

Pregestational Diabetes in Pregnancy



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KEYWORDS

• Pregestational diabetes • Pregnancy • Pregnancy outcomes • Preconception care

KEY POINTS

- Pregestational diabetes affects 1% to 2% of pregnancies in the United States.
- Poor diabetes control is associated with both maternal and fetal adverse outcomes.
- Optimization of glucose control with intensive self-monitoring of blood glucose, lifestyle management, and pharmacologic therapy preconception and throughout pregnancy reduces risk of developing these outcomes.

INTRODUCTION

In the last 30 years, the prevalence of diabetes mellitus in women of childbearing age has grown. Much of this is attributable to the obesity epidemic, which estimates suggest will worsen over the next decade.¹ Pregestational diabetes mellitus (PDM) now affects 1% to 2% of pregnancies in the United States, and its prevalence continues to grow. Since the 1990s, PDM has increased significantly in across all age groups, ethnicities, and geographies in the United States and Canada (**Fig. 1**).^{2–4} Rates of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) continue to increase,⁵ of whom more than 20% are undiagnosed.⁶

Glucose Metabolism in Pregnancy

In women with normal carbohydrate metabolism, first-trimester fasting blood glucose levels are lower than at baseline due to estrogen-mediated increases in both insulin sensitivity and insulin production.⁷ In the second and third trimesters, fasting blood glucose increases as hepatic glucose production increases and insulin sensitivity decreases.⁸ Placental hormones, including human placental lactogen and progesterone,

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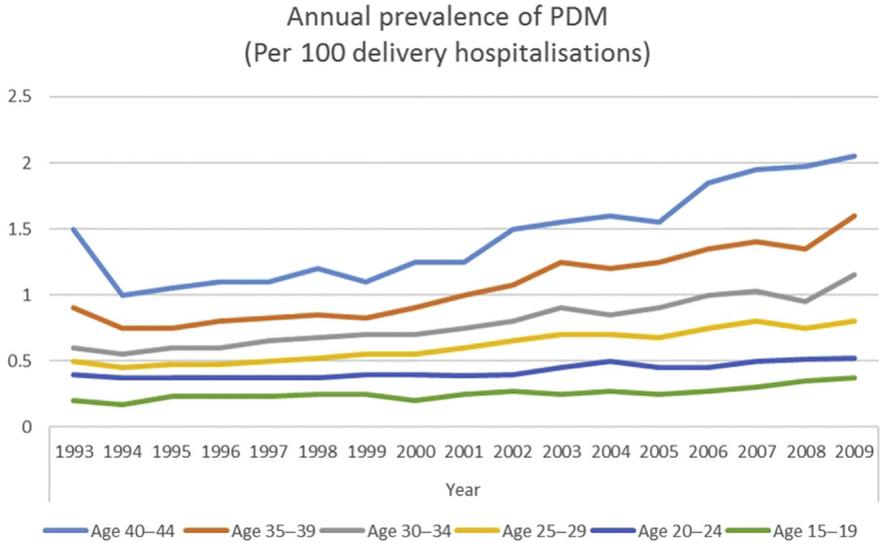


Fig. 1. Annual prevalence of pregestational diabetes in the United States. (Adapted from Fig. 2, Correa A, Bardenheier B, Elixhauser A, et al. Trends in prevalence of diabetes among delivery hospitalizations, United States, 1993-2009. *Matern Child Health J* 2015;19(3):635-42; with permission.)

also increase peripheral insulin resistance.⁹ In women with normal pancreatic function, increased insulin secretion is sufficient to overcome physiologic insulin resistance and maintain normal blood glucose (Fig. 2).¹⁰

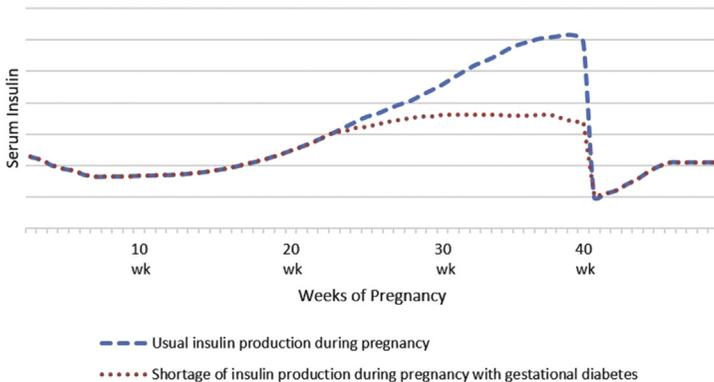


Fig. 2. Insulin requirements during pregnancy. (Data from Catalano PM, Tyzbir ED, Roman NM, et al. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol* 1991;165(6 Pt 1):1667-72.)

Classification

Diabetes mellitus is a syndrome of impaired glucose metabolism due to reduced or absent pancreatic insulin secretion, abnormal peripheral insulin sensitivity, or both.¹¹ According to the American Diabetes Association (ADA), the criteria for diagnosis of diabetes include the following¹¹:

- Fasting blood glucose greater than 126 mg/dL (7.0 mmol/L)
- Two-hour postprandial glucose greater than 200 mg/dL (11.1 mmol/L) after ingestion of a 75-g glucose load
- A1c >6.5% (48 mmol/mol)
- A random plasma glucose greater than 200 mg/dL (11.1 mmol/L)

T1DM is an autoimmune condition that often develops early in life because of destruction of insulin-producing beta cells in the pancreas.¹² T2DM is characterized by late onset, increased peripheral insulin resistance, and reduced insulin sensitivity. It is associated with age, obesity, family history, and history of gestational diabetes.¹³ Both mother and fetus are exposed to a wide range of risks and complications in pregnancy that are predominantly a function of glycemic control in PDM.¹⁴ With appropriate therapy, the likelihood of these complications can be reduced to background population rates.¹⁵

RISKS OF PREGESTATIONAL DIABETES DURING PREGNANCY

Maternal Complications

Chronic hypertension

Chronic hypertension, defined as hypertension present before 20 weeks of gestation,¹⁶ affects 6% to 8% of pregnant women with PDM. It is likely due to disruption of the renal-angiotensin system through reduced renal vascular compliance and glomerular sclerosis caused by diabetes.¹⁷ The risks of hypertension include the following¹⁸:

- Intrauterine growth restriction (IUGR)
- Fetal demise
- Superimposed preeclampsia
- Iatrogenic preterm delivery

The goal of antihypertensive treatment in pregnancy for women with diabetes is to avoid severe range blood pressures (systolic >160 mm Hg, diastolic >105 mm/Hg). Safe antihypertensives include the following:

- Beta-blockers (eg, labetalol)
- Calcium-channel blockers (eg, nifedipine)
- Alpha-2 agonists (eg, methyldopa)

Angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers (ARBs) are contraindicated in pregnancy because of risk of fetopathy, including IUGR, fetal renal dysplasia, and oligohydramnios.¹⁹ Although women exposed to angiotensin-converting-enzyme inhibitors or ARBs can be reassured that first-trimester use is not likely associated with congenital anomalies, switching to an antihypertensive medication compatible with pregnancy before conception is recommended.²⁰

Nephropathy

Nephropathy, defined as microalbuminuria greater than 300 mg/24 hours with or without impaired renal function, occurs in 2% to 5% of pregnancies in women with PDM.²¹ As the glomerular filtration rate increases during pregnancy, proteinuria often increases.²² Women with nephropathy are at high risk for preeclampsia.²¹ Approximately 50% undergo indicated preterm delivery for maternal or fetal indications, including IUGR (15%) and preeclampsia (50%).²³ Permanent deterioration in baseline kidney function during pregnancy is uncommon; however, end-stage renal disease

can occur in women with severe proteinuria in pregnancy (>3 g per 24 hours) or creatinine levels in excess of 1.5 mg/dL.²⁴ Aggressive antihypertensive control has been associated with better outcomes in women with nephropathy.²⁵

Preeclampsia

The incidence of preeclampsia is higher in women with PDM, including 10% to 20% in those with T1DM.²⁶ Glycemic control in early pregnancy is associated with risk of preeclampsia.²⁷ Although randomized controlled trial data are lacking specifically for women with PDM, the authors recommend aspirin for preeclampsia prophylaxis from 16 weeks, consistent with US Preventive Services Task Force recommendations.²⁸

Retinopathy

Diabetic retinopathy is associated with PDM and can worsen during pregnancy.²⁹ Factors associated with progression include duration of diabetes, presence of hypertension, and adequacy of glycemic control.³⁰ Although tight glycemic control has been associated with progression,³⁰ the benefits of glycemic control for other outcomes outweigh this risk. All women with PDM should therefore undergo thorough ophthalmic assessment early in pregnancy.²² Women with proliferative retinopathy can be treated with laser photocoagulation during pregnancy; antivascular endothelial growth factor agents are not routinely recommended.³¹

Neuropathy

There are limited data regarding the prevalence and prognosis of neuropathy during pregnancy. Gastroparesis should be considered in women presenting with hyperemesis.³² Diabetes-associated distal symmetric polyneuropathy may occur.³³ Multidisciplinary management of neuropathic pain may be helpful.³⁴

Coronary artery disease

Coronary artery disease is uncommon in pregnancy but should be considered in symptomatic women with PDM. Women with a history of myocardial infarction should be discouraged from becoming pregnant.³⁵ A baseline electrocardiogram (ECG) is recommended, with consideration of echocardiogram (ECHO) as indicated.

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a life-threatening emergency affecting 5% to 10% of women with T1DM during pregnancy.³⁶ DKA remains a common first presentation in pregnant patients with undiagnosed diabetes, and distinct from non-pregnant women, can occur with mildly elevated glucose levels.³⁷ Women with T1DM should have specific education on DKA detection and prevention.

Fetal Complications

PDM is associated with increased risk of fetal and neonatal morbidity and mortality.²⁴ Known complications include congenital anomalies, abnormal fetal growth, fetal loss, birth injury, neonatal hypoglycemia, and hyperbilirubinemia.³⁸

Normal fetal glucose physiology

From the time of placental formation, glucose crosses the placenta via facilitated diffusion.³⁹ Although the exact relationship between maternal and fetal glucose concentrations is complex, fetal glucose levels are directly related to maternal glucose levels: maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia.⁴⁰

Risks to fetus in early pregnancy

Uncontrolled hyperglycemia during the first trimester affects organogenesis.⁴¹ Spontaneous abortion and congenital malformation, of the central nervous system, cardiac, gastrointestinal, and genitourinary tract, are significantly more incident with A1c >7%, and the risk is proportional to A1c⁴²: the overall risk of fetal anomalies in women with PDM is 6% to 12%.⁴³ A meta-analysis of 33 observational studies found no differences in incidence of major congenital malformations between mothers with T1DM and T2DM.⁴⁴

Abnormal fetal growth

Fetal growth is determined by constitutional growth potential, genetic and epigenetic influences, and maternal characteristics, including nutritional state.⁴⁵ Maternal diabetes is associated primarily with fetal overgrowth, but also growth restriction.⁴⁶ Pedersen and colleagues⁴⁷ are credited with the hypothesis that maternal hyperglycemia drives fetal hyperinsulinemia, stimulating insulin-like growth factor receptors, resulting in excessive growth.⁴⁸ More recent understanding of fetal growth includes abnormalities in early placental oxidative stress, placental glucose, amino acid, and lipid transport.^{49,50}

Amniotic fluid abnormalities

Polyhydramnios in PDM may be related to increased amniotic fluid glucose concentration or fetal polyuria.⁵¹ Severe polyhydramnios in PDM is uncommon and should prompt consideration of other causes.⁵²

Stillbirth

Stillbirth occurs in 3.1 to 5.8 per 1000 women with PDM in the United States.⁵³ Despite differences in underlying pathophysiology, women with T2DM do not have better perinatal outcomes than those with T1DM.⁴⁴ Risk factors for stillbirth include large for gestational age⁵⁴ and poor glycemic control.⁵⁵ Fetal acidosis is one postulated mechanism of intrauterine fetal death.⁵⁶

Prematurity

The incidence of preterm delivery and associated neonatal risks is significantly elevated in women with PDM.⁵⁷

MANAGEMENT OF PREGESTATIONAL DIABETES IN PREGNANCY**Preconception Counseling**

Perinatal and maternal outcomes are best when glucose control is optimized before conception.⁵⁸ Women may benefit from multidisciplinary teams that include obstetrics, endocrine, and nutrition providers familiar with diabetes in pregnancy.⁵⁹ Recommended preconception measures are outlined in **Box 1**.^{60–62}

Nutrition

Women with PDM should have access to a certified dietician to provide them with an individualized nutrition program. The Institute of Medicine recommends that gestational weight goals depend on maternal prepregnancy body mass index.⁶³ Calorie requirements in a singleton pregnancy are 300 to 350 kilocalories per day higher than prepregnancy requirements.⁶⁴ Monitoring intake of carbohydrates facilitates optimal glycemic control.⁶⁵

Intensive Glucose Monitoring

Fasting and postprandial monitoring of blood glucose is recommended to achieve metabolic control in women with PDM.⁶⁶ Although a 2017 *Cochrane Review*

Box 1**Fundamentals of preconception care for women with pregestational diabetes mellitus****A. General measures**

- Institution of a minimum of 400 µg folic acid daily to reduce risk of neural tube defects
- Monthly monitoring of A1c until stable less than 6.0%
- Effective use of contraception until pregnancy is desired or until diabetes is optimally controlled

B. Evaluation for complications of diabetes

- Urinalysis for glucose, leukocytes, nitrites, and ketones
- Urine culture test for asymptomatic bacteriuria
- A 24-hour urine collection for protein and creatinine clearance or spot albumin-creatinine ratio to assess for nephropathy
- Serum creatinine to assess for nephropathy
- HbA1c for as a measure of 6-weekly glucose control
- Thyroid-stimulating hormone for associated autoimmune thyroid dysfunction, which occurs in up to 40% of women with type 1 diabetes
- Referral for ophthalmologic assessment for retinopathy
- A baseline ECG or ECHO if prior history of chronic hypertension or ischemic heart disease

C. Education

- Counseling regarding specific maternal, fetal, and obstetric risks associated with diabetes in pregnancy, including fetal anomaly
- Effectiveness of optimizing control in reducing adverse maternal, fetal, and obstetric outcomes in pregestational diabetes
- Effective use of contraception during periods when pregnancy is not desired, or where diabetes and lifestyle are not optimized
- Understanding resources and information available for women of childbearing age through their primary care provider, obstetrician, diabetologist, or the American Diabetes Association (<http://www.diabetes.org/living-with-diabetes/complications/pregnancy/>)

Data from The American College of Obstetricians and Gynecologists. ACOG Committee Opinion #313: the importance of preconception care in the continuum of women's health care. *Obstet Gynecol* 2005;106(3):665–6; and Hanson MA, Bardsley A, De-Regil LM, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First." *Int J Gynecol Obstet* 2015;131(Suppl 4):S213–53.

concluded there was insufficient evidence to recommend a specific glucose monitoring technique,⁶⁷ a recent randomized controlled trial suggests that women with T1DM may benefit from continuous glucose monitoring.⁶⁸ The American College of Obstetricians and Gynecologists (ACOG) and the ADA targets for women with PDM are outlined in **Box 2**.⁶⁹

Hemoglobin A1c in Pregnancy

A1c levels decrease during pregnancy because of physiologic increased red blood cell turnover.⁷⁰ Recommended target A1c in pregnancy is less than 6% (42 mmol/mol) based on observational studies showing the lowest rate of adverse fetal outcomes in this cohort.⁷¹ These levels should be achieved without hypoglycemia, which can increase risks to both mother and fetus.⁷² Of note, A1c may not adequately capture postprandial hyperglycemia and therefore remains a secondary measure of glucose control.

Insulin Requirements Through Pregnancy

Total daily insulin requirements typically decrease in the first trimester of pregnancy.⁷³ Women with well-controlled diabetes in early pregnancy may experience episodes of

Box 2**Recommended glucose targets**

- Fasting glucose concentrations ≤ 95 mg/dL (5.3 mmol/L)
- Preprandial glucose concentrations ≤ 100 mg/dL (5.6 mmol/L)
- One-hour postprandial glucose concentrations ≤ 140 mg/dL (7.8 mmol/L)
- Two-hour postprandial glucose concentrations ≤ 120 mg/dL (6.7 mmol/L)
- Mean capillary glucose 100 mg/dL (5.6 mmol/L)
- During the night, glucose levels ≥ 60 mg/dL (3.3 mmol/L)

Data from American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(S1):S14–80.

hypoglycemia requiring adjustment of insulin dosage. Insulin requirements increase in the second trimester as placental hormone production begins, requiring frequent up-titration of insulin to achieve desired targets.⁸ In the third trimester, insulin requirements continue to increase until plateauing near term.⁷⁴

Insulin

The goal of insulin therapy is to achieve capillary glucose levels between 70 mg/dL and 110 mg/dL without maternal hypoglycemia. Both multiple daily injection regimens and continuous subcutaneous insulin infusion are reasonable choices in women with PDM.⁷⁵ No trials have demonstrated an optimal multiple dose injection regimen, and therefore, treatment should be individualized to optimize glycemic control.⁷⁶ Insulins commonly used in pregnancy are summarized in **Table 1**.

Basal insulin delivered as intermediate-acting or long-acting insulin suppresses hepatic gluconeogenesis in the fasting state and is necessary for women with T1DM. Neutral protamine Hagedorn is commonly used for basal dosing in pregnancy.⁷⁷ An alternative is the intermediate insulin analogue detemir (Levemir),⁷⁸ which has similar outcomes with no increased risk of hypoglycemia.⁷⁹ Although not recommended as first-line basal insulin for women initiating therapy during pregnancy, insulin glargine (Lantus) may be continued for those who benefit from once-daily basal insulin dosing.⁸⁰

Bolus dosing of short-acting insulin analogues is usually required with meals to mimic prandial insulin secretion. Both Lispro (Humalog) and Aspart (Novolog) are safe for use in pregnancy and have been shown to normalize postprandial blood glucose better than human regular insulin in women with PDM.⁸¹

Table 1**Common types of insulins used**

Duration of Action	Type	Derivation	Onset (h)	Peak (h)
Short	Regular	Human	0.5	2–4
	Lispro		0.25	1–2
	Aspart		0.25	1–2.5
Intermediate	Hagedorn		1–2	5–7
	Lente		1–3	4–8
Long	Glargine		1.1	5
	Detemir		1–2	5

Dosing Regimens

Insulin requirements are weight based and vary by gestational age. A typical starting dose range could be as follows⁵⁴:

- First trimester: 0.7 to 0.8 units per kilogram per day
- Second trimester: 0.8 to 1 units per kilogram per day
- Third trimester: 0.9 to 1.2 units per kilogram per day

Regimens will typically require 50% to 60% of total daily insulin requirement given as basal insulin, with prandial requirement divided into 3 or more injections of short-acting insulin.

Oral Hypoglycemics

Many women with T2DM are on oral hypoglycemics before pregnancy; however, there are limited data on their use during pregnancy.⁸² Metformin and glyburide are currently the only oral agents considered safe for use during pregnancy and are used as alternatives to therapy in women with T2DM who decline insulin.⁸³

Glyburide

In small-cohort studies of women with gestational diabetes, glyburide has been found to be comparable to insulin in optimizing serum glucose control in pregnancy without evidence of significant maternal and neonatal complications.⁸⁴ However, more recent evidence has shown that concentrations in umbilical cord plasma are approximately 70% of maternal serum levels, and that use is associated with higher incidence of fetal macrosomia and neonatal hypoglycemia than metformin or insulin.⁸⁵

Metformin

Metformin has been studied extensively in women without overt diabetes in pregnancy; however, there are limited data on use in women with PDM.⁸⁶ Metformin freely crosses the placenta but does not seem to be associated with fetal risks. Use in the first trimester is associated with a lower risk of miscarriage⁸⁷ and no increased risk of congenital malformations⁸⁸; long-term follow-up data for exposed offspring are lacking at this time, with limited evidence suggesting possible changes in body composition in children exposed in utero.⁸⁹ In women with obesity but no diabetes, metformin is associated with reduced risk of preeclampsia⁹⁰ and lower risk of macrosomia⁹¹; however, these benefits have not been demonstrated in women with PDM.⁹² Based on data from a randomized controlled trial of metformin for treatment of gestational diabetes in which most of the participants needed supplemental insulin, it is likely to be insufficient for glycemic control in women with T2DM.⁸⁴

Hypoglycemia

Hypoglycemia occurs more frequently in pregnancy than at other times.⁹³ Patients and families should be educated on signs of and treatment of hypoglycemia. Glucagon is a peptide hormone normally secreted from pancreatic alpha cells in response to hypoglycemia, which raises the blood glucose concentration and should be made available to relatives of pregnant women on insulin for use in life-threatening hypoglycemia.⁹⁴

Management of Diabetic Ketoacidosis

Aggressive rehydration, insulin, and electrolyte replacement as required are initial therapy. Plasma glucose and potassium levels should be rechecked frequently to avoid untreated hypoglycemia and hypokalemia.⁹⁵ If infection is a possible precipitant

based on clinical presentation, empirical treatment with broad-spectrum antimicrobials is advisable.⁹⁵ The management of DKA is summarized in **Box 3**.⁹⁶

Reported rates of fetal mortality in DKA are 10% to 35%.⁹⁷ Continuous fetal monitoring may show recurrent late decelerations with maternal acidosis,⁹⁸ but fetal acidemia is reversible with appropriate treatment of maternal acidemia.

Intrapartum Glucose Control

Maternal hyperglycemia during labor is associated with risk for neonatal hypoglycemia.⁹⁹ Data are limited on the best approach to intrapartum glycemic control; however, intravenous insulin is often needed to maintain glucose at a goal of 70 to 110 mg/dL.¹⁰⁰ Institutional protocols for insulin management during labor may be useful.

Fetal Monitoring

ACOG recommends antepartum fetal testing for pregnancies complicated by PDM.⁶¹ There are limited data to guide specific test choice and frequency; however, ACOG

Box 3

Management of diabetic ketoacidosis

Laboratory assessment (every 1–2 hours)

- Arterial blood gases to quantify acidosis
- Glucose
- Electrolytes
- Ketones

Insulin

- Low-dose, intravenous
- Loading dose: 0.2 to 0.4 U/kg
- Maintenance: 2 to 10 units per hour

Fluids

- Isotonic normal saline or lactated Ringer
- 4–6 L total replacement in first 12 hours
- 1 L in first hour
- 500 mL to 1 L/h for 2 to 4 hours
- 250 mL/h until 80% replaced

Glucose

- Begin 5% dextrose in normal saline when plasma level reaches 250 mg/dL

Potassium

- If initial levels are normal or decreased, add 20 to 30 mEq/h to an intravenous solution. If levels are elevated, wait until levels decrease

Bicarbonate

- Add 1 ampule of 1 L of 0.45 normal saline if pH is <7.1

Data from American Diabetes Association. Standards of medical care in diabetes–2014. Diabetes Care 2014;37(S1):S14–80.

advises antepartum monitoring using fetal movements, biophysical profile, nonstress tests, and/or contraction stress test at appropriate intervals.⁶¹ The authors start testing by 32 weeks and increase to twice weekly by 34 to 36 weeks.

Timing of Delivery

In the absence of compelling data to drive decision making,¹⁰¹ delivery timing should be individualized based on maternal glycemic control, balancing the risk of intrauterine fetal death and ongoing fetal overgrowth with maternal and fetal morbidity associated with early delivery. Delivery in the late preterm or early term (37 weeks) may be indicated in patients with end-organ disease, persistently poor glucose control, or a previous intrauterine fetal demise.¹⁰²

Mode of Delivery

PDM increases risk for cesarean delivery, independent of birth weight and other factors.¹⁰³ Cesarean delivery should be considered in women with diabetes and an estimated fetal weight greater than 4500 g.¹⁰⁴ Although no large randomized trials have been conducted in women with PDM, in one single-center study, a policy of elective cesarean delivery for an estimated fetal weight greater than 4250 g and induction of labor if greater than 90 percentile but less than 4250 g was associated with a decreased rate of shoulder dystocia and no change in cesarean delivery rate.¹⁰⁵

Postpartum Care

Maternal insulin requirements

Insulin requirements decrease dramatically following the third stage of labor and placental delivery and return to prepregnancy levels over the subsequent 1 to 2 weeks.⁸ Typically, insulin dosing is halved or changed to a prepregnancy dosing regimen. Particular caution should be paid to women taking insulin while breastfeeding, who may be at risk for hypoglycemia.

Breastfeeding

Breastfeeding is recommended as the standard for infant nutrition in the absence of contraindications.¹⁰⁶ Lactation may be of additional benefit to women with PDM because it reduces overall insulin needs.¹⁰⁷ It may also be associated with long-term maternal metabolic benefits.¹⁰⁸

Contraception

All women of childbearing age with PDM should have access to family planning and contraceptive options to reduce the risk of future unplanned pregnancy. Although diabetes should not impact options for contraception, infant feeding and postpartum status may impact choice. Preferred postpartum contraceptive options in breastfeeding include long-acting reversible contraceptives (copper or progestin intrauterine devices, etonogestrel implants) and progestogen-only pills. Combination hormonal contraceptives may pose more risk than benefit in women with PDM because of the thromboembolic effects of estrogen and are not recommended in the immediate postpartum period.¹⁰⁹ Depot medroxyprogesterone acetate (DMPA) may also be associated with a higher risk for thromboembolism in mothers with PDM because of increased peripheral conversion of DMPA to peripheral estrogen than other progestogens.¹¹⁰

Postpartum transition of care

There are limited data to support specific care models for women with PDM after pregnancy; however, optimization of long-term maternal health should be a goal of all obstetric and primary care providers.¹¹¹

SUMMARY

Diabetes is a common chronic condition in women of reproductive age. Preconception care reduces the risks associated with poor glycemic control in early pregnancy. Adverse pregnancy outcomes, including hypertensive disorders, abnormal fetal growth, traumatic delivery, and stillbirth, can be minimized with optimal glycemic control. Insulin is the preferred medication to optimize glucose control in women with T2DM, and frequent dose adjustments are needed during pregnancy. Team-based multidisciplinary care may help women achieve glycemic goals and optimize pregnancy outcomes. Postpartum care should include lactation support, counseling on contraceptive options, and transition to primary care.

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