND DIABETES

A planned pregnancy is the goal of preconception care. Sexually active women with diabetes who are in their reproductive years should take steps to prevent pregnancy if their blood glucose is uncontrolled, if they are using medications contraindicated in pregnancy, if they have untreated complications of diabetes, or if they do not desire pregnancy.

Some medications used to treat pre-existing diabetes (e.g., metformin, pioglitazone) can increase a woman's fertility [16]. Women of childbearing potential should be warned of the increased risk for pregnancy while using these medications. Birth control counseling or considering a change of medication may be warranted.

Sexual abstinence is the only guaranteed form of birth control and is the best personal choice for some women. However, abstinence is not feasible or desired for all patients, and other contraceptive options to avoid unplanned pregnancy should be discussed. No single method of contraception is right for every woman, whether she has diabetes or not. Effectiveness, ease of use, medical risk, and other factors guide individual decision making. A patient-centered approach should be utilized to make this decision [16].

Oral Contraceptives

When used as directed, oral contraceptives are 98% effective [13]. The oral agent of choice in women with diabetes is a low-dose combined estrogen plus progestin pill. These agents have not been associated with increasing insulin resistance, as the higher dose pills have. For postpartum women who are breast-feeding, it is safe to start low-dose contraceptives six to eight weeks after delivery [13].

The major disadvantage of oral contraceptive pills is their association with increased risk for thromboembolism, stroke, and heart attack, especially in older women and those who smoke. In addition, women who have reported migraines with aura should not be taking combined hormonal progestin-estrogen contraception for due to the increased risk of venous thromboembolism [154]. These risks are minimized when the formulation contains less than 35 mcg of estradiol and a low progestin dosage.

Barrier Methods

Barrier methods for contraception include the diaphragm and condoms. The concurrent use of spermicide increases the effectiveness of both options. The greatest advantage of a barrier method is that there are virtually no medical risks to using them. In addition, the condom is effective against some sexually transmitted infections.

Theoretically, if used properly, barrier methods have a 98% effectiveness rate [47]. However, in actual practice, they have effectiveness closer to 85% due to a high incidence of "user failure," mainly due to couples not using the method faithfully or correctly. Insertion of the diaphragm up to one hour before intercourse, so it does not interfere with foreplay, may improve effective use.

Natural Family Planning

Natural family planning, or the rhythm method of birth control, relies on knowledge of the ovulatory cycle to avoid intercourse during fertile periods. With this method, the woman predicts her time of ovulation based upon the time of the last menstrual period, changes in cervical mucus, and basal body temperature. A major advantage of this method is that it does not present any medical risks. In the general population, this method has an effectiveness rate of only 75% to 80%, mainly due to related to inconsistencies in tracking [48]. For women with diabetes, the failure rate may be even greater, as they are more likely to have irregular menstrual cycles.

Sterilization

Male or female permanent sterilization is an option for those who have completed childbearing. Because it is essentially irreversible, people considering this method of birth control must be fully educated that they are making a permanent choice. The inherent risks of any surgical procedure are present for those undergoing permanent sterilization. However, for those with diabetes, the ongoing risk of pregnancy may outweigh the temporary risk of the surgical procedure.

MANAGING PRE-EXISTING DIABETES DURING PREGNANCY

As discussed, hormonal influences during normal pregnancy cause a progressive increase in maternal insulin resistance, which can result in maternal hyperglycemia, leading to adverse pregnancy outcomes. The normal hormonal changes of pregnancy require women with pre-existing diabetes to intensify their prepregnancy diabetes management plan to maximize their chances for an optimal outcome to the pregnancy. For example, women with pre-existing diabetes will usually face stricter nutritional recommendations during pregnancy. Those using oral antidiabetic medications will likely require a switch to insulin. If already using insulin, increased or more frequent dosing may be necessary.

Being pregnant often motivates women to take better care of their diabetes than they do during their nonpregnant state. Patient educators can capitalize on this time of enhanced readiness by teaching skills and fostering behavior that patients may continue for the rest of their lives. Indeed, preconception care for the next pregnancy should begin in the immediate postpartum period. According to an ADA position statement, optimal long-term outcomes require "seamless continuation of intensified management in the years after pregnancy and in preparation for the next desired conception" [10].

GLYCEMIC CONTROL DURING PREGNANCY

Excellent glycemic control, beginning in the first trimester and maintained throughout the pregnancy, is linked with the lowest risk for maternal, fetal, and neonatal complications. First-trimester hyperglycemia is associated with excess spontaneous abortion and fetal malformation, and this risk rises as glucose control worsens. In addition, second-trimester hyperglycemia is the most reliable predictor of macrosomia and related complications.

The ADA's goals for glycemic control during pregnancy are to achieve and maintain near normal glycemia while minimizing hypoglycemia throughout the pregnancy. Glycemic targets are [25; 40]:

- Pre-meal, bedtime, and overnight: 60–99 mg/dL
- Peak postprandial: 100–129 mg/dL
- Mean daily glucose: <110 mg/dL
- A1C: <6%

Individualized higher targets may be necessary for those with hypoglycemia unawareness or who are unable to tolerate intensified management.

Research on the benefits of glycemic control in GDM suggests that the targets may need to be lower than these recommendations from the ADA, a finding that could generalize to the women with pre-existing diabetes [49].

Self-Monitoring of Blood Glucose

Pregnant women with diabetes require frequent self-monitoring of blood glucose (SMBG) to carefully assess for either high or low blood glucose. Pregnancy can give rise to an increased potential for wide blood glucose fluctuations. For example, there is a greater risk for rapid-onset hypoglycemia during pregnancy when fasting or when physical activity is increased. Conversely, there is a greater hyperglycemic response to carbohydrate intake, stress, and illness.

SMBG provides patients with immediate feedback on how daily choices affect blood glucose levels. This gives the patient reliable information for problem solving and decision making. Blood glucose testing results are also used to assess the effectiveness of therapy and to guide adjustments in diet, medications, and activity levels.

Women with type 1 diabetes may perform SMBG testing as many as eight times per day throughout pregnancy, with testing often completed before and after each meal, at bedtime, and in the middle of the night. This gives patients the opportunity to promptly recognize blood glucose fluctuations and make needed adjustments in their insulin doses [10; 16].

Postprandial glucose levels are most strongly associated with excess birth weight and are the best guide to SMBG during pregnancy [16]. In women with diabetes, postprandial glucose peaks approximately 90 minutes after beginning a meal. However, there is considerable individual and day-to-day variability in this. The postprandial sample should be taken one hour after the beginning of the meal to best measure the peak glucose following the meal. Patients who use rapid-acting insulin before meals should also test their blood glucose before eating so they can adjust their insulin dose appropriately.

Alternate Site Testing

Although some manufacturers of blood glucose monitoring devices offer alternative site testing, the finger-stick method is considered the most accurate for all patients with diabetes. Alternate site testing allows people to collect the blood test sample from the palm of the hand or the forearm, areas that have less innervation and may be more comfortable for the tester. However, alternate site testing may not identify the rapid changes in glucose levels that are characteristic of pregnant women. It may also give different results than finger stick. For these reasons, alternate site testing is not recommended for pregnant patients with diabetes.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) may be useful in select pregnant patients with type 1 diabetes, especially in those with hypoglycemia unawareness [25]. CGM systems check glucose levels in the interstitial fluid using a small sensor that is placed under the skin. The sensor can remain in place for up to one week before being replaced. The sensor sends information about glucose levels through a transmitter to a small, wireless monitor. CGM devices provide real-time measurements of glucose levels, displaying them every one to five minutes. Users can set alarms to alert themselves when glucose levels are too low, too high, or rapidly fluctuating.

Approved CGM devices are not as accurate or reliable as standard blood glucose meters. Furthermore, interstitial fluid glucose levels are 20% to 50% lower than blood glucose levels. Therefore, users must calibrate the device with several capillary glucose levels per day to correct this difference. Because interstitial glucose levels are not the same as blood glucose levels, the user must still perform SMBG before making a change in treatment, such as modifying an insulin dose [25].

Glycosylated Hemoglobin (A1C)

The A1C is a laboratory test that uses a venous blood sample to show the average blood glucose over the previous two- to three-month period. The test works by measuring the amount of glucose that is chemically attached to the red blood cells (RBCs). RBCs that have been exposed to high amounts of glucose over their life span, which is about 90 to 120 days, will have more glucose attached to them. Results of the A1C test are expressed as a percentage, reflecting the relative amount of glucose that has been in the blood over the previous two or three months. Based on extensive studies, the ADA recommends a general A1C goal of less than 7% in nonpregnant people to prevent microvascular and macrovascular complications of diabetes [25].

The A1C is routinely measured every three to six months in people with diabetes [25]. A position statement by the ADA for managing pre-existing diabetes during pregnancy recommends checking the A1C at the initial prenatal visit, then monthly until target levels are achieved and every two to three months thereafter [10].

Frequent testing of A1C during pregnancy may be a useful tool to guide therapy, based on the premise that the A1C is affected by the normal physiology of pregnancy, during which the lifespan of the RBC is closer to 90 days, as opposed to nearly 120 days in the nonpregnant state. Therefore, the A1C of a pregnant woman is indicative of glucose control during a shorter time interval, reflecting the rate of change in glycemic control over just a few weeks' time. Healthcare providers can observe the rate of glycemic change by measuring the A1C at weekly prenatal visits and comparing them to the previous week's value. Thus, providers can use this information to effectively guide treatment decisions [50].

Ketones and Diabetic Ketoacidosis

Ketoacidosis can develop rapidly in a pregnancy complicated by diabetes due to the physiologic insulin resistance, increased fat metabolism, and rapid depletion of insulin stores that occurs naturally in the pregnant state [25]. Diabetic ketoacidosis (DKA) is usually associated with type 1 diabetes but can also occur in type 2 diabetes and can develop at lower levels of hyperglycemia in pregnant women with either type of diabetes. DKA during pregnancy is associated with a high fetal mortality rate. Maternal fasting ketonemia is associated with decreased intelligence and poor development of fine motor skills in the offspring.

Predisposing factors for DKA include:

- Infection
- Vomiting
- Dehydration
- Gastroparesis
- Omission of insulin doses
- Some medications used to manage obstetrical complications

DKA should be suspected in patients who present with vomiting, nausea, abdominal pain, fever, and poor oral intake. Ketoacidosis requires urgent and aggressive treatment, including correction of blood glucose levels, electrolyte imbalance, and dehydration by means of multiple intravenous infusions. Fetal monitoring is also indicated [51]. These interventions usually take place in intensive care or special care units that specialize in high-risk pregnancies.

Patient teaching of pregnant women with diabetes includes education on the risks, prevention, and treatment of DKA [25]. Pregnant patients with pre-existing diabetes should know how to check urine for ketones when sick or if blood glucose exceeds 180 mg/dL. If moderate-to-large ketones are present in the urine, the patient should alert her physician immediately, as this can be a sign of impending DKA.

While urine ketone tests help identify impending DKA, they are not reliable for diagnosing DKA. Therefore, healthcare providers should order blood testing to confirm ketonemia when ketones are detected in the urine [16]. Ketone testing is especially important for those using continuous subcutaneous insulin infusions (CSII), also known as insulin pumps. Malfunction of the pump or infusion site problems can cause an inadvertent and life-threatening drop in insulin levels.

Starvation ketosis may occur during pregnancy when women limit their carbohydrate intake according to nutritional recommendations or in those who have difficulty eating due to nausea and vomiting. While there is insufficient data to be certain if starvation ketosis is associated with decreased intelligence in the offspring, it is important to take measures to prevent it in pregnant patients.

Insulin

Insulin is the treatment of choice for pregnant and nonpregnant patients with type 1 diabetes. It is also the recommended agent for women with type 2 diabetes during pregnancy, as oral agents do not usually provide adequate glycemic control [25]. Additionally, insulin does not cross the placenta, easing concern that the drug may cause harm to the fetus [52]. The primary goal of insulin replacement during pregnancy is to achieve plasma glucose concentrations nearly identical to those observed in nondiabetic women. However, achieving the goal of rigid glycemic control is less important than avoiding symptomatic hypoglycemia [16].

A basal-bolus insulin regimen usually produces the best results. This type of regimen provides sufficient insulin throughout the 24-hour period to maintain "background" insulin requirements while providing the appropriate surge of rapid-acting insulin to meet increased needs at mealtime. Anticipated carbohydrate intake, pre-meal blood glucose, and expected activity level guide the dosage decision for the pre-meal insulin. Human insulin should be used exclusively during pregnancy. For consistency of absorption, the abdomen or hips are the best choice for injection sites [10]. Inhaled bolus insulin is also an option [53].

Intermediate-Acting Insulin

Until recently, neutral protamine Hagedorn (NPH), an intermediate-acting insulin, was the only basal insulin recommended for use in pregnancy. Although other options now exist, it is still the favored choice of most prescribers.

Long-Acting Insulin Analogs

Researchers are investigating the safety of the long-acting insulin analogs detemir (Levemir) and glargine (Lantus) during pregnancy [145]. These long-acting agents produce a low, steady level of insulin replacement to satisfy basal requirements, closely imitating normal physiologic basal insulin secretion. In nonpregnant people with diabetes, long-acting insulin analogs have the benefit of having a lower risk for hypoglycemia because of their long elimination half-life and lack of peak insulin action.

In 2012, the U.S. Food and Drug Administration (FDA) gave insulin detemir an improved safety rating for use in pregnancy, upgrading it from category C to category B. The category B rating means that animal studies have not demonstrated a risk to the fetus, but well-controlled studies in humans are still pending. (It should be noted that in 2014, the FDA made a final ruling that pregnancy categories should be removed and replaced with detailed information that would more accurately assist healthcare providers in determining benefit versus risk for their patients [146].) Detemir received an improved safety rating after research concluded that infants born to women with type 1 diabetes who used insulin detemir were not at increased risk for fetal anomalies compared to those taking NPH insulin [44]. Furthermore, women who used insulin detemir had a similar reduction in A1C and lower fasting plasma blood glucose at weeks 24 and 36 compared to those using NPH insulin. Detemir is the first and only basal insulin analog to have received a pregnancy category B rating from the FDA [54; 55].

Glargine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [56; 57]. Insulin glargine previously carried a pregnancy category C rating, meaning that adverse effects have been seen in animals and there are no adequate human studies [25; 44; 57]. A major concern about glargine is that it can bind with growth factors that may influence fetal growth [44].

While meta-analyses comparing insulin glargine and NPH insulin suggest that there is no increased risk for adverse maternal and fetal outcomes with glargine use during pregnancy, clinical trials to demonstrate its safety in humans during pregnancy are pending [44]. Research also indicates that glargine does not cross the placenta [42; 58; 59].

Rapid- and Fast-Acting Insulin

Rapid-acting analogs, such as insulin lispro and insulin aspart, are safe for use during pregnancy, demonstrating minimal transfer across the placenta and no evidence of teratogenesis, as well as being effective [44]. These agents are preferred over regular insulin because they tend to produce better postprandial control and a lower risk for hypoglycemia [10; 13; 44]. Most formulations available are administered subcutaneously. A newer option, Afrezza, is an inhaled rapid-acting insulin administered prior to each meal, however, information specific to the use of inhaled insulin during pregnancy is limited [44; 53].

Insulin Pumps

Insulin pumps, also known as continuous subcutaneous insulin infusion (CSII) devices, are small, battery-operated microcomputers that resemble a standard pager device in size and appearance. Usually worn on the belt or waistband, the pump is connected by a small plastic tube to a subcutaneous catheter inserted into the abdomen. The infusion set is usually changed every two to three days. The pump is programmed to deliver a continuous infusion of insulin all day, known as the basal rate. When food is eaten, the user programs the pump to deliver a bolus infusion of insulin appropriate to the amount of carbohydrate to be ingested.

In nonpregnant populations, the major advantage of the pump is the opportunity for tight blood glucose control. This is possible because insulin delivery becomes very similar to the normal physiologic pattern. Pumps are an alternative to multiple-dose injections and are thus more commonly used in type 1 diabetes. There is evidence that using CSII devices may result in more stable blood glucose while avoiding excessive high and low blood glucose [60]. Pumps also offer the benefit of a more normal lifestyle, allowing users added flexibility with meal and activity patterns.

Proper education is vitally important for any patient who uses the CSII system. Improper use can result in dangerous or life-threatening hypoglycemia or hyperglycemia. In people with type 1 diabetes, DKA can result when there is a failure of insulin delivery due to the catheter tubing becoming kinked, the infusion site losing patency, or malfunctions of the device.

Insulin pumps may be most helpful for pregnant women who have frequent hypoglycemia and pronounced dawn phenomenon. When the patient-centered team deems pump therapy the best choice for an individual pregnant patient, she will likely require at least three different infusion rates during a 24-hour period. An example regimen is [16]:

- Midnight to 4:00 a.m.: Lowest basal dose rate
- 4:00 a.m. to 10:00 a.m.: Basal rate increased to meet the demands of cortisol and growth hormone levels that rise during this time
- 10:00 a.m. to midnight: Moderate rate based on individual needs

Furthermore, it is necessary to adjust basal rates of insulin throughout the pregnancy to match the natural hormonal changes that occur during gestation. While insulin pumps are safe and may be effective when used during pregnancy, there is not sufficient evidence that their use results in improved outcomes over multiple daily injections [10; 60; 61].

Insulin Needs for Type 1 Diabetes During Pregnancy

Pregnant women with type 1 diabetes require multiple daily injections of insulin to achieve excellent glycemic control. The optimal regimen for type 1 diabetes is three injections of NPH and three injections of a rapid-acting analog per day in the following manner [16]:

- NPH insulin every eight hours
- Rapid-acting insulin before each meal

Injections of rapid-acting insulin before each meal provide meal flexibility and proper dosage adjustment to avoid hypoglycemia. This is especially helpful during early pregnancy, when anorexia and vomiting may be a problem. The patient on this regimen must perform SMBG frequently and learn to match her insulin dose with anticipated carbohydrate intake at each meal while taking the pre-meal blood glucose and anticipated exercise into account [16].

Blood glucose is unstable during early pregnancy, and nocturnal hypoglycemia is common. Patients with type 1 diabetes should check blood glucose between 3:00 a.m. and 4:00 a.m. and know the symptoms of nocturnal hypoglycemia, including restlessness, sweating, nightmares, and morning headache. Fasting hyperglycemia in the morning may signify that there has been low blood glucose in the middle of the night. To prevent nocturnal hypoglycemia, advise patients to take the evening dose of NPH at bedtime so its peak action occurs at breakfast time and not in the middle of the night [16].

A woman's insulin needs begin to increase at 18 to 24 weeks' gestation. In twin pregnancies of mothers with type 1 diabetes, the required insulin dose is double that of singleton pregnancies between 14 and 27 weeks [62]. Insulin needs continue to rise successively until about 35 to 36 weeks, when they may level off or decline.

In the postpartum period, insulin-opposing hormones rapidly clear from the circulation following the delivery of the placenta. This results in a significant decline in the mother's insulin needs during this time. Meanwhile, high doses of insulin taken prior to birth become unbound and released into circulation. For these reasons, the mother with type 1 diabetes may not require any subcutaneous insulin injections for up to 72 hours postpartum [16].

Insulin Needs for Type 2 Diabetes During Pregnancy

As noted, insulin is the treatment of choice for women with pre-existing type 2 diabetes during pregnancy. Women who use oral diabetes medications should generally discontinue these and start insulin during the preconception period or soon after becoming pregnant. If a woman becomes pregnant while taking metformin or glyburide, it is safe to continue these drugs for a short time, pending the initiation of insulin, as they appear to be relatively safe compared to the teratogenic effects of hyperglycemia [10].

The normal physiologic changes of pregnancy add to the pre-existing insulin-resistant state associated with type 2 diabetes, requiring intensification of the diabetic care regimen. The total daily insulin dose begins at 0.7–1.0 units/kg actual body weight and will require ongoing adjustment throughout the pregnancy. Obese patients with pre-existing diabetes usually require higher insulin doses, and their requirements may double or triple during pregnancy [10].

Hypoglycemia

From a physiologic standpoint, the risk for hypoglycemia increases during early pregnancy. Additionally, insulin-induced hypoglycemia is more pronounced in pregnancy and is more dangerous to the fetus. Blood glucose control that is too tight is associated with growth restriction and can result in microsomia and other neonatal and developmental problems.

Experts recommend higher blood glucose targets for any patient with hypoglycemia unawareness. The family and other support people should be included in patient teaching. Some of the signs of hypoglycemia may be difficult to discriminate from symptoms of pregnancy, such as nausea, hunger, headache, and weakness. The patient and family should be advised to check blood glucose to verify that it is less than 60 mg/dL before instituting aggressive treatment with fast-acting carbohydrates. In some cases, family members will require education regarding how to administer glucagon. Patient and family teaching also includes strategies to prevent hypoglycemia.

Frequent SMBG will help identify early trends toward low blood glucose. Patients also benefit from instruction on the careful administration of insulin, proper timing of meals, maintaining the adequacy of meals, and careful management of exercise. If hypoglycemia develops, the patient should immediately consume 15–20 grams of a fast-acting carbohydrate. The best treatment choices for mild hypoglycemia during pregnancy are 1 cup of milk or three to five glucose tablets. For blood glucose less than 50 mg/dL, patients may drink one cup of orange juice. Fifteen minutes after treatment, patients should recheck blood glucose and treat again if hypoglycemia persists. Foods such as candy bars, cookies, and ice cream are less desirable choices for treating hypoglycemia, as their fat content delays absorption and slows the response to treatment. After correction of hypoglycemia, patients should eat a meal or snack to prevent a recurrence. When hypoglycemia is very severe, the patient will be unable to swallow. In this case, another person should give 1 mg glucagon intramuscularly to the patient and call for emergency assistance. After she is awake and alert, the patient should have a meal or snack to prevent relapse.

MEDICAL NUTRITION THERAPY DURING PREGNANCY

In pregnancies complicated by pre-existing diabetes, medical nutrition therapy involves managing the nutritional needs of the pregnancy along with the role of diet in diabetes. The criterion standard for nutritional management in these patients is referral to a registered dietitian, which ensures an individualized meal plan that meets the nutritional needs for fetal growth and development while also meeting the glycemic goals of the mother [16]. As a cornerstone of diabetes management, all members of the diabetes care team should be well-informed about the nutrition goals and be supportive of the meal plan.

According to the ADA, the goals of medical nutritional therapy during pregnancy are to provide adequate energy and nutrients needed for optimal outcomes. In its 2023 guideline, the ADA recommends that nutrition counseling for pregnant patients should endorse a balance of macronutrients, including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with omega-3 fatty acids that include nuts and seeds and fish in the eating pattern [150]. General guidelines for the nutritional management of pre-existing diabetes are to [63]:

- Include carbohydrates from whole grains, fruits, vegetables, and milk
- Base the daily carbohydrate allowance upon total carbohydrate intake from all sources
- Provide 60% to 70% of daily caloric intake from carbohydrate and monounsaturated fat
- Provide 15% to 20% of daily energy intake from protein (if renal function is normal)
- Provide less than 10% of the daily energy intake from saturated fats

Special considerations for pregnancy with prior-onset type 1 or type 2 diabetes are to [63]:

- Individualize the meal plan.
- Advise eating on a consistent basis to avoid hypoglycemia.
- Advise consuming an evening snack to decrease the risk for nocturnal hypoglycemia and fasting ketosis.
- Encourage good record-keeping of SMBG results and food intake to assist in decision making with regard to insulin and dietary adjustments.

Weight Gain

The Institute of Medicine (IOM) provides national guidelines for recommended weight gain during pregnancy [64]. The recommended caloric intake and rate of weight gain depends upon the woman's pregravid body mass index (BMI). For example, a woman with a prepregnancy BMI in the normal range has the lowest risk for obstetrical complications and premature birth with weight gains of 25 to 35 pounds during pregnancy. Overweight women should gain 15 to 25 pounds, and obese women should gain about 15 pounds for optimal outcomes. These recommendations are appropriate for women with diabetes if they are getting adequate nutrition and maintaining glycemic goals.

Morning Sickness

Nausea and vomiting during pregnancy can add to the challenges of caring for a woman with diabetes. When vomiting occurs, it is often necessary to adjust the insulin dosage. In cases of recurrent vomiting, the woman may need to modify the time interval between her pre-meal injection and the start of her meal in order to ensure that the meal will stay down as the insulin approaches its peak action [16].

Because nausea is a symptom that overlaps both pregnancy and hypoglycemia, patients should check blood glucose to rule out low blood glucose as the cause. Glucagon may be prescribed to prevent or treat hypoglycemia that can exacerbate nausea. Glucagon may also be used if a patient vomits her meal after taking pre-meal insulin.

In severe cases, the woman with hyperemesis may require hospitalization in order to prevent dehydration, resolve electrolyte imbalance, and prevent weight loss. Indications for hospitalization include protracted vomiting of greater than eight hours duration, recurring hypoglycemia, and/or ketonuria. Treatment involves IV fluids and potassium replacement, blood glucose monitoring, and ketone testing. Antiemetic medications may be appropriate in some pregnant women who experience excessive vomiting.

EXERCISE

Exercise helps create a sense of well-being and has many other health benefits. In a pregnant woman with diabetes, it can reduce fetal adiposity, improve glucose control, limit weight gain, and promote better tolerance of labor. Patient care includes education on these benefits.

For pregnant women without contraindications, experts recommend at least 150 minutes of moderate-intensity aerobic activity per week. If more convenient, patients can divide exercise into more frequent, shorter bouts, such as three 10-minute sessions [10]. For pregnant patients who have been sedentary, a fitness program of low-impact walking, swimming, and stationary bicycling is recommended. Yoga exercises provide stretching and strengthening of the muscles used for labor and childbirth. If a woman has been exercising prior to becoming pregnant, she may continue her normal routine under the supervision of her healthcare provider, with modifications as necessary as the pregnancy progresses [65].

Patients at risk for hypoglycemia should check their blood glucose prior to exercise and consume 15 grams of carbohydrates if the level is less than 100 mg/dL. Patients can use SMBG to monitor the effects of exercise and to adjust carbohydrate and/or insulin intake as indicated. Patients with pre-existing diabetes may have complications, such as CVD, retinopathy, nephropathy, or neuropathy, requiring modification of the exercise plan.

For pregnant women, experts recommend exercise types that avoid the supine position and minimize the risk of loss of balance. Patients should terminate exercise and seek medical attention if they have painful contractions, difficulty breathing, lightheadedness or dizziness, chest pain, headache, vaginal bleeding, or leaking of amniotic fluid during exercise.

DIABETES COMPLICATIONS AND PREGNANCY

The chronic complications of diabetes have a profound effect on the healthcare system and the individual. In the United States, uncontrolled diabetes is the foremost cause of adult-onset blindness and a leading cause of end-stage renal disease. It also causes significant morbidity and disability due to foot ulcers and lower extremity amputation. In addition, having diabetes increases the individual risk for CVD by two to four times. It can also lead to periodontal disease, sexual disorders, and a host of other health problems.

A large body of research since the 1990s has shown that good glycemic control can prevent or slow the progression of the chronic complications of diabetes. Based on these findings, the ADA recommends maintaining an A1C of 7% or less for most people with diabetes in order to prevent complications. Furthermore, blood pressure control, maintaining healthy lipid levels, and abstaining from tobacco use offer additional and significant reduction of risk for chronic complications [25].

The long-term complications of diabetes are classified as microvascular or macrovascular, according to the type of blood vessel damage that is affected. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications of diabetes are CVD, cerebral artery disease, and peripheral vascular disease.

Microvascular Complications

Prolonged hyperglycemia leads to changes in the structure of the microscopic vessels that supply the retina of the eye, the glomeruli of the kidney, and the peripheral and autonomic nerves. These complications are especially aggressive in young people with type 2 diabetes.

Retinopathy

As stated, the risk of developing new diabetic retinopathy during pregnancy is low. However, if it is already present, the risk of its progression during pregnancy is high. While as many as half of women with underlying retinopathy experience deterioration during pregnancy, many cases improve following delivery and can return to the pre-pregnant state within six months postpartum [66].

Poor blood glucose control, either before or during pregnancy, is associated with a more rapid advancement of retinopathy during pregnancy. Other risk factors for progression include a longer duration of diabetes, elevated first-trimester A1C, chronic hypertension, nephropathy, and pre-eclampsia. Rapid normalization of glycemia is also associated with the deterioration of retinopathy during pregnancy [66].

As mentioned, the dilated eye exam is a vitally important aspect of preconception care for women with pre-existing diabetes. It is prudent to repeat the exam in the first trimester of pregnancy, with close follow-up throughout the term. The patient's retinopathy status will determine the interval of subsequent retinal exams.

If a patient has significant proliferative retinopathy in the preconception period, it should be stabilized before she becomes pregnant. If there is preproliferative eye disease before pregnancy, it is likely to progress to active proliferation. Generally, pregnant women with preproliferative disease will go through laser treatment soon after the detection of pregnancy. Because retinopathy can progress very quickly, these patients are likely to require many laser sessions. Referral to an ophthalmologist may be warranted.

If proliferative disease develops during pregnancy, the patient urgently requires laser treatments to preserve her vision. Retinal and vitreous hemorrhage can occur during vaginal delivery in women with untreated diabetic retinopathy. Pregnancy does not complicate routine laser treatment for retinopathy, and the mydriatic drops used to dilate the pupils are generally very safe [67].

Nephropathy

Fortunately, pregnancy does not seem to accelerate the time progression of renal disease in the mother with diabetes, nor does it precipitate end-stage renal disease. Progression to renal disease is more closely related to the duration of diabetes and the degree of glycemic and blood pressure control, just as it is in the nonpregnant woman with diabetes [66].

Although the future risk to the mother's renal status is low, diabetic nephropathy during pregnancy poses other serious risks to both the mother and the fetus. Impaired renal function is a strong risk factor for fetal growth restriction, pre-eclampsia, and premature delivery. Even early nephropathy is associated with an increased risk for fetal growth restriction. There is usually a decline in the renal function of pregnant women with underlying diabetic nephropathy. As renal blood flow and the glomerular filtration rate increase by 30% to 50% during pregnancy, the risk for proteinuria increases.

Significant renal disease is associated with a high risk of infant mortality, and these risks are even greater when hypertension accompanies renal disease. For the post-renal transplant patient who is medically stable, pregnancy may be safe, although it remains high risk [16].

Neuropathy

Pregnancy does not increase the risk for or affect the progression of most common neuropathies of diabetes. For example, peripheral neuropathy affecting the sensory nerves of the feet and hands usually does not worsen during pregnancy. However, certain autonomic neuropathies, such as gastroparesis, can have a significant impact on the course of a pregnancy.

Autonomic neuropathies affect the nervous supply to the internal and regulatory organs. Gastrointestinal problems associated with autonomic neuropathy include slowed digestion of food in the stomach—a condition known as gastroparesis. Gastroparesis can cause irregular absorption of nutrients, inadequate nutrition, and erratic blood glucose levels in the pregnant woman. This can make it difficult to maintain glycemic control and appropriate nutritional status. Clinicians may prescribe metoclopramide or erythromycin to treat gastroparesis in pregnancy. When gastroparesis causes severe and retracted emesis, patients may require total parenteral nutrition (TPN). Severe gastroparesis is a contraindication of pregnancy [16].

Macrovascular Complications

The development of serious large-vessel disease is also associated with diabetes. Macrovascular complications of diabetes involve the cardiovascular, cerebrovascular, and peripheral vascular systems, leading to high incidences of heart attack, stroke, and lower extremity disease.

While hyperglycemia has injurious effects on large blood vessels, hyperinsulinemia is also responsible for the damaging effects to the cardiovascular system. High blood levels of insulin result from insulin resistance in the tissues, and insulinemia is associated with a series of adverse metabolic changes that greatly increase the risk for CVD. These changes characterize metabolic syndrome, a cluster of disorders that includes two major independent risk factors for myocardial infarction: hypertension and dyslipidemia.

Cardiovascular Disease

Diabetes is an independent risk factor for the development of CVD both during pregnancy and postpartum [68; 69]. Since the 1990s, there has been a dramatic and unprecedented rise in type 2 diabetes in younger people. In turn, more cases of CVD in the pregnant population have been noted. The incidence of active or previously treated coronary heart disease is about 1 in 350 in diabetic pregnancies, as compared with 1 in 10,000 pregnancies in the general population. The risk of ischemic stroke is four to eight times greater in women with type 1 or type 2 diabetes as compared to similarly aged women without diabetes [10]. Therefore, CVD risk assessment and risk factor management are important in women of reproductive age with diabetes. Factors that further increase the risk for CVD include:

- Age older than 35 years
- Duration of type 1 diabetes greater than 15 years
- Duration of type 2 diabetes greater than 10 years
- Family history

Hypertension

The prevalence of hypertension in pregnancy increases with age and with the duration of diabetes. It can be associated with serious perinatal complications, such as premature delivery, eclampsia, and neonatal morbidity. Therefore, every prenatal visit should include a measure of blood pressure. According to the ADA, the blood pressure goal in pregnant women with diabetes is [10; 40]:

- 110–140 mm Hg systolic
- 80–85 mm Hg diastolic

If blood pressure is greater than or equal to 130/80 mm Hg, a repeat measurement at or above this level on a separate day confirms the diagnosis of hypertension. When blood pressure exceeds 140/90 mm Hg, the ADA recommends pharmacologic treatment in addition to lifestyle modification [10; 40]. Dietary interventions include a moderate restriction of salt consumption while ensuring adequate potassium intake. Healthcare providers should closely monitor pregnant women with hypertension for the development of pre-eclampsia, characterized by hypertension and proteinuria after the 20th week of gestation. Pre-eclampsia will be discussed in detail later in this course.

To achieve target blood pressure goals, combination drug therapy using two to three antihypertensive agents may be necessary. Among many clinicians, methyldopa is the first-line treatment for use in pregnant patients with hypertension. Methyldopa is an alpha-2 adrenergic receptor agonist with no teratogenic effects. While methyldopa is not widely used in the United States due to the availability of more effective options, the medication is used internationally due to its low cost [155]. Although it is a relatively weak antihypertensive agent, methyldopa has a reassuring safety profile for use in pregnancy. Other antihypertensive agents considered safe for use in pregnancy include long-acting calcium channel blockers and some beta-blockers. While ACE inhibitors and ARBs are commonly used for blood pressure control in patients with diabetes, these medications are contraindicated in pregnancy [44].

Dyslipidemia

Dyslipidemia is a CVD risk factor associated with diabetes. Elevated triglycerides and reduced levels of high-density lipoprotein (HDL) cholesterol typify the dyslipidemia of type 2 diabetes. In normal pregnancy, triglyceride levels may double by 20 weeks' gestation; the increase in triglycerides may be even more pronounced in a pregnancy complicated by type 2 diabetes. Triglyceride levels greater than 2,000 mg/dL pose a serious risk for pancreatitis. To assist with risk management, healthcare providers should order a lipid profile as part of preconception care and/or early in pregnancy.

Nonpharmacologic management of dyslipidemia during pregnancy may include [10; 40]:

- Reduced dietary intake of saturated fats, trans fats, and cholesterol
- At least two meals of oily fish per week, while avoiding high-mercury-content fish, such as swordfish, tilefish, king mackerel, and shark
- Plant sterol-containing margarine in conjunction with a low-fat diet
- Moderate daily exercise
- Intensified glycemic control
- Fish oil supplementation

Not many cholesterol-lowering medications are safe for use during pregnancy. While statin medications are used in patients with diabetes, they are not safe during pregnancy. Bile acid-binding resins, such as cholestyramine, are the only approved lipid-lowering medications for use in pregnancy. The ADA recommends using fibric acids and niacin as secondary strategies in pregnant women who have triglyceride levels greater than 1,000 mg/dL [10].

The Endocrine Society suggests that bile acid-binding resins may be used in women with diabetes to treat hypercholesterolemia; however, this is seldom warranted.

(https://academic.oup.com/jcem/article/98/11/4227/2834745. Last accessed June 12, 2023.)

Strength of Recommendation/Level of Evidence:
2|++OO (Weak recommendation based on low-quality evidence)

Thyroid Disorders

Individuals with diabetes have an increased risk of developing thyroid disorder, and thyroid dysfunction during pregnancy is three times more common in women with diabetes. Autoimmune thyroid disease is especially prevalent in young women with type 1 diabetes, occurring in 30% to 40% of this population [70]. As individuals with one form of autoimmune disorder, such as type 1 diabetes, have an increased chance of developing other autoimmune disorders, there is a clear association between these two conditions. The prevalence of hypothyroidism is greater in people with type 2 diabetes, although this association is not well understood [10; 70].

Normal thyroid function is essential to regulate energy metabolism, so abnormal thyroid function may have profound effects on blood glucose control in diabetes. Both hyperthyroidism and hypothyroidism can affect the course of diabetes. For these reasons, healthcare providers should screen for thyroid dysfunction before or during early pregnancy in all patients with diabetes [10; 40].

Hypothyroidism

Hashimoto disease, also known as autoimmune thyroiditis, is characterized by antibodies reacting against proteins in the thyroid gland and causing destruction of the gland itself, resulting in hypothyroidism. This can adversely affect glycemic control and lipid metabolism during pregnancy. Furthermore, maternal hypothyroidism can inhibit brain development and is associated with pregnancy loss and premature delivery [70].

Adequate maternal thyroxine replacement is essential for fetal neurologic development in utero. Women who have pre-existing hypothyroidism and who take thyroxine medication often require an increase in dose during pregnancy. Fortunately, when hypothyroidism is adequately treated, there is a good chance for normal pregnancy outcomes [70].

Hyperthyroidism

Graves disease, an autoimmune disorder, is the most common cause of hyperthyroidism in pregnancy [71]. In this condition, antibodies stimulate the thyroid to enlarge and overproduce thyroid hormone. The disease may first appear during pregnancy or may be a pre-existing condition. In either case, hyperthyroidism is associated with worsening blood glucose control and increased insulin requirements due to the action of excess thyroid hormone, which causes increased glucose production in the liver, rapid absorption of glucose through the intestines, and increased insulin resistance.

Poorly controlled hyperthyroidism during pregnancy increases the risk for complications such as preeclampsia, premature delivery, miscarriage, birth defects, and postpartum thyroiditis. A successful pregnancy outcome depends on maintaining normal thyroid function and excellent glycemic control [70; 71].

Propylthiouracil (PTU) is the safest anti-thyroid medication for use in pregnant women. Healthcare providers should closely monitor the effects of PTU and adjust dosages accordingly, as this drug can affect the fetal thyroid gland. Although radioactive iodine is a very effective treatment for other patients with hyperthyroidism, it is a contraindicated treatment during pregnancy [71].

Remission of Graves disease in later pregnancy may result from the natural suppression of the immune system during pregnancy. A woman with pre-existing Graves disease may experience an improvement in symptoms in the second and third trimesters. The disease usually worsens again in the first few months after delivery. Healthcare providers should monitor thyroid function of pregnant women with Graves disease monthly [70].

Postpartum Thyroiditis

Postpartum thyroiditis is an autoimmune condition that causes thyroid inflammation and dysfunction within a few months after delivery of a child, and women with diabetes have a threefold risk for developing this condition. Thyroiditis causes hormone levels to fluctuate widely in the months following delivery. Initially, postpartum thyroiditis usually causes hyperthyroidism that may last for several weeks. Eventually, hypothyroidism develops when the injured gland stops producing enough thyroid hormone. These fluctuations in thyroid hormone levels can affect blood glucose control and alter insulin requirements.

Healthcare providers should be alert to the potential for postpartum thyroiditis and monitor thyroid function tests carefully. New mothers do not always recognize symptoms of hyperthyroidism or hypothyroidism and may attribute them to postpartum depression, lack of sleep, or reproductive hormonal changes [72].

Postpartum thyroiditis usually resolves in one to four months. Approximately 25% to 30% of women with postpartum thyroiditis will not recover from the hypothyroid phase and will go on to develop a permanently underactive thyroid gland [72]. If chronic thyroid hormone deficiency develops, it is usually treated with levothyroxine. Levothyroxine fully corrects the thyroid hormone deficiency and, when used in the correct dose, does not usually cause adverse effects [70; 71]. Long-term monitoring of thyroid function is necessary in women who experience postpartum thyroiditis, as about 30% will develop permanent hypothyroidism within three to four years [70].

GESTATIONAL DIABETES

Although the true prevalence of GDM is unknown, it complicates an estimated 1% to 14% of pregnancies in the United States annually. Data from the Pregnancy Risk Assessment Monitoring System (PRAMS) indicates that the prevalence of GDM in the United States is as high as 9.2% [73]. Experts predict that the prevalence of GDM would increase to 18% if proposed diagnostic criteria become widely adopted [74]. With existing diagnostic criteria, cases of GDM have doubled since 2000, with record high levels in some developing countries, such as India and China, and throughout the continent of Africa [75]. According to the International Diabetes Federation (IDF), an estimated 20 million or 16% of live births to women worldwide in 2019 had some form of hyperglycemia in pregnancy. Approximately 84% were due to gestational diabetes. The IDF estimates that one in six births are affected by gestational diabetes [76].

According to the ADA, GDM is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" [25]. GDM is typically a disorder of the later gestational period and may be previously unrecognized type 1 or type 2 diabetes discovered during pregnancy [16]. In 90% of GDM cases, the mother's blood glucose returns to normal after childbirth. A glucose tolerance test performed six to eight weeks postpartum confirms that the diabetes has resolved.

About 5% percent of women with GDM develop type 2 diabetes within six months after delivery, and 60% develop type 2 diabetes within 10 years. New cases of diabetes continue to appear 10 to 20 years after GDM [13]. Women who develop GDM earlier in pregnancy have a higher risk for onset of type 2 diabetes postpartum [77].

Due to the many significant risks of hyperglycemia in pregnancy, early detection of GDM is crucial. The ADA recommends screening for diabetes as soon as pregnancy is confirmed in high-risk women. They recommend screening for all other pregnant women at 24 to 28 weeks' gestation [25].

The U.S. Preventive Services Task Force recommends screening for gestational diabetes in asymptomatic pregnant women at or after 24 weeks' gestation.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/gestational-diabetes-screening. Last accessed June 12, 2023.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

MATERNAL RISK FACTORS FOR GESTATIONAL DIABETES

Risk factors for GDM that require screening strategies are [78;158]:

- Age older than 25 years
- Overweight or obesity (i.e., BMI greater than 25)
- African American, Hispanic, Native American, Alaska Native, Native Hawaiian, or Pacific Islander race
- History of GDM
- History of delivery of a macrosomic infant (i.e., weighing more than 9 pounds)
- Family history of diabetes
- Physical inactivity
- Hypertension
- Low high-density lipoprotein cholesterol level less than 35mg/dL and triglyceride level greater than 250mg/dL
- Polycystic ovarian syndrome
- Clinical conditions associated with insulin resistance (e.g., acanthosis nigricans)

Body Mass Index (BMI)

BMI is a commonly used screening tool to identify weight problems and associated health risks. Calculated from a person's height and weight, BMI is highly correlated to obesity or fat mass and risk for disease. The BMI is used to identify high-risk individuals, make treatment decisions, assess the effects of interventions, inform policy for healthcare programs, and guide insurance reimbursement. While there are other ways to assess body fat that are more accurate, the BMI provides a method that is inexpensive and easy to determine.

Weight status categories classify health risk based on body mass determined by the BMI. Using the BMI calculation, the World Health Organization (WHO) defines weight status as follows [79]:

- BMI less than 18.5: Underweight
- BMI 18.5–24.9: Normal
- BMI 25–29.9: Overweight (pre-obese)
- BMI 30.0 or greater: Obese

Ethnic Variations

Several studies have shown that women of Asian heritage are at the greatest risk for developing GDM, but risk is even greater among ethnic sub-categories [80; 81]. According to a large study of 16,000 women in Hawaii, the greatest prevalence of GDM appeared among Chinese and Korean Americans, followed by Filipinas. This investigation of fourteen ethnic groups demonstrated that 10% of women of Chinese or Korean heritage were at risk for developing GDM, more than double that of White and Black/African American women [80]. Pacific Islanders and Samoans also had higher than average risk, while White, Native American, and Black/African American women had lower than average risk [80]. However, the lower risk for GDM in Native American and Black/African American populations found in this study contradicts the risk factors published by the CDC [75]. Another study also showed that African American women were less likely to develop GDM compared to most other ethnic or racial groups. However, when African American women

do develop GDM, their risk for future onset of type 2 is greater than any other racial and ethnic group [82]. Additional research of GDM rates across Asian American subgroups showed that the prevalence is highest in Asian Indian, Chinese, Filipina, Korean, and Vietnamese women [81]. These trends, while not well understood, are likely due in part to genetics, lifestyle, sociocultural, and other environmental factors [156].

In some racial and ethnic groups, women face increased risk for GDM even when their BMI is less than 25, the standard cut point for being overweight. This appears to be true for Asian and Filipina women [83]. The WHO recognizes that Asian individuals generally have a higher percentage of body fat than White people; however, after convening a panel to discuss lowering the BMI cut-off points for the Asian population, the WHO recommended that the BMI cut-off points be retained as the international classification and that all countries use all categories [79]. Nevertheless, strategies other than weight management are more helpful in preventing diabetes in Asian populations.

Cardiometabolic Risk Factors

Research indicates that women with cardiometabolic risk factors prior to pregnancy have an increased risk for GDM. Cardiometabolic risk factors associated with the metabolic syndrome include:

- Elevated blood glucose (i.e., fasting plasma greater than 100 mg/dL)
- Overweight or obesity (i.e., BMI of 25 or greater)
- Prehypertension and hypertension (i.e., blood pressure greater than 120/80 mm Hg)
- Elevated total cholesterol (i.e., 200 mg/dL or greater)

One study showed that the risk for GDM increased with the number of pregravid cardiometabolic risk factors [84]. According to this study, cardiometabolic risk profile could predict the risk for GDM as early as seven years before pregnancy. Obesity appears to be the single greatest risk factor. The combination of obesity with mild hyperglycemia was associated with the greatest overall risk. The study concluded that the pregravid cardiometabolic risk profile might help clinicians to identify high-risk women for primary prevention and early management of GDM [84].

Sleep-Disordered Breathing

Sleep-disordered breathing appears to be common in women with GDM, and greater BMI is associated with a higher incidence of sleep-disordered breathing in all populations. The most common form of sleep-disordered breathing is obstructive sleep apnea, which causes recurrent episodes of hypoxia during sleep hours due to airflow restriction. Obstructive sleep apnea is associated with numerous health conditions, including hypertension, heart attack, heart failure, and stroke. It is also associated with an increase in the incidence of adverse pregnancy outcomes. The treatment of choice for sleep apnea is the use of a continuous positive airway pressure device during sleep, which will deliver a steady stream of air through a mask to help prevent pauses in breathing and to maintain normal oxygen levels [85; 86; 87; 88].

Advanced Maternal Age

Advanced maternal age increases the risks of pregnancy complications, including, but not limited to, ectopic pregnancy, spontaneous abortion, fetal chromosome abnormalities, congenital abnormalities, placenta previa and abruption, gestational diabetes, pre-eclampsia, and cesarean delivery. The number of pregnancies in women older than 35 years of age continues to increase in the United States [159].

Pre-existing conditions, such as diabetes and hypertension, are more common in older pregnant patients. Pre-existing diabetes and GDM increase up to sixfold in women older than 40 years of age compared with those 20 to 29 years of age. The incidence of GDM in patients older than 40 years of age is nearly 12%; in those older than 50 years of age, the incidence is 40% [159]. GDM in pregnant patients older than 35 years of age increases the risk of congenital anomalies and perinatal morbidity and mortality.

Patient education in pregnant patients older than 35 years of age can play a key role in facilitating clinical decision making. Providers should incorporate patients' personal beliefs, behaviors, and culture into treatment planning [159].

DIAGNOSING GESTATIONAL DIABETES: AN EVOLVING CONTROVERSY

For decades, there has been a general lack of agreement on diagnostic criteria for GDM, both within the United States and internationally, due to a shortage of outcome data to validate evidence-based criteria for making a diagnosis. Historically, guidelines have relied upon expert consensus drawn from observational data to define criteria for GDM. However, this differs among domestic entities and international communities.

The body of data to support evidence-based diagnostic criteria for GDM has grown in the past years, but healthcare professionals still dispute the validity and applicability of these findings. For instance, two of the leading authorities on pregnancy (the American Congress of Obstetricians and Gynecologists [ACOG]) and diabetes (the ADA) provide differing recommendations for diagnosing GDM. To that end, healthcare providers in the United States may follow different recommendations for diagnosis, which can cause confusion.

The potential for agreement on diagnostic criteria for GDM came in 2008, upon publication of the findings from a landmark study on the effects of hyperglycemia and pregnancy. Known as the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, this research data generated a flurry of controversy that continues today. The major finding from the HAPO study was that even mild elevations of blood glucose in pregnant women could have detrimental effects on both mother and child [89]. This prompted a movement for enhanced diagnostic criteria to identify and treat lower levels of blood glucose in pregnant women than previously considered.

Soon after publication of the HAPO findings, an international consensus group representing 40 countries and multiple obstetrical and diabetes organizations met to review and deliberate on the results of HAPO and other relevant studies. The goal of this forum was to formulate evidence-based, universally endorsed recommendations for the screening and diagnosis of GDM to clarify the definition of GDM, and to allow for the meaningful comparison of clinical outcomes and scientific studies. This diverse group of experts came to a consensus on diagnostic and screening guidelines that the ADA later accepted [90; 91; 92]. However, not all authoritative groups universally embraced these recommendations [93; 94]. According to one expert, "It is quite remarkable that of all the areas of diabetes research, few have [caused] such confusion and controversy as gestational diabetes" [25; 95].

THE HAPO STUDY

As noted, the HAPO study, a landmark study on the effects of hyperglycemia in pregnancy, led to the first evidence-based criteria for the diagnosis of GDM. According to the study's authors, the objective of HAPO was "to clarify risks of adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus" [89]. Its conclusions were groundbreaking, as they suggested the range of maternal glycemia that was previously considered normal could actually be detrimental to mother and fetus.

Study Design and Methods

The HAPO study included 25,505 pregnant women at 24 to 32 weeks' gestation, taking place at 15 centers in nine countries. All participants underwent a 75-gram, two-hour oral glucose tolerance test (OGTT) at as close to 28 weeks' gestation as possible. Only women whose results were blinded were included in the analysis of results [89].

Outcomes

The study measured four primary outcomes:

- Birth weight above the 90th percentile for gestational age
- Primary cesarean delivery
- Clinical neonatal hypoglycemia
- Cord-blood serum C-peptide level above the 90th percentile

There is a strong correlation between C-peptide serum levels and insulin production, and C-peptide levels can provide an indication of how much insulin the body produces. Both C-peptide and insulin are derived simultaneously from an inactive molecule called proinsulin. When the body requires insulin, proinsulin splits into both C-peptide and insulin at the same rate. While the tissues utilize insulin, C-peptide remains inactive, making it a useful marker of insulin production.

The C-peptide level in cord blood indicates fetal insulin levels. The higher the cord serum C-peptide, the more likely it is that mother had high glucose that crossed to the fetus and evoked fetal insulin production. In the HAPO study, the operational definition of fetal hyperinsulinemia was cord-blood serum C-peptide above the 90th percentile.

HAPO and its follow-up studies supported the Pedersen hypothesis, published in 1952, which postulated that hyperglycemia in the mother is transmitted to the fetus, causing the fetus to produce and release large amounts of insulin [89; 96]. The resulting fetal hyperinsulinemia would lead to the deposition of large amounts of body fat in the fetus and result in macrosomia, a common characteristic of infants born to mothers with GDM.

Secondary outcomes of HAPO included:

- Premature delivery (before 37 weeks' gestation)
- Shoulder dystocia or birth injury
- Need for intensive neonatal care
- Hyperbilirubinemia
- Pre-eclampsia

Results and Conclusions

The HAPO researchers concluded that there was a strong correlation between maternal glycemia at 24 to 32 weeks' gestation and the risk for poor maternal, fetal, and neonatal outcomes. Furthermore, adverse events occurred at maternal glucose levels below those diagnostic for diabetes. According to the study authors, "maternal hyperglycemia less severe than that used to define overt diabetes is related to clinically important perinatal disorders or problems and their effects can be reduced by means of treatment, although a threshold for the need for treatment is not established" [89]. Notably, HAPO researchers found that there was a continuous relationship between maternal hyperglycemia and pregnancy outcomes rather than a definitive cut-off point.

The strongest finding in the HAPO study was that increasing levels of fasting and/or postprandial glycemia were associated with birth weight above the 90th percentile, or macrosomia. Increasing levels of maternal glycemia were also associated with:

- Cesarean delivery
- Neonatal hypoglycemia
- Premature delivery
- Shoulder dystocia or birth injury
- Intensive neonatal care
- Hyperbilirubinemia
- Pre-eclampsia

The HAPO study supported the findings of the 2005 Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), a randomized clinical trial that evaluated whether diagnosing and treating women with mild GDM would decrease the risk for perinatal complications. The study found that when women were diagnosed and treated for mild GDM, they experienced significantly lower rates of perinatal morbidity and mortality than those who received standard contemporary treatment [97].

While the original HAPO study used OGTT to make associations between maternal glucose tolerance and pregnancy, a follow-up study investigated the relationship between maternal A1C and adverse pregnancy outcomes. This research followed the ADA's endorsement of using A1C to diagnose diabetes and identify those at risk for developing diabetes. The follow-up study measured maternal A1C at 24 to 32 weeks' gestation, using serum from the same cohort that had been collected and stored in the original study. It concluded that the measurement of A1C is not a useful alternative to OGTT in pregnant women, based upon significant lack of association with birth weight and cord serum C-peptide levels [98].

The results of HAPO, ACHOIS, and other comparative studies suggest that current screening and diagnostic criteria for GDM should be strengthened so that women with mild hyperglycemia, who would not be diagnosed using previous criteria, would become positive for the disease state. This leads to questions about what constitutes appropriate intervention for mild hyperglycemia in pregnancy, what the threshold for treatment would be, and the cost-effectiveness of finding and treating a significant number of new cases.

APPROACHES TO SCREENING AND DIAGNOSING OF GDM

Prior to publication of the HAPO findings, a two-step approach was most widely used to screen for and diagnose GDM in the United States. Many healthcare providers still use this approach, as universal acceptance of newer recommendations is not yet achieved. The ACOG still adheres to this two-step approach, while the WHO uses a one-step system, and the ADA acknowledges that either approach may be used.

One-Step Approaches

World Health Organization

On a global level, clinicians base the screening and diagnosis of GDM on recommendations from the WHO. By these criteria, screening takes place at 24 to 28 weeks' gestation after the patient has fasted overnight. She then drinks a glucose load, with a blood glucose measurement taken after two hours. If blood glucose is equal to or greater than 140 mg/dL at that time, she is diagnosed with GDM [99].

ADA

In response to the HAPO and ACHOIS studies, an international conference composed of 225 experts on diabetes and obstetrics met to make recommendations for universally sanctioned screening practices and diagnostic criteria for GDM. Their recommendations were published in 2010 and were adopted by the ADA in 2011 [90; 91]. Under these criteria, only one abnormal glucose value is sufficient to make a diagnosis of GDM.

In 2011, the ADA revised its standards of medical care to recommend testing for undiagnosed type 2 diabetes at the first prenatal visit in all women with risk factors for diabetes, such as personal history of GDM, obesity, or previous delivery of an LGA infant. If a high-risk woman is found to have blood glucose levels diagnostic for diabetes at her first prenatal visit, her diagnosis is type 2 diabetes, not gestational [100].

In pregnant women not known to have diabetes, the ADA recommends screening at 24 to 28 weeks' gestation using a 75-gram two-hour OGTT that should be performed in the morning after an overnight fast of at least eight hours. The test is diagnostic for GDM if any of the following values result [100; 147]:

- Fasting (prior to glucose load): ≥92 mg/dL
- One hour after glucose load: ≥180 mg/dL
- Two hours after glucose load: ≥153 mg/dL

The ADA recommended these changes in diagnostic criteria because they "were the only ones based on pregnancy outcomes rather than end points" (e.g., prediction of subsequent maternal diabetes) [25].

Benefits of Adopting a One-Step Diagnostic Approach

Under criteria including a one-step approach to the diagnosis of GDM, only one abnormal glucose value is sufficient to make a diagnosis of GDM. Supporters of these proposed guidelines contend that the underlying research is based on robust data and is applicable to diverse populations. They claim that the conclusions from the HAPO study passed rigid statistical analysis and that sound evidence is available for new GDM diagnostic guidelines. While HAPO was an observational study, at least two other randomized clinical trials show that the diagnosis and treatment of mild GDM is associated with improved pregnancy outcomes [101; 102; 147].

The proposed one-step approach provides a simplified diagnostic approach, resulting in more identified cases of GDM and more opportunities to reduce the risk of adverse pregnancy outcomes. Due to the worldwide epidemic of obesity, cases of GDM are already on the rise, even without the new criteria. According to the ADA, "these diagnostic criteria changes are being made in the context of worrisome worldwide increases in obesity and diabetes rates, with the intent of optimizing gestational outcomes for women and their babies" [91].

In addition to identifying more cases of GDM, enhanced screening practices also identify more cases of undetected type 2 diabetes, as diabetes screening would occur at the first prenatal visit for all women with risk factors. In response to concern that enhanced diagnostic criteria would be a burden on resources, proponents argue that implementing the new treatment criteria would not significantly increase healthcare costs. As projected by the ADA, 80% to 90% of women with mild GDM could be effectively treated with lifestyle therapy alone [25]. Ultimately, providing education on lifestyle modification to more pregnant women could result in a decrease in diabetes prevalence in the next generation. Research has suggested that the one-step approach for diabetes screening in pregnancy is cost-effective, especially with regard to preventing future diabetes when the patient receives post-delivery counseling and intervention [25; 103].

Drawbacks of the One-Step Diagnostic Approach

Opponents of the one-step diagnostic criteria believe the benefits do not outweigh the costs. They state that the HAPO study does not provide sufficient evidence for a universal change, as it was an observational study, not a treatment trial. In addition, evidence for a critical cutoff level of plasma glucose that predicts adverse outcomes is lacking, implying there is nothing to substantiate universal screening for GDM.

One argument opposing the new criteria is that identifying significantly more cases of GDM would place an unnecessary burden on the healthcare system. The rate of GDM diagnoses with existing criteria is about 7% of all pregnancies. A universal change to the simplified approach would result in two to three times more GDM diagnoses, an estimated 18% of pregnancies [95]. The ADA estimates that the rate of increase of GDM diagnosis under the new criteria would be between 5% and 20% of all pregnancies [25]. Some contend that many of these diagnoses would be unnecessary and cause undue burden to the healthcare system and to individuals.

There is also an argument that the enhanced diagnostic criteria would label many pregnancies "high risk" that were previously considered normal [25]. This leads to more tests and therapies, many of which would be unnecessary. A high-risk pregnancy usually involves additional prenatal visits, more discomfort and inconvenience to the patient, and the added cost of blood testing supplies. Conventionally, a pregnancy complicated by GDM involves more ultrasound scans for fetal growth assessment and has a higher likelihood for labor induction and cesarean delivery. In addition to the potential burden to the healthcare system, a pregnancy with increased medical surveillance is a source of anxiety and worry for the patient.

Those who challenge the new criteria also argue that evidence to support the benefits of lifestyle modification on pregnancy outcomes at lower levels of maternal glycemia is insufficient; there are few data from randomized clinical trials regarding therapeutic interventions in pregnant women with mild hyperglycemia [25]. Further, if mild hyperglycemia begins to be treated more aggressively, an increased number of pregnant women might use insulin, creating an increased risk for hypoglycemia [74; 101].

Two-Step Approach

National Institutes of Health

Recognizing the significance of the changes in the diagnostic criteria for GDM, the National Institutes of Health (NIH) held a consensus development conference on the issue in 2013. Conference panel members reviewed the available evidence regarding the benefits and drawbacks of the one-step diagnostic approach for GDM and concluded that the two-step approach should be continued. In particular, the panel was concerned that adoption of the new criteria would "increase the prevalence of GDM, and the corresponding costs and interventions, without clear demonstration of improvements in the most clinically important health and patient-centered outcomes" [104]. However, the experts also stated that additional research to resolve some of the uncertainties associated with the one-step approach could result in a change in their recommendations.

American Congress of Obstetricians and Gynecologists

The ACOG continues to recommend the two-step approach based on the findings of the NIH consensus conference [94]. According to the ACOG guideline, screening for GDM should take place at 24 to 28 weeks' gestation, or earlier in the presence of risk factors, using the two-step approach [94]. The first step of diagnosis is the one-hour oral glucose tolerance test (OGTT). For this test, the patient drinks a 50-gram glucose solution and the blood glucose level is measured one hour later. Common blood glucose cutoffs for the one-hour challenge are between 130 mg/dL and 140 mg/dL [25]. The ACOG recommends that healthcare providers select either the 135 mg/dL or the 140 mg/dL cutoff and that they use the value selected as a single consistent cutoff for their practice, considering such factors as community prevalence rates of GDM [25; 94]. If, after one hour, the blood glucose level is higher than the cutoff value selected, the provider should proceed to a 100-gram three-hour OGTT (step two). The 100-gram OGTT should be performed when the patient is fasting. Two or more values meeting or exceeding the following criteria determine a diagnosis of GDM [94; 106]:

- Fasting (prior to glucose load): ≥95 mg/dL
- One hour after glucose load: ≥180 mg/dL
- Two hours after glucose load: ≥155 mg/dL
- Three hours after glucose load: ≥140 mg/dL

American Diabetes Association

In its 2017 standards of medical care, the ADA recommends both the one-step and the two-step approach. It states that "the conflicting recommendations from expert groups underscore the fact that there are data to support each strategy" [25; 147]. For example, a cost-benefit analysis comparing the two approaches found the one-step approach to be cost-effective only if patients with GDM were also receiving postpartum counseling and care to prevent development of type 2 diabetes. Also, data comparing population-wide outcomes with the one-step versus the two-step approach have been inconsistent to date [25].

TREATMENT OF GESTATIONAL DIABETES

Nutritional management is the foundation of treatment in GDM, supplemented by regular physical exercise for most women [25]. When these lifestyle interventions do not achieve target glycemic goals, insulin or oral medication is necessary. Regardless of the tools used to treat GDM, frequent SMBG by the patient is essential.

Good glycemic control improves pregnancy outcomes for both mother and child. While it is logical to recommend that women with GDM strive for blood glucose levels that approximate those of nondiabetic pregnant women, experts do not fully understand what these norms actually are. Pooling several data sources, the best assessment of normoglycemia during pregnancy would be [107]:

- Fasting: 63–79 mg/dL
- One-hour postprandial: 96–122 mg/dL
- Two-hour postprandial: 89–109 mg/dL

An ADA conference consensus on GDM concluded that the mean peak postprandial glucose concentration for nondiabetic pregnant women is approximately 94–126 mg/dL. But there appears to be significant variation of the time to peak glucose elevation after starting the meal, ranging anywhere from 45 to 120 minutes [13].

Blood Glucose Monitoring

According to the ADA, target goals for SMBG in GDM are [25]:

- Pre-meal: 95 mg/dL or less
- One hour post-meal: 140 mg/dL or less
- Two hours post-meal: 120 mg/dL or less

Postprandial blood glucose values are the most significant in GDM. A typical SMBG regimen for GDM includes testing four times each day, before breakfast and one hour after starting each meal [16]. As mentioned, experts do not recommend alternate site testing during pregnancy; the fingertip is the preferred site for capillary blood collection. Patients with GDM and severe hyperglycemia, weight loss, or concerns about starvation ketosis should test their urine for ketones [13].

Medical Nutritional Therapy

The mainstay of GDM management is dietary intervention. Medical nutritional therapy for GDM involves adherence to the nutritional needs of pregnancy combined with the nutritional management of diabetes. Women with GDM should have a consultation with a registered dietitian whenever possible, which should include an individualized nutritional assessment and meal plan. The woman's height, weight, cultural preferences, lifestyle, and activity level help determine the optimal meal plan [25]. The meal plan is then modified as needed throughout the pregnancy to achieve treatment goals [10; 13; 16].

General patient teaching points for the nutritional management of GDM are:

- Avoid concentrated sweets.
- Avoid highly processed foods.
- Eat three small-to-moderate sized meals per day.
- Eat two to four snacks per day.
- Eat a small, low-carbohydrate breakfast.
- Eat plenty of non-starchy vegetables.
- Keep a food diary.

Goals of Medical Nutritional Therapy

The primary goal of medical nutritional therapy for GDM is to keep postprandial blood glucose as close to normal as possible. Other goals of medical nutritional therapy are to [10; 13; 16; 25]:

- Provide adequate nutrition for maternal health and fetal development
- Prevent ketosis
- Avoid maternal weight loss or excessive weight gain
- Promote healthy eating behavior that can be continued postpartum for preventing future development of type 2 diabetes

Carbohydrates

Carbohydrate distribution is the cornerstone of the diabetes meal plan. Because post-meal glycemia is highly correlated with the amount of carbohydrate consumed at the meal, patients with GDM should check postprandial blood glucose to follow the effects of carbohydrate consumption [25]. Processed foods containing sugar have the most dramatic effect on blood glucose levels, including dessert products, fruit juices, and soft drinks. The peak effect of these simple sugars on blood glucose is about one hour after consumption. Blood glucose levels from whole food carbohydrates, such as legumes, vegetables, and whole grains, peak about two hours after ingestion [16].

Consistency, Content, and Timing of Meals

Dietitians usually advise eating small, frequent meals for the management of GDM to help avoid post-meal blood glucose excursions and to prevent pre-meal starvation ketosis. The timing and consistency of meals are important, as consistent food consumption daily helps stabilize the blood glucose pattern.

A common regimen for patients with GDM is to eat three meals and three snacks per day. Benefits of this program include the prevention of extreme hunger between meals and the alleviation of nausea, heartburn, and other digestive discomforts common in pregnancy. However, a risk of recommending frequent meals is that patients may take in too many calories if portion sizes are not carefully controlled.

Women with GDM should be encouraged to eat good sources of protein, as these foods yield a slower glycemic response and provide greater satiety than most carbohydrate foods. Non-starchy vegetables, such as cabbage, onions, leafy greens, broccoli, and celery, are "free foods" that patients can eat at any time, as desired [16; 25].

Blood glucose levels are often high in the morning in women with GDM. Therefore, dietitians usually recommend a small, low-carbohydrate breakfast. This means avoiding fruit and fruit juices as well as highly processed breakfast cereals [16; 25].

A food diary may be helpful to assess if a food plan is meeting established goals. It can also identify individual variations in glycemic response to certain foods, allowing the patient to make decisions about what to eat and to improve self-management skills. A food diary is a record of meal items and measured glucose levels.

A patient's food diary may be used to ascertain her understanding of and adherence to the recommended meal plan. It is helpful to have the patient record her food intake for one week prior to medical visits. This will allow the provider to assess the adequacy of the patient's nutritional intake and to compare carbohydrate intake with SMBG results.

Low Glycemic Index Diet

The glycemic index appraises the effect of specific foods on blood glucose. Foods that are high on the glycemic index tend to increase blood glucose more than foods low on the index. High-glycemic foods include white bread, pasta, rice, low-fiber cereals, and baked goods; low-glycemic foods include fruits, vegetables, whole grains, and legumes.

The ADA does not endorse the glycemic index as a tool for diabetes medical nutritional therapy [25]. One reason for this is that there tend to be significant differences among individuals in their glycemic response to the same foods. Furthermore, the way food is prepared and the effect of other foods consumed at the same time can lead to variations in postprandial glycemia.

The safety and effectiveness of the glycemic index for women who have GDM has been the subject of research, and the results remain inconclusive. One study showed that using a low-glycemic diet reduced the number of patients with GDM needing to use insulin by half without increasing the risk for obstetrical or fetal complications [108]. Another study compared a low-glycemic diet with a conventional high-fiber diet. The researchers concluded that there are similar pregnancy outcomes in women with GDM who follow a conventional high-fiber diet vs. a low-glycemic diet [109].

Gestational Weight Gain

Among women giving birth in the United States in 2014, 25.6% were overweight and 24.8% were obese [110]. A significant percentage of women who are overweight or obese will develop GDM when they become pregnant. Data from the HAPO study reveal that women with GDM who are obese have a significantly higher risk for adverse pregnancy outcomes, including macrosomia, fetal hyperinsulinemia, and pre-eclampsia. Greater weight gain during pregnancy also increases the likelihood of the need for insulin and the incidence of preterm delivery, although it reduces the risk for low birth weight. Furthermore, the combination of both GDM and obesity together has a greater impact on health outcomes than either one alone. The obesity epidemic has spurred interest in the effects of calorie restriction for obese women who are pregnant, including those with GDM. Calorie restriction during pregnancy raises concerns regarding the consequences of limited maternal weight gain on the growth of the fetus [111; 112; 113].

As discussed, the pregnancy weight gain recommendations from the IOM were revised in 2009 [64]. While these guidelines recommend less gestational weight gain for overweight and obese women, some experts feel that selected obese women should gain even less weight than the IOM suggests. Studies suggest that some obese women can gain less than 15 pounds, or even lose up to 10 pounds during pregnancy, without adverse outcomes. In these women, research indicates that moderate caloric restriction does not seem to impair fetal growth and may prevent macrosomia [114; 115; 116].

Several other studies suggest that calorie restriction in obese women during pregnancy can result in positive outcomes. Obese pregnant women restricting calories by 30% to 33% appears to be safe, with no associated increase in perinatal morbidity. Calorie restriction may increase a woman's insulin sensitivity, resulting in a decreased need for injections. Even so, continued research is necessary to determine the effects of calorie restriction during pregnancy on the future health of the child [16].

Although evidence-based guidelines for the optimal management of maternal obesity during pregnancy are lacking, the ACOG published a practice bulletin on obesity during pregnancy in 2015. The bulletin addresses clinical management questions about appropriate interventions before and during pregnancy, recommendations for weight gain, potential alterations to antepartum and intrapartum care, labor and delivery considerations, and the most effective postpartum care and strategies [117]. Additionally, experts recommend that pregnant women avoid excessive gestational weight gain, exercise moderately, and eat a healthy diet. Women should only attempt weight loss during pregnancy under the supervision of a qualified healthcare provider [16; 25; 113].

Exercise

As discussed, there are many benefits of exercise during pregnancy. Physical activity and exercise help overcome insulin resistance and increase insulin's ability to bind to receptor sites. Other benefits include an enhanced sense of well-being, decreased weight gain, reduced fetal adiposity, and improved tolerance to labor [10; 118].

Experts recommend 150 minutes of moderate-intensity aerobic exercise per week for all pregnant women who do not have contraindications, equaling approximately 20 to 30 minutes per day. The patient can divide this time into shorter segments, such as 10- to 15-minute intervals [13].

Exercise during pregnancy must not cause fetal distress, uterine contractions, or maternal hypertension. Patients with GDM should adhere to standard safety precautions for exercise during pregnancy, such as avoiding abdominal trauma and loss of balance. Pregnant women should also avoid exercises done in the supine position and those that place excessive mechanical stress or weight bearing on the trunk. Women should modify or limit their physical activity when there is evidence of fetal growth restriction [118].

If a patient experiences any signs of impending labor or fetal distress, she should immediately cease the activity and seek medical advice. Signs that exercise should be halted include [10]:

- Dyspnea or shortness of breath
- Headache
- Calf pain or swelling
- Vaginal bleeding
- Leakage of amniotic fluid
- Painful uterine contractions
- Decreased fetal movement

Oral Diabetes Medications During Pregnancy

Certain oral antidiabetic medications appear to be safe for use during pregnancy. However, most agents available for treating type 2 diabetes are not widely used due to lack of efficacy or insufficient data to justify their use [25]. While insulin is safe and effective, it is not appealing to many women and may have a lower rate of adherence. It also carries a greater risk for hypoglycemia than oral antidiabetic medications.

Two medications, glyburide and metformin, are effective for lowering blood glucose and appear to be safe for use in pregnancy, although the FDA has not approved their use for these women. Both agents cross the placenta to a measurable extent, with metformin likely crossing to a greater extent than glyburide [25; 44]. Supported by evidence from the HAPO and ACHOIS studies, most experts advocate the use of medication for glycemic control during pregnancy when diet and exercise are not sufficient [119]. Despite this, there are few long-term follow-up studies of infants whose mothers were treated with the oral agents during pregnancy [25]. It is therefore possible that these medications could affect fetal programming in utero or have consequences in regard to insulin sensitivity later in the life of the offspring. It is also unclear if these agents cause undetected hypoglycemia in the fetus [120].

Sulfonylureas

Sulfonylureas have been widely used to treat type 2 diabetes since the 1950s. This drug class includes glyburide and glipizide, among others, and acts mainly to increase insulin production from the pancreas. The primary adverse effect associated with the sulfonylureas is hypoglycemia, and instruction on hypoglycemia prevention and treatment is necessary when using these drugs. Severe hypoglycemia lasting 4 to 10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery. Glyburide may be associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. If an oral agent is needed for the treatment of GDM, agents other than glyburide are preferred [44].

Glipizide is another sulfonylurea used to treat type 2 diabetes. Glipizide does not cross the placenta, and animal data suggest low risk to the fetus. However, there is limited human data to support the use of glipizide during pregnancy. If used, patients should discontinue the agent before delivery to decrease risk of neonatal hypoglycemia, although the optimal time of discontinuation is unknown [44].

Metformin

As of 2020, the only biguanide available in the United States was metformin. The primary action of metformin is to reduce glucose production from the liver, with a secondary action of increasing insulin sensitivity in the muscle and liver tissue, providing for better utilization of existing insulin [44].

Because metformin does not cause the body to make more insulin, it rarely causes hypoglycemia when used alone. Minor but common side effects of metformin include gastrointestinal disturbances such as diarrhea, nausea, and abdominal cramping. Taking metformin with meals can reduce these side effects [44].

In pregnancy, metformin crosses the placenta in significant amounts. This raises the concern that it could affect fetal physiology or cause congenital anomalies. However, congenital malformations take place during the first nine weeks of pregnancy, while the diagnosis of GDM usually takes place at 24 to 28 weeks. Nevertheless, even if safe regarding organogenesis, it will be important to study metformin's effect on the offspring during the growth years and later in life. Metformin may slightly increase the risk of prematurity [25].

The Metformin in Gestational diabetes (MiG) trial was an important study that assessed the efficacy and safety of metformin in pregnancy. It included 751 women with GDM at 22 to 33 weeks' gestation and compared the use of insulin to metformin on measures of neonatal hypoglycemia, respiratory distress, neonatal jaundice, birth trauma, Apgar scores, and prematurity [121]. The trial results indicated that almost half of patients using metformin ended up requiring supplemental insulin to meet blood glucose targets [25]. Neonatal complications did not differ significantly between the two groups, and there were no serious adverse events associated with use of metformin. Women who used metformin reported a higher rate of satisfaction compared to insulin. While the results of MiG are promising, guidelines recommend avoiding metformin as routine therapy for GDM pending further clinical trials [10; 25; 75].

A smaller study concluded that GDM outcomes for women treated with metformin were more favorable than those for women who were treated with insulin. In this study, only 8% of patients required insulin supplementation, compared to 43% in the MiG trial. Ethnic variation may have played a role in this smaller study, as more than half of the participants were Indian, Polynesian, or Chinese [122].

The MiG Trial Offspring Follow-Up (MiG TOFU) continued to follow the offspring of mothers with GDM who used metformin during pregnancy [123]. The focus of the 2011 MiG TOFU was to examine the body composition of these children at 2 years of age. Results suggest that metformin exposure in utero might lead to improved insulin sensitivity in the fetus and result in a metabolically healthier pattern of growth in early childhood, including less development of visceral fat (central adiposity), a significant component of metabolic syndrome [123]. A 2018 MiG TOFU report showed no significant differences between offspring of those treated with metformin versus insulin at 7 years of age. However, at 9 years of age, metformin offspring were larger by measures of BMI, weight, and arm and waist circumferences. Levels of fasting glucose, triglyceride, insulin, insulin resistance, A1C, cholesterol, liver transaminases, leptin, and adiponectin were similar, as were body fat percentage and abdominal fat percentages [124]. The results of MiG TOFU, while promising at first, now suggest that in utero exposure to metformin may lead to negative implications for the prevention of diabetes in the offspring of women with GDM later in life.

Other studies have shown that metformin may help decrease the risk for macrosomia in the offspring, but it does not appear to help obese mothers lose weight [122]. More follow-up studies and longitudinal research are needed to clarify these results.

Insulin

While certain oral medications are feasible during pregnancy, insulin is often the treatment of choice in GDM. When prescribing insulin to treat GDM, it is important to individualize the regimen and frequently adjust the dosage, as in cases of pre-existing diabetes [25]. Decisions about starting insulin for GDM are based upon fasting and post-prandial responses to the meal plan. Typically, women with GDM follow a basal-bolus regimen that may include four to six injections per day.

EVIDENCE-BASED PRACTICE RECOMMENDATION

When pharmacologic treatment of gestational diabetes is indicated, the American College of Obstetricians and Gynecologists recommends insulin as the preferred therapy.

(https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/02/gestational-diabetes-mellitus. Last accessed June 12, 2023.)

Level of Evidence: A (Good and consistent scientific evidence)

A small study concluded that using a 50/50 mix of NPH/lispro could effectively manage GDM and provide the patient with a simplified regimen [125]. Delivered as three pre-meal injections per day, the 50/50 mix appeared to be a safe and reasonable alternative to more frequent injections of NPH and rapid-acting insulin. In this small study, glycemic control was comparable, and the authors proposed that the simplified regimen could improve adherence to insulin use in patients with GDM [125].

IMPACT OF STRESS

In any type of diabetes, physical or psychologic stress can influence blood glucose control, which manifests as feelings of nervousness, sweating or shaking, dry mouth, a pounding heart, or "butterflies in the stomach." These common reactions reflect the response of the sympathetic nervous system to stress. Hormones released during the sympathetic stress response (e.g., cortisol, epinephrine, norepinephrine, glucagon, growth hormone) make diabetes more difficult to control. Cortisol plays an important role in diabetes, as it stimulates glucose production by the liver in addition to increasing insulin resistance. In patients with diabetes, this will have the effect of raising blood sugar.

Physiologic stress, such as concurrent illness, infection, surgery, or trauma, can disrupt homeostasis and lead to loss of blood sugar control in individuals with diabetes. All patients with diabetes should be educated regarding the risks involved during illness. Women with GDM are especially vulnerable to extreme blood glucose changes during illness.

Psychologic stress in general can also have an undesirable effect on blood glucose control, in many of the same ways as physiologic stress. General psychologic stress can be brought on by significant life events, such as the death of a spouse, changing jobs, or dealing with a loved one's illness. It can also be related to other life factors, such as economic hardship, pressures at work, interpersonal relationships, or family dynamics. Stress management options will be discussed in detail later in this course.

POSTPARTUM CARE OF PATIENTS WITH GDM

In the early postpartum period, women with GDM should continue to monitor their blood glucose or allow hospital staff to monitor it several times per day until discharge. In some cases, glucose levels remain elevated for 24 to 48 hours postpartum before returning to normal [16]. If a patient developed GDM early in her pregnancy or had very unstable blood glucose levels during her GDM, she is more likely to have underlying type 1 or type 2 diabetes. These women should continue to perform SMBG; postpartum initiation of long-term treatment may be necessary. The ADA recommends that the OGTT be performed at the time of the 4- to 12-week postpartum visit. Because GDM is associated with increased risk for diabetes, women should also be tested every one to three years thereafter if the 4- to 12-week 75-gram OGTT is normal, with frequency of testing depending on other risk factors (e.g., family history, prepregnancy BMI). Ongoing evaluation may be performed with any of the recommended glycemic tests [25].

Risk for Type 2 Diabetes

As noted, the risk for later development of type 2 diabetes is significant for women who have had GDM. Although most women with GDM will have normal glucose levels within six weeks postpartum, 40% to 60% will develop type 2 diabetes in the next 5 to 10 years. Women who have a higher prepregnancy BMI or who gain more weight during pregnancy have a higher risk for developing type 2 diabetes following GDM [9; 25]. In addition, women who have metabolic syndrome three months after pregnancy are

at greater risk for developing type 2 diabetes than those who do not. The risk factors associated with increased diabetes risk include impaired glucose tolerance, HDL cholesterol less than or equal to 50 mg/dL, and age older than 35 years [126].

There may also be racial and ethnic variables that affect the future risk for development of type 2 diabetes in women with a history of GDM. Although, the prevalence of GDM in Black and White women is similar (approximately 7% of all pregnancies), Black women with a history of GDM have a 52% higher risk for developing type 2 diabetes later in life [82].

Traditionally, women who have had LGA infants are categorized as high risk for future development of type 2 diabetes, even if they do not have GDM during the pregnancy. However, one study indicated that non-GDM women who deliver LGA infants do not show postpartum metabolic dysfunction, arguing against the presumption that they had undetected GDM. The authors conclude that LGA may be due to other factors, such as maternal obesity [127].

In general, compliance with postpartum screening for type 2 diabetes is poor, with perhaps more than half of patients failing to have their blood glucose tested after childbirth [128; 148]. However, multiple studies suggest that telephonic nurse management programs and automated reminders increase women's adherence to postpartum glucose testing recommendations [129; 149]. Another study found that Latina women with GDM were more likely to participate in postpartum glucose testing following involvement in a program with bilingual, bicultural community health workers (promotoras) who provide education and reminders about the importance of postpartum diabetes screening [130].

Prevention of Type 2 Diabetes

As stated, the ADA standards of medical care call for screening every one to three years for diabetes or prediabetes in women with a history of GDM [25]. If a woman with a history of GDM has prediabetes, she should make appropriate alterations in lifestyle and perhaps use metformin to prevent the development of frank diabetes [25].

A landmark study published in 2002 concluded that people at risk for type 2 diabetes could delay or prevent its onset with lifestyle modification [6]. Results of the Diabetes Prevention Program showed that weight loss and exercise helped prevent or delay diabetes in people with higher-than-normal blood glucose who were also overweight. These findings have provided a valuable opportunity for individuals and healthcare providers to reduce the incidence of type 2 diabetes and its related morbidities.

For the prevention and early detection of type 2 diabetes, important patient teaching recommendations are to:

- Know the risk factors for type 2 diabetes
- Have follow-up blood glucose testing at 4 to 12 weeks postpartum
- Notify primary healthcare provider(s) of a history of GDM
- Plan future pregnancies
  - Seek preconception care
  - Have blood glucose tested prior to conception
- Adhere to a lifestyle that prevents the onset of type 2 diabetes
  - Achieve and maintain a healthy body weight
  - 150 minutes of moderate-intensity aerobic exercise per week
- Have screening blood test for diabetes at least every three years
- Breastfeed for at least 6 to 12 months

As a patient advocate, nurses and other healthcare providers can take the opportunity to educate patients on the importance of screening for type 2 diabetes 4 to 12 weeks postpartum. Explain that early detection and treatment of type 2 diabetes is strongly associated with fewer and less severe complications. If postpartum screening reveals that a patient has impaired glucose tolerance, advise that she have ongoing blood glucose tests at regular intervals for early detection of type 2 diabetes.

Breastfeeding is highly encouraged for women who have had GDM because it increases insulin sensitivity in the mother and can protect both mother and child against diabetes. Breastfeeding will be discussed in greater detail later in this course.

PREVENTION OF GESTATIONAL DIABETES

Because extensive research is lacking, it is not clear if GDM is preventable. However, there is data to suggest that maternal diet before pregnancy, maternal weight gain between pregnancies, and physical activity can influence the risk for GDM [131; 132; 133].

Maternal Diet Prior to Pregnancy

A mother's diet before pregnancy appears to influence her metabolism during pregnancy, which may have important associations with a child's health at birth and later in life. Data from more than 13,000 women enrolled in the Nurses' Health Study II indicated that a prepregnancy diet high in animal fat and cholesterol could increase the risk of developing GDM. Those with the highest intake of animal fat had an increased risk for GDM compared to those with the lowest percentage. Women whose diets were high in other types of fats, such as plant-based oils, did not have an increased risk. This research suggests that reducing the amount of animal fat and cholesterol in the diet prior to pregnancy may help prevent GDM [134]. A systematic review of 14 randomized controlled trials were analyzed to determine whether dietary intervention in pregnant women could prevent GDM [133]. Three of the trials compared diet with standard antenatal care in 455 women (mean age 27.7 years in the diet group vs 29.0 years in the standard care group). All three studies reported a statistically significantly lower incidence of GDM with dietary intervention compared to standard care. Meta-analysis of two of the studies also showed a statistically significant lower incidence of gestational hypertension with dietary intervention [133].

Maternal Weight Gain Between Pregnancies

Women who gain weight between their first and second pregnancies may be more likely to have GDM in the second pregnancy compared to women whose inter-pregnancy weight remained stable [25]. Gains of approximately 2 BMI units between pregnancies are associated with double the risk for development of GDM in the second pregnancy. An increase of three BMI units, or approximately 18 pounds, increases GDM risk by more than three times. Furthermore, weight loss between pregnancies appears to reduce the risk for GDM in the subsequent pregnancy [25].

As such, avoiding weight gain between pregnancies can reduce the risk of recurrence of GDM. Loss of gestational weight after pregnancy and avoiding postpartum weight gain may also reduce the risk. This research also supports the promotion of preconception weight loss in overweight or obese women [135].

Physical Activity Before and During Pregnancy

A large body of evidence supports the beneficial impact of exercise on glucose homeostasis in virtually every population. A systematic review and meta-analysis concluded that these benefits extended to women at risk for GDM [136]. Researchers found that higher levels of physical activity before pregnancy or in early pregnancy were associated with a significantly lower risk for developing GDM. It follows that promoting physical activity among women of childbearing age may prevent GDM and its subsequent complications [136].

OBSTETRICAL AND POSTPARTUM MANAGEMENT OF PREGNANCY COMPLICATED BY DIABETES

The implications of a high-risk pregnancy, such as one complicated by GDM, require specialized attention and monitoring throughout labor and delivery, in addition to surveillance and treatment of problems with the infant. In the postpartum period, mothers can help offset some of the risks to herself and her infant by breastfeeding as early and often as possible.

FETAL SURVEILLANCE

Fetal Ultrasound

Fetal ultrasound can detect major anatomic abnormalities in the fetus, assess fetal growth status, and provide an estimate of fetal weight. It can also detect polyhydramnios, a common finding in pregnancies complicated by diabetes. The ADA recommends fetal ultrasound to screen for congenital anomalies when the pregnant woman has an A1C greater than 7% or a fasting plasma glucose greater than 120 mg/dL, as these values are associated with a greater risk for congenital malformations [13; 16].

Fetal ultrasound can detect macrosomia by providing a means to measure fetal abdominal circumference (FAC), starting in the second or third trimester and repeated every few weeks. FAC measurements provide useful information to guide management decisions and may improve perinatal outcome. For example, if the FAC indicates excessive growth for gestational age, lower glycemic targets may be indicated for the mother. Less intensified management may be allowed when there is normal fetal growth, as measured by FAC, although the ADA recommends continued SMBG in these cases [13; 16].

Detection of Fetal Movement

Monitoring "kick counts" is a method of assessing fetal movements during the last 8 to 10 weeks of pregnancy. With this method, the mother counts the number of fetal movements she perceives in a specified amount of time. Any perceived reduction in fetal movement should be reported immediately. Kick counts may provide a sufficient level of fetal surveillance in women with GDM who are at lower risk, such as those meeting targets with nutrition and exercise and in whom fetal growth is appropriate for age [16].

Alpha Fetoprotein

Alpha fetoprotein (AFP) is a fetal product that appears in the amniotic fluid and maternal circulation. When AFP levels increase, it may indicate that there is an open fetal defect, originating in the spine or ventral wall. Some chromosomal abnormalities, such as trisomy 21, cause a low concentration of AFP. Pregnant women with type 1 diabetes should have tests of AFP concentration, as the genetic anomalies are more likely [16]. AFP screening is best done at approximately 16 weeks' gestation, as this increases accuracy [16].

LABOR AND DELIVERY

A pregnancy complicated by diabetes is always considered a high-risk pregnancy, and when labor begins, the labor and delivery team will continually evaluate status with electronic fetal monitoring. Because labor involves intense physical activity for the mother, it will produce physiologic changes. The energy needs of labor naturally lower maternal blood glucose concentrations and reduce the body's need for insulin. However, stress and pain can cause an increase in blood glucose. Because maternal hyperglycemia is strongly associated with neonatal hypoglycemia, the mother's blood glucose should be carefully monitored during labor.

Cesarean delivery is more common in pregnancies complicated by diabetes. In type 1 diabetes, the rate of cesarean delivery is two to four times higher than the general population, affecting 45% to 73% of births [137].

Conventionally, obstetric professionals plan earlier deliveries for women with diabetes, usually at 38 to 39 weeks' gestation. The benefit is to reduce the risk of fetal death and other complications associated with macrosomia. However, increased antepartum fetal surveillance and improved maternal glycemic control may decrease risk, so more women are being allowed to continue to term [16; 137].

POSTPARTUM

Immediately after delivery of the placenta, the insulin requirements of the mother diminish abruptly. As noted, many women who use exogenous insulin will not require a dose for 24 to 72 hours postpartum.

Quality of the maternal diet is important in the postpartum period. The mother is recovering from the physiologic stresses of pregnancy and childbirth, in addition to needing to meet the energy demands of lactation. During this time, the patient should continue to follow her pregnancy meal plan or receive counseling from a registered dietitian who can advise her on appropriate changes.

Postpartum weight loss should be a gradual loss of the weight gained during pregnancy, in some cases in addition to excess prepregnancy weight. The aim should be to lose 0.5 to 1 pound per week [16]. A more rapid weight loss may lead to fatigue and nutrient depletion.

CARE OF NEONATAL COMPLICATIONS

Hypoglycemia

It is normal for the healthy newborn infant to have a transient decline in blood glucose immediately following birth. This is part of the normal physiologic adjustment to extrauterine life and does not usually have adverse effects. In most cases, the infant's body compensates by decreasing insulin production and releasing glycogen stores, thereby normalizing plasma concentration of blood glucose.

Hypoglycemia in the newborn is defined as blood glucose of 45 mg/dL or less, usually without any other signs. It tends to be more severe in infants of mothers with pre-existing type 1 or type 2 diabetes and occurs in 25% to 40% of these births [138]. Elevated maternal glucose levels prior to birth stimulate overproduction of insulin by the infant's pancreas, leading to hypoglycemia in the early postpartum period. Macrosomic and preterm infants are at the greatest risk for hypoglycemia.

At the time of delivery, a blood sample from the umbilical cord may be used to check the neonate's plasma glucose level. Neonatal hypoglycemia can occur within 30 minutes of clamping the umbilical vessels or may develop after 24 hours and persist for up to 48 hours. The lowest point of glycemic concentration is usually at one to two hours after birth. Infants born to mothers with diabetes should undergo sequential blood glucose testing during the first one to two days of life, as neonatal hypoglycemia is usually transitory and resolves spontaneously [28; 138].

One measure to stabilize hypoglycemia in the newborn is to keep the infant warm and dry. A cold, wet baby requires a greater expenditure of energy to maintain its core temperature, increasing the risk for hypoglycemia. Maintaining skin-to-skin contact immediately after birth also reduces thermal stress and stabilizes the newborn's blood glucose [138].

Early initiation of breastfeeding also helps prevent hypoglycemia. New mothers should initiate breastfeeding within the first hour of life whenever possible. Continuing to breastfeed at least every two hours will help keep the infant's blood glucose in the target range of between 50 mg/dL and 120 mg/dL.

If an infant is in a special care nursery or is otherwise unable to receive breast milk, measures should be taken to avoid the use of cow's milk-based formulas, as these tend to be diabetogenic. The preferred choice is expressed colostrum from the mother, which can be done prenatally and frozen and may be spoon-fed to the infant, if necessary [138].

Intravenous glucose is used to treat neonatal hypoglycemia that is recurrent or persistent [138]. The infant usually receives a small bolus initially, followed by a continuous infusion of dextrose. After plasma glucose stabilizes in the target range, the infusion may be slowly decreased while oral feedings are advanced. When treated appropriately, neonatal hypoglycemia does not have any adverse central nervous system complications [16].

Respiratory Distress

Respiratory distress is a common and potentially severe complication in infants born to mothers with diabetes. Signs and symptoms include tachypnea, intercostal retractions, nasal flaring, and respiratory grunting in the first hours of life. Careful fetal surveillance and allowing a pregnancy to come to full term can reduce the risk. Respiratory distress is managed with fluid administration, oxygen administration, correction of acidosis, and ventilator support when necessary.

Hypocalcemia

An estimated 50% of neonates born to mothers with type 1 diabetes develop hypocalcemia during the first three days of life [139]. There is a direct relationship between the severity of hypocalcemia and the glycemic control of the mother. Treatment includes calcium gluconate infusion, monitoring heart rate, and oral or parenteral maintenance therapy.

Hypomagnesemia

Hypomagnesemia occurs in 33% of infants born to mothers with diabetes [139]. Like hypocalcemia, the severity of hypomagnesemia is in direct relation to maternal status. Treatment includes intravenous or intramuscular administration of magnesium and monitoring of the infant's heart rate.

Erythremia and Hyperbilirubinemia

Treatment of neonatal erythremia involves partial-exchange transfusion through the umbilical vein with plasma protein fraction or albumin. The increase in red cell mass of erythremia can cause a blockage in the blood vessels and lead to hyperbilirubinemia (also known as jaundice). Infants born before full term are more likely to need treatment for hyperbilirubinemia, and the degree and acceleration of the bilirubin level in the blood determine the need for treatment.

Phototherapy is often used to break down bilirubin in the skin. Keeping the newborn well hydrated with frequent feedings helps remove bilirubin through the stools. Less commonly, infants require intravenous hydration therapy. In the most severe cases of jaundice, an exchange blood transfusion or treatment with intravenous immunoglobin may be necessary [140].

BREASTFEEDING

Breastfeeding offers many health benefits to women, including those with diabetes. Furthermore, it offers immediate and future benefits to both mother and child. Healthcare providers who work with patients with diabetes should advocate for breastfeeding and support institutional policies that facilitate breastfeeding.

Lactation increases the caloric needs of the mother [141]. The initial energy demands of breastfeeding exceed the prepregnancy demand by approximately 650 calories per day. This decreases by about 100 calories in the second half of the first year of breastfeeding. The ADA recommends that breastfeeding mothers with diabetes consume at least 1,800 calories per day to meet the requirements for lactation while allowing for gradual weight loss [16]. Stored fat meets some of this need, providing about 150 calories per day. Therefore, an increase of about 500 calories per day over the prepregnancy allowance may be needed [16].

In addition, the insulin requirements for nursing mothers are about 25% lower during lactation. In GDM, breastfeeding may be associated with lower rates of postpartum diabetes and lower fasting glucose levels [13; 141]. In fact, lactation results in more favorable cardiometabolic profile among postpartum women in general, including women with GDM. This may protect against metabolic syndrome later in life [141].

Infant/Offspring Benefits

Breast milk has a unique composition of macronutrients and other bioactive substances that may influence the young infant's metabolic programming in a beneficial way. The first weeks of extrauterine life appear to be a critical time in establishing the body's fat volume and its distribution. Breast-fed babies have an estimated 13% to 22% reduction in risk for childhood and later-life obesity [142].

Mothers with diabetes who breastfeed their infants may protect them from obesity and early-onset diabetes in the future. One study showed that children exposed to diabetes in utero who were breast fed for at least six months had lower BMI, smaller waist circumference, and less subcutaneous fat tissue at 6 to 13 years of age [142]. Several studies indicate that receiving cow's milk-based formula during the first months of life can significantly increase the risk for diabetes in susceptible infants [138].

Breastfeeding in Mothers with Postpartum Diabetes

Because lactation increases the energy demands on a woman's body, women with diabetes may experience wide fluctuations in their glycemic patterns while breastfeeding. Hypoglycemia is common, most markedly within an hour of breastfeeding. Nocturnal hypoglycemia is also common in this population. Measures to prevent hypoglycemia and avoid frequent adjustments in insulin dosage for breastfeeding women with diabetes include [16; 138; 141]:

- Check blood glucose one hour after breastfeeding.
- Eat a small snack containing carbohydrates and protein before or during breastfeeding.
- Check blood glucose periodically throughout the night.
- Increase caloric intake as needed.
- Eat a high-protein snack at bedtime if nocturnal hypoglycemia is a problem.
- Decrease the bedtime dose of NPH insulin.

Women with pre-existing diabetes may experience challenges with breastfeeding related to their chronic medical condition. Diabetes and poor glycemic control are associated with:

- Decreased milk production
- Delay in the onset of lactation
- Bacterial and *Candida* infections of the breast and nipple
- Lower infant intake
- Immature sucking pattern of the infant

Lower infant intake may be due to the increased incidence of neonatal morbidity and perinatal problems that can separate the mother and child during the important early time when breastfeeding is established. Furthermore, women with diabetes can have colostrum for two to three days longer than nondiabetic women do, causing frustration when attempting to satisfy an infant's hunger needs.

Despite these challenges, many women with diabetes can successfully breastfeed for prolonged periods with the proper support [138].

Women with diabetes are more likely to develop bacterial infections and fungal colonization of the nipples when breastfeeding, and in turn, these infections can cause high blood glucose levels. Proper nipple-areolar placement during breastfeeding can help avoid trauma to the nipple and prevent infections.

Approximately 21% to 27% of women with type 2 diabetes have polycystic ovary syndrome (PCOS). This endocrine disorder can affect milk supply in the breastfeeding woman, most likely due to hormonal irregularities. As a condition of insulin resistance, healthcare providers often prescribe the drug metformin to treat PCOS, which may also increase milk production [138]. While metformin may be used in breastfeeding women, due to the potential for hypoglycemia in the infant, the manufacturer recommends that a decision be made whether to discontinue breastfeeding or discontinue metformin, taking into account the importance of breastfeeding [44].

PSYCHOSOCIAL CARE IN PREGNANCY COMPLICATED BY DIABETES

Pregnancy is a life-changing event that brings many emotions to a patient and her family. These normal psychosocial concerns are likely to intensify in a pregnancy complicated by diabetes. Complete patient management incorporates psychosocial assessment into the plan of care, including screening for depression, anxiety, and stress.

Pregnancies in patients with diabetes (pre-existing or gestational) are considered high risk and have a greater potential for a poor pregnancy outcome than those in nondiabetic patients. As such, these patients are more likely to face fetal demise or newborns with serious illness or congenital anomaly. While these situations represent a crisis for the healthcare team, responses to the patient and her family play a crucial role in their grieving process. Unfortunately, it has been reported that many families perceive that the physician provided inadequate emotional support following perinatal death. Furthermore, families can usually recall the response from the healthcare team many years after the critical event [143].

Normal pregnancy is a time of hormonal fluctuations, and this metabolic flux effects physiologic and psychologic changes within the mother's body, which can naturally induce stress. In addition to physiologic causes of stress, patients are dealing with lifestyle changes and the psychosocial demands of pregnancy, including changes in body image, role change, medical demands, fear of labor, and fear of the unknown.

When a woman has diabetes, her emotional responses to the pregnancy may be more profound. The increased risk for problems and additional medical surveillance can cause anxiety. Women with GDM may have concerns about the implications that diabetes has for her future, while those with pre-existing diabetes are likely to require changes to their therapeutic regimen. These demands may cause a woman to feel ambivalent about her pregnancy, even if it was planned [12; 16].

REACTION TO GDM DIAGNOSIS

When a seemingly normal pregnancy becomes complicated by the onset of diabetes, the potential for emotional unrest intensifies. At this point, the woman learns that she has a high-risk pregnancy that requires a demanding self-care regimen involving additional education, time commitments, and behavior modification. Many young women in this position have never experienced a serious health problem, and they perceive that the road ahead is daunting. Fear of SMBG is common, and anxiety may interfere with the patient's ability to learn. These perceived threats may be greater if insulin therapy is necessary. Although patients with GDM may be overwhelmed with the current situation, they also face making long-term adjustments to their lifestyle to address a future risk for type 2 diabetes.

DEPRESSION

As noted, the hormonal fluctuations of pregnancy can increase the risk for depression, and severe depression is associated with poor glycemic control and ultimately poor pregnancy outcomes. Psychotherapy is the first line of treatment for depression during pregnancy. Referral to a mental health professional is appropriate. The safety of antidepressant medications during pregnancy is questionable, as some have been linked to congenital anomalies and infantile withdrawal syndrome. In the most severe cases, the benefits of using antidepressant medication may outweigh the risks, as fetal exposure to untreated major depressive disorder is significant. Balancing the risks to the fetus exposed to severe maternal depression and to the medications to treat depression is necessary [10].

STRESS MANAGEMENT

As noted, stress can have significant effects on diabetes symptoms and management. One way of curtailing the negative effects of stress on health can be to limit the number or intensity of stressors that one experiences. Because this is not always possible, learning how to cope with stress is another way of curbing its adverse health effects.

Certain techniques and behaviors can be encouraged to improve coping. Patients experiencing stress may benefit from visualization, progressive muscle relaxation, and breathing exercises. Keeping a stress diary may help some patients identify events that can trigger responses. Blood glucose logs can be used to keep track of stressful events and feelings. Correlating these events and feelings with blood glucose results may help to monitor the effect of stress on blood glucose control.

Another suggestion for reducing stress is to prioritize the demands a patient has in her life. By doing this, some tasks may be eliminated or delegated, making the patient more likely to address important tasks fully and to experience a greater degree of satisfaction. Patients may also be advised to direct stress-related energy toward something more positive, such as exercise, hobbies, charity, or other pursuits of interest.

Techniques such as progressive relaxation, biofeedback, and guided visual imagery are generally accepted as effective stress-reduction methods. Audio tapes, videos, and books are available to guide the delivery of these interventions. Furthermore, many professional therapists use these methods, and patients can access them online or in other publications.

CRISIS MANAGEMENT

Most families anticipate positive outcomes to a pregnancy. Unfortunately, this is not always the case, particularly in pregnancies complicated by diabetes. Crises related to diabetes in pregnancy include fetal demise and neonates with congenital anomalies. While these represent a crisis to the mother and her family, they are also a crisis for the medical team [143].

The initial reaction to a perinatal crisis is normally shock and disbelief. While the family wants information at this time, they will probably not be able to process all of it initially; repetition of the information will be necessary. Nurses should have excellent communication with physicians to allow for continuity and accuracy when answering questions [143].

Fetal Demise

Obviously, a family experiences great feelings of grief with the loss of a fetus. As VanDinter eloquently writes, the loss of the fetus represents the "loss of their future" [143]. As with any loss, grieving is normal and necessary in order to process one's feelings and eventually accept the loss. Feelings associated with fetal demise may include guilt, anxiety, depression, deprivation, frustration, victimization, and anger. Patients may also worry about how this incident will affect future pregnancies. When a woman fails to acknowledge and resolve a previous adverse pregnancy outcome, she is at risk for greater psychosocial distress in future pregnancies [143].

An appropriate response from the healthcare provider is empathic listening, or being present with the grieving person and remaining nonjudgmental. To be effective, nurses must allow the woman and her family to grieve in their own way and accept the emotions that they demonstrate [16]. It is important to facilitate attachment and bonding with the deceased infant, which can involve [143]:

- Calling the infant by name
- Allowing parents to hold the infant
- Allowing family the time and space to bond with infant and to say good-bye
- Offering to save mementos, such as a footprint or lock of hair

Congenital Anomalies and the Severely Ill Infant

The reaction to an ill newborn may be very similar to those experienced with fetal demise. In essence, having a child with serious medical problems represents the loss of the parents' vision of the future. In addition to shock and grief, parents may experience hurt pride and diminished self-esteem [16]. They are also likely to experience significant anxiety related to anticipating a future of increased medical responsibilities and associated costs.

When a neonate suffers serious health problems, the appropriate response from healthcare providers is to provide emotional support to the mother and her family, which may include help with decision making [143]. It is important to stay positive without being unrealistic and to remember that parents may be faltering in their self-esteem during this time and need encouragement. Bonding with the infant is of critical importance, and parents should be allowed to touch and be with the newborn even if it is critically ill [16].

CONCLUSION

Nurses and healthcare providers in virtually every medical setting encounter patients with diabetes. In most cases, diabetes makes other medical conditions more complicated, and the obstetrical arena is no exception—diabetes is a common but serious complication to any pregnancy.

Diabetes may be present in the form of pre-existing type 1 or type 2 diabetes, or in the case of GDM, its onset may be first recognized during pregnancy. In any of these situations, hyperglycemia poses a serious threat to the health and well-being of both the mother and the fetus.

There is substantial evidence to support the importance of glycemic control during pregnancy. Serious complications can occur when glycemic control is poor, including macrosomia, birth trauma, hypoglycemia, preterm delivery, congenital anomalies, and fetal demise. Later in life, offspring of mothers with diabetes are more likely to develop metabolic conditions such as diabetes, obesity, and CVD.

Mothers who experience diabetes during pregnancy face health risks as well, including complicated labor and delivery, cesarean delivery, pre-eclampsia, infection, and difficulty with breastfeeding. Importantly, women with GDM have a substantial risk for developing type 2 diabetes in the future. Therefore, lifelong preventive and screening measures are necessary for these women.

Preconception care is of vital importance for women with pre-existing diabetes. A planned pregnancy and excellent glycemic control before conception provide the best chance for a favorable pregnancy outcome. Preconception care also allows for a thorough evaluation of diabetes complications that may affect the course of the pregnancy and the health of the mother.

Diet, especially carbohydrate management, is the cornerstone of diabetic management of any type. Physical activity supplements medical nutritional therapy, to the degree that physical activity is appropriate. The mainstay of pharmacologic treatment of diabetes during pregnancy is insulin, although oral antidiabetic medication is a feasible choice for some women. Frequent SMBG helps patients and their healthcare team evaluate the effectiveness of therapy and make adjustments as needed.

The obstetrical and postpartum care of pregnancy complicated by diabetes requires additional surveillance due to the high-risk nature of the pregnancy. Fetal ultrasound and kick counts are common methods of assessing fetal well-being. After delivery, the infant is monitored for hypoglycemia, hyperbilirubinemia, hypomagnesemia, and hypocalcemia.

Breastfeeding has substantial benefits to both mother and child in pregnancies complicated by diabetes. Healthcare providers should make every opportunity to encourage and support early and frequent breastfeeding.

Finally, pregnancy complicated by diabetes has the potential to carry significantly more psychosocial stress than an uncomplicated pregnancy. Providers who work with this population may be in the unique position to assist women and their families through the process of grief when a pregnancy ends in stillbirth or when an infant is born with significant health problems.

This course has reviewed the many aspects of pregnancy complicated by diabetes. Importantly, healthcare professionals should appreciate the arsenal of tools available to improve pregnancy outcomes in this population. Providing preconception care, pregnancy surveillance, and assistance with glycemic control can prevent immediate problems for the mother and child. For the future, advocacy of breastfeeding, careful patient teaching, and lifestyle modification will have a positive influence on patients' health and well-being.

GLOSSARY

A1C: a test that measures the percentage of hemoglobin that has become glycated from excess glucose in the blood.

Body mass index (BMI): the ratio of the weight of the body in kilograms to the square of its height in meters. A body mass index of 25–29.9 in adults is considered an indication of overweight, and 30 or more is an indication of obesity.

Colostrum: milk secreted for a few days after parturition and characterized by a high protein and antibody content.

Dawn phenomenon: a rise in the level of glucose in the blood plasma that occurs in the early morning (before breakfast) and that may progress to hyperglycemia in diabetics, especially those with type 1 diabetes.

Erythropoiesis: the production of red blood cells (as from the bone marrow).

Gastroparesis: partial paralysis of the stomach.

High-density lipoprotein (HDL) cholesterol: a lipoprotein of blood plasma that is composed of a high proportion of protein with little triglyceride and cholesterol and is associated with decreased probability of developing atherosclerosis.

Hypoglycemia unawareness: loss of warning symptoms that normally allow one to recognize low blood glucose.

Metabolic syndrome: the presence of usually three or more of a group of factors (e.g., high blood pressure, abdominal obesity, high triglyceride levels, low HDL levels, and high fasting levels of blood sugar) that are linked to an increased risk of CVD and type 2 diabetes.

Polycystic ovary syndrome (PCOS): a variable disorder that is marked especially by amenorrhea, hirsutism, obesity, infertility, and ovarian enlargement and is usually initiated by an elevated level of luteinizing hormone, androgen, or estrogen, resulting in an abnormal cycle of gonadotropin release by the pituitary gland.

Polycythemia: condition marked by an abnormal increase in the number of circulating red blood cells.

Teratogen: an agent that causes developmental malformations.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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