



A Review of the Pathophysiology and Management of Diabetes in Pregnancy

Aoife M. Egan, MB, BCh, PhD; Margaret L. Dow, MD; and Adrian Vella, MD

Abstract

Diabetes is a common metabolic complication of pregnancy and affected women fall into two subgroups: women with pre-existing diabetes and those with gestational diabetes mellitus (GDM). When pregnancy is affected by diabetes, both mother and infant are at increased risk for multiple adverse outcomes. A multidisciplinary approach to care before, during, and after pregnancy is effective in reducing these risks. The PubMed database was searched for English language studies and guidelines relating to diabetes in pregnancy. The following search terms were used alone and in combination: *diabetes, pregnancy, gestational diabetes, GDM, prepregnancy, and preconception*. A date restriction was not applied. Results were reviewed by the authors and selected for inclusion based on relevance to the topic. Additional articles were identified by manually searching reference lists of included articles. Using data from this search we herein summarize the evidence relating to pathophysiology and management of diabetes in pregnancy. We discuss areas of controversy including the method and timing of diagnosis of GDM, and choice of pharmacologic agents to treat hyperglycemia during pregnancy. Therefore, this review is intended to serve as a practical guide for clinicians who are caring for women with diabetes and their infants.

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From the Departments of Endocrinology (A.M.E., A.V.) and Obstetrics and Gynecology (M.L.D.), Mayo Clinic, Rochester, MN.

More than 21 million births are affected by maternal diabetes worldwide each year.¹ In 2016 in the United States, pre-existing (including type 1 or 2) and gestational diabetes mellitus (GDM) had a prevalence of 0.9% and 6.0%, respectively, among women who delivered a live infant.² Recently, efforts have redoubled to diagnose and treat diabetes earlier in pregnancy.³ Diabetes during pregnancy has significant implications for the maternal-fetal dyad. Type 1 diabetes is associated with a two- to five-fold increased risk of major complications including congenital anomaly, stillbirth, and neonatal death; and 50% of infants experience complications such as prematurity, large for gestational age (LGA), and admission to a neonatal intensive care unit.⁴⁻⁶ Women with type 2 diabetes typically have less dramatic changes in glucose metabolism and are less prone to diabetic ketoacidosis (DKA) and caesarean delivery compared with those with type 1 diabetes.^{7,8} However, studies are conflicting on whether their offspring have similar or

lower rates of congenital malformations and stillbirth compared with those with type 1 diabetes.⁸ GDM is diabetes diagnosed in the second or third trimester of pregnancy in the absence of overt diabetes before gestation.⁹ Women with GDM have a 30% increased risk of cesarean delivery and a 50% increased risk of gestational hypertension. Their offspring have a 70% increased risk of prematurity and are 30% more likely to be LGA.¹⁰ GDM is strongly associated with future maternal type 2 diabetes¹¹; there is increasing evidence that exposure to all forms of diabetes in pregnancy confers a higher risk of childhood adiposity, insulin resistance, and adverse neurodevelopmental outcomes.¹¹⁻¹⁴

The aim of this review is to provide an update on the pathophysiology and management of diabetes in pregnancy.

METHODS

The PubMed database was searched for English language studies and guidelines relating to diabetes in pregnancy. The

following search terms were used alone and in combination: *diabetes, pregnancy, gestational diabetes, GDM, prepregnancy, and pre-conception*. A date restriction was not applied. Results were reviewed by the authors and selected for inclusion based on relevance to the topic. Additional articles were identified by manually searching reference lists of included articles.

PATHOPHYSIOLOGY

Normal Maternal Glucose Metabolism

Although early pregnancy is a time of relative insulin sensitivity, this sensitivity decreases sharply in the second and early third trimester of pregnancy.^{15,16} This reduces insulin-dependent glucose uptake in tissues such as muscle and fat and serves as a maternal physiologic adaption to preserve carbohydrate for the rapidly growing fetus.¹⁷ In addition, impaired insulin-mediated suppression of maternal lipolysis and fat oxidation provides fatty acids as an alternative energy source.¹⁸ This process is likely mediated by a number of factors including an increase in progesterone, estrogen, cortisol, and human placental growth hormone.¹⁹⁻²¹ Typically a two- to three-fold increase in insulin production is sufficient to meet this challenge, and studies confirm an increase in pancreatic fractional beta cell area in human pregnancy.²² It would appear that insulin secretion increases significantly by early pregnancy, even before increases in insulin resistance.²³ In animal models, lactogenic hormones seem to stimulate this process through a direct effect on beta cells; however, it is uncertain if this is the case in humans.^{24,25}

GDM. Frequently, the insulin secretory response is inadequate and hyperglycemia develops, leading to a diagnosis of GDM in women without pre-existing diabetes. Limited evidence from physiologic studies in such women suggests that subtle abnormalities of insulin secretion precede pregnancy and persist after parturition. In one such study of high-risk women with GDM, independent predictors of a postpartum

ARTICLE HIGHLIGHTS

- Annually, maternal diabetes affects more than 21 million births worldwide.
- Women may be categorized into those with pre-existing diabetes (including either type 1 or type 2 diabetes) or those with gestational diabetes mellitus where diabetes develops during, and is a consequence of, pregnancy.
- Gestational diabetes mellitus is typically diagnosed in the late second trimester of pregnancy and resolves following delivery, although long-term risk of developing type 2 diabetes is substantial.
- Women of childbearing age with pre-existing diabetes should receive pre-pregnancy care to optimize their medical status before conception.
- During pregnancy, intensive glycemic control and close follow-up by a multidisciplinary team is essential to ensure the best possible clinical outcomes.

abnormality of glucose tolerance were hyperglycemia before 22 weeks' gestation and a low first-phase insulin response during an intravenous glucose tolerance test.²⁶ The first-phase insulin response to intravenous glucose represents an early burst of insulin release and is followed by a gradually increasing phase of insulin secretion over several hours.²⁷ This first-phase response plays a significant role in maintaining glucose homeostasis in healthy individuals and is lost in the early stages of diabetes.²⁸ The degree of insulin resistance in the third trimester of pregnancy is not an important predictor of abnormal glucose tolerance within 6 months after GDM. This suggests a chronic beta cell defect exacerbated by pregnancy.^{15,29,30}

Pre-existing Diabetes. Women with pre-existing diabetes face similar changes in insulin resistance. The ability of the beta cell to compensate is more profoundly impaired in type 2 diabetes and negligible in type 1 diabetes. Although the clinical impact may be insignificant, a pregnancy-induced increase in C-peptide (suggesting improved beta cell function) has even been observed in women

with established type 1 diabetes and undetectable C-peptide levels at baseline.^{31,32}

Early Pregnancy Hyperglycemia — Fetal Effects

Maternal hyperglycemia both preconceptually and during the first trimester of pregnancy can result in major birth defects and pregnancy loss.^{5,33} Whereas these outcomes typically affect pregnancies with pre-existing diabetes, in women with GDM the risk of malformations increases with maternal fasting glucose, body mass index (BMI), and earlier gestational age at diagnosis.³⁴ Most commonly these malformations affect the cardiac or central nervous system and include transposition of the great arteries, septal defects, neural tube defects, and caudal regression syndrome — the latter of which is almost universally associated with diabetes in pregnancy.^{33,35} Oxidative stress has been suggested to play a role in the development of such complications, but further studies of mechanism are needed.^{36,37} Although maternal hyperglycemia in the second and third trimester is typically associated with excessive fetal growth, women with pre-existing diabetes may have impaired fetal growth through two mechanisms. Maternal microvascular disease confers a significant risk of intrauterine growth restriction, whereas hyperglycemia in the first trimester may impair placental development and subsequent fetal growth through poorly understood mechanisms.^{38,39}

Fetal Overnutrition

Maternal glucose is transferred to the fetus across the placenta down a concentration gradient determined by both maternal and fetal glucose levels. Maternal hyperglycemia therefore promotes fetal hyperglycemia and stimulates fetal insulin secretion.⁴⁰ This process constitutes the “hyperglycemia-hyperinsulinemia hypothesis” or the “Pedersen hypothesis.”⁴¹ Taking this process a step further, fetal glucose use increases with fetal hyperinsulinemia, lowering fetal glucose and increasing the transplacental glucose gradient and rate of glucose transfer. This is described as the “fetoplacental glucose

steal phenomenon” and once established, is believed to favor a high glucose flux with stimulation of fetal triacylglycerol formation and deposition of excess fetal adipose tissue even when maternal blood glucose is normal.⁴⁰ The Pedersen hypothesis was developed in an era when most cases of hyperglycemia in pregnancy were due to type 1 diabetes. However, during the past 50 years, increases in maternal obesity have changed this landscape, and the metabolic milieu to which the developing fetus is exposed is undoubtedly different in obesity (with or without type 2 diabetes).⁴² For example, maternal triglyceride levels are 40% to 50% higher in mothers with obesity and GDM compared with normal-weight mothers during pregnancy. Placental lipases can hydrolyze maternal triglycerides to free fatty acids for fetal-placental availability, and there is increasing evidence that these are also important substrates for fetal fat accretion and overgrowth.⁴³

Excessive fetal growth may be expressed as macrosomia or LGA. Macrosomia is typically defined as an absolute birthweight of greater than 4000 to 4500 g, whereas LGA refers to a birthweight greater than 90th percentile for gestational age. Affected infants are at risk for asphyxia, perinatal death, shoulder dystocia with or without birth injury, respiratory distress, and hypoglycemia.³⁸ Additional metabolic complications that may be present at birth and arise from maternal hyperglycemia include hypocalcemia, hypomagnesemia, polycythemia, and hyperbilirubinemia.

Long-Term Offspring Outcomes

It is difficult to separate the role of fetal exposure to maternal hyperglycemia from factors such as maternal obesity and environmental exposures. However, offspring of mothers with pre-existing diabetes or GDM are heavier at birth and at every age with an increased risk of type 2 diabetes compared with those born to mothers without diabetes.³⁸ Epigenetic variation established in utero may explain the link between the uterine milieu and later disease susceptibility.⁴⁴ Although a number of

offspring methylation variants appear to be independently associated with GDM and type 2 diabetes, these observations have not led to the development of biomarkers to predict which children are most at risk of metabolic disease.^{44,45} Another emerging concern is the potentially negative effect of maternal diabetes on offspring cognitive development, but reports have been conflicting and causal pathways are unclear.⁴⁶ Type 1 diabetes risk is increased in offspring with maternal or paternal diabetes of any type, and appears even higher with paternal diabetes.⁴⁷

Impact of Treatment on Outcomes

GDM. In the case of GDM, two randomized controlled trials confirm that treating women from 24- to 28-wk gestation improves pregnancy outcomes. In the Australian Carbohydrate Intolerance Study in Pregnant Women study, 490 women with GDM were assigned to an intervention arm that involved dietary advice, glucose monitoring, and insulin therapy as required and 510 women were assigned to routine care. There was a reduction in the primary outcome of serious perinatal complications (including death, shoulder dystocia, bone fracture, and nerve palsy) when GDM was treated.⁴⁸ Landon et al⁴⁹ randomized women with mild GDM to either nutritional counseling and diet therapy along with insulin if needed (treatment group) or usual prenatal care (control group). They found that more intensive care of women with mild GDM reduced the risk of secondary outcomes including fetal overgrowth, shoulder dystocia, caesarean delivery, and hypertensive disorders. There was no effect on the primary outcome, a composite of stillbirth or perinatal death and neonatal complications including hyperbilirubinemia, hypoglycemia, hyperinsulinemia, and birth trauma.⁴⁹ Other retrospective data show increased risks of neonatal hypoglycemia and intensive care admission in women with suboptimal glucose control.⁵⁰

Pre-Existing Diabetes. There is a large body of evidence indicating that a structured, evidence-based approach to care of women

with pre-existing diabetes before and during pregnancy can reduce the risk of major adverse outcomes including congenital malformations and stillbirths.^{4,33}

MANAGEMENT

Preconception Care

Pre-Existing Diabetes. Preconception counseling should form part of every consultation for women of reproductive age with diabetes. Long-acting, reversible forms of contraception such as intrauterine devices or implantable progestin are highly effective and should be recommended until pregnancy is desired.⁵¹ For women who are actively contemplating pregnancy, targeted pre-pregnancy care delivered by a multidisciplinary team on a 1- to 2-month basis is both clinically and cost effective (Table 1).^{52,53} An A1c target of less than or equal to 6.5% is associated with the lowest risk of congenital anomalies,⁵⁴ and a goal A1c of less than 6.0% is recommended.⁵⁵ However, this is not always achievable due to issues such as hypoglycemia, and women should be encouraged that any improvement in HbA1c will improve their chances of a positive pregnancy outcome. Hypoglycemia management should be reviewed and glucagon prescribed if insulin is used. Preconception visits should include baseline laboratory investigations (including thyroid function) and assistance with smoking cessation if indicated. Folic acid should be prescribed and continued until 12-wk gestation. Advisory groups vary on the suggested dose of folic acid. A minimum of 400 µg per day is advised^{55,56}; however, higher doses of up to 5 mg per day have also been recommended based on a theoretical benefit of reducing the increased risk of neural tube defects associated with pre-existing diabetes.^{57,58}

Potentially teratogenic medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins should be discontinued.⁵⁹ Women must be screened for diabetes complications. Diabetic retinopathy has the potential to worsen during pregnancy particularly if there is a rapid

TABLE 1. Components of Prepregnancy Care for Women With Established Diabetes^a

Discuss
Timeline for pregnancy
Contraceptive options
Positive ways to reduce risk of adverse outcomes
Complete baseline laboratory studies including
HbA1c
Creatinine
Thyroid-stimulating hormone
Urine albumin-creatinine ratio
Stop/replace medications with possible teratogenic effects including
Hypoglycemic agents other than metformin and insulin
Statins
ACE inhibitors and ARBs
Initiate prenatal vitamins which should include
Folic acid (up to 5 mg/d)
1000 mg elemental calcium
600 IU vitamin D
Review
HbA1c target of <6.5%
Blood pressure (<135/85 mm Hg)
Hypoglycemia management (if indicated)
Nutritionist referral and weight optimization
Screening for complications including
Retinal assessment
Electrocardiogram
Evaluation for coronary artery disease if indicated

^aACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

improvement in glycemic control.⁶⁰ An ophthalmologist with expertise in diabetic retinopathy should perform a comprehensive eye exam and any necessary treatment before pregnancy. A baseline creatinine, estimated glomerular filtration rate and urine albumin:creatinine ratio are an important indications of pre-pregnancy renal function and can play critical roles in determining timing of delivery in women with even mild underlying renal compromise. Nephrology referral should be considered if serum creatinine is abnormal or if total protein excretion exceeds 2 g/d.⁵⁹ Pregnancy does not result in worsening of kidney function in women with diabetic nephropathy

and normal serum creatinine; but complications including pre-eclampsia and preterm delivery are more common.⁶¹ Although fertility declines significantly as kidney disease progresses, pregnancy is still possible.⁶² However, for women with end-stage renal disease, deferral of pregnancy until after kidney transplantation may be appropriate. Renal function is closely linked with blood pressure, which must be monitored closely during pregnancy. Tight blood pressure control before and during pregnancy is associated with improved outcomes.⁶³ Nifedipine and labetalol are commonly used agents. α -Methyldopa is also a reasonable choice but is commonly associated with postural dizziness,⁶⁴ and requires less convenient frequent dosing. A reasonable blood pressure goal in women with diabetes and chronic hypertension is less than 135/85 mmHg.⁵⁶ An electrocardiogram is suggested for all women⁵⁵ and further screening for coronary artery disease should be considered in those who are at high risk — for example, due to advanced maternal age, pre-existing hypertension, chronic kidney disease, tobacco use, or a family history of premature coronary artery disease.⁵¹ Although all women with diabetes should meet with a dietician before pregnancy, this is particularly important for women with overweight or obesity who should be offered advice on ways to lose weight before pregnancy.^{51,59}

TABLE 2. Risk Factors for GDM^a

Overweight or obese BMI
GDM in a prior pregnancy
Family history of diabetes
Non-European ethnicity
Polycystic ovarian syndrome
Increasing age
Physical inactivity
Multiple pregnancy
Previous delivery of a macrosomic baby
Previous stillbirth

^aBMI = body mass index; GDM = gestational diabetes mellitus.

TABLE 3. Options for GDM Screening and Diagnosis^{a,b}

Criteria	No. abnormal values required	Oral glucose load, g	Glucose cut-offs, mg/dL (mmol/L)
Two-step strategy			
Non- fasting glucose challenge test	1	50	≥130, 135, or 140 (7.2, 7.5, or 7.8)
Followed by either of the options below			
1. Carpenter and Coustan	≥2 ^c	100	Fasting ≥95 (5.3) 1-h ≥180 (10.0) 2-h ≥155 (8.6) 3-h ≥140 (7.8)
2. NDDG	≥2 ^c	100	Fasting ≥ 105 (5.8) 1-h ≥190 (10.6) 2-h ≥165 (9.2) 3-h ≥145 (8.0)
One-step strategy			
2010 IADPSG / 2013 WHO	≥1	75	Fasting ≥92 (5.1) 1-h ≥180 (10.0) 2-h ≥153 (8.5)

^aGDM = gestational diabetes mellitus; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; NDDG = National Diabetes Data Group.
^bFrom the American Diabetes Association.⁹
^cACOG notes that one elevated value may be used for diagnosis.

GDM. As the majority of women have at least one risk factor for GDM (Table 2) and 50% of pregnancies are unplanned, delivering effective GDM prevention interventions pre-pregnancy is challenging.^{65,66} Many studies, including a recent large Finnish study and a meta-analysis, have shown the efficacy of intervention when patients seek care before pregnancy, thus this remains a potent target for improving care.^{67,68}

Diagnosis of GDM

There is a general consensus that women with risk factors for type 2 diabetes should have testing for undiagnosed diabetes using standard diagnostic criteria at their initial prenatal visit.^{9,69}

Standard GDM screening is recommended at 24- to 28-weeks' gestation and a number of options are available (Table 3). The most common approach in the United States is to screen all women with a non-fasting, 50-gram glucose challenge followed by a 1-hour venous glucose test. Thresholds for the 1-hour glucose value vary from 130 to

140 mg/dL with resultant implications for sensitivity and specificity. Women whose glucose levels meet or exceed the pre-specified threshold then undergo a 100-gram, 3-hour diagnostic test and GDM is diagnosed in the setting of two or more abnormal values.⁹

The International Association of the Diabetes and Pregnancy Study Groups recommend a one-step process with a 2-hour, 75-gram oral glucose tolerance test (OGTT) and diagnostic cutoffs based on outcomes from the Hyperglycemia and Adverse Pregnancy Outcome Study.^{70,71} The cutoff points chosen convey an odds ratio of at least 1.75 for outcomes including LGA, neonatal C-peptide greater than 90th percentile, and neonatal body fat percentage greater than 90th percentile compared with women with mean glucose levels at 24 to 28 weeks in the study. Neonatal risks appeared to be linearly related to the degree of maternal dysglycemia. Nonetheless, with older data suggesting overall low frequency of neonatal risks, there has been a reluctance to introduce these guidelines at many institutions

TABLE 4. IOM Guidelines for Gestational Weight Gain During Pregnancy^{a,b}

Pre-gestational BMI category	BMI, kg/m ²	Recommended total weight gain, kg	Recommended mean weight gain: trimesters 2 and 3, mean kg/wk (range)
Underweight	<18.5	12.5-18.0	0.51 (0.44-0.58)
Normal weight	18.5-24.9	11.5-16.0	0.42 (0.35-0.50)
Overweight	25.0-29.9	7.0-11.5	0.28 (0.23-0.33)
Obese	≥30.0	5.0-9.0	0.22 (0.17-0.27)

^aBMI = body mass index; IOM = Institute of Medicine.

^bAdapted from The National Academies Press⁷⁸ with permission.

due to the expectation of higher rates of GDM and resultant demands on resources in the setting of a lack of perceived improvement in outcomes.

There are differing opinions on how and when to diagnose diabetes in early pregnancy. The American College of Obstetricians and Gynecologists (ACOG) accepts the 24-week criteria applied to a 100-gram OGTT in early pregnancy, but there are few data to support this practice.⁶⁹ Whereas accelerated fetal growth may occur before 24- to 28-weeks' gestation in women with GDM,⁷² early elevations in glucose levels are often no longer present by the time of routine OGTT.⁷³ This makes identification of at-risk women challenging. Given this difficulty, there is an impetus to discover alternate diagnostic markers for hyperglycemia in early pregnancy.⁷⁴

Glycemic Goals During Pregnancy

The American Diabetes Association and ACOG recommend similar glucose targets for women with pre-existing diabetes and GDM as follows: fasting glucose less than or equal to 95mg/dL, 1 hour after eating less than or equal to 140 mg/dL, and 2 hours after eating less than or equal to 120 mg/dL.^{55,56,69} HbA1c levels naturally decrease during pregnancy due to increased red blood cell turnover and may not fully capture transient glycemic excursions, which can drive macrosomia.^{56,75} Therefore, whereas a first-trimester HbA1c of less than 6.0% is associated with the lowest rates of adverse fetal outcomes, it should be considered a secondary measure of glycemic control later in pregnancy.^{54,56} Unfortunately, even highly

motivated patients can struggle to achieve these goals, particularly in the setting of type 1 diabetes and/or hypoglycemia. In this scenario, individualized, less-stringent targets are acceptable. One should bear in mind that in type 2 diabetes, the contribution of fasting glucose (versus postprandial) to the HbA1c level becomes greater as control declines, increasing up to 70% in those with an HbA1c greater than 10.0%.⁷⁶ Fasting glucose elevations (as opposed to postprandial elevations) are also more predictive of fetal macrosomia.⁷⁷ This information can be useful when adjusting insulin regimens.

Gestational Weight Gain and Diet

In women with and without diabetes, excessive gestational weight gain is associated with poorer pregnancy outcome. The Institute of Medicine guidelines for gestational weight gain are based on pre-pregnancy BMI and are outlined in Table 4.⁷⁸ Close attention to food intake is necessary during pregnancy to avoid excessive gestational weight gain while ensuring strict glycemic control.⁵¹ The dietary reference intakes for pregnant women should be followed and they recommend a minimum of 175 grams of carbohydrates, 71 grams of protein, and 28 grams of fiber.⁵⁶ In practice, many providers follow Endocrine Society guidance that advises limiting carbohydrates to 35% to 45% total calories and distributing throughout three meals and up to four snacks throughout the day.⁵⁷ Sugars and refined carbohydrates should be eliminated with ideal carbohydrate sources including fresh vegetables, some fruits, and whole grains.⁷⁹ Approximately 80% of women

with GDM can reach their glycemic goals with diet and lifestyle modifications alone.¹⁰

Pharmacotherapy

Insulin. In women with type 1 diabetes, multiple daily injection and continuous subcutaneous insulin infusion regimens (also known as insulin pump therapy) are both effective during pregnancy.⁵⁹ There is insufficient evidence to recommend one mode of insulin delivery over another, and there is need for trials evaluating modern pumps which integrate with glucose sensors and have features such as low glucose suspend.⁸⁰ The currently available hybrid closed loop system (Medtronic MiniMed 670G insulin pump) is not appropriate for use in automode during pregnancy as its algorithm targets a glucose of 120 mg/dL, which is above the recommended fasting goal.⁸¹ The Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes (CONCEPTT) trial found that pregnant women who used continuous glucose monitoring (CGM) (with or without pump therapy) had a lower incidence of LGA infants (odds ratio, 0.51; 95% CI, 0.28 to 0.9, $P=.0210$) and fewer incidences of neonatal hypoglycemia (0.45; 95% CI, 0.22 to 0.89, $P=.0250$).⁸² It is anticipated that these findings will translate into increased use of CGM technology during pregnancy. At the moment, there is no evidence for use of technology such as insulin pumps or CGM in women with type 2 or gestational diabetes.

Aspart and lispro are safe and effective options for rapid acting insulin during pregnancy. Isophane insulin (neutral protamine Hagedorn) was traditionally used as a longer-acting insulin; however, insulin analogues are increasingly used. Detemir, for example, has been studied during pregnancy in a randomized controlled trial⁸³; and there is extensive clinical experience with glargine during pregnancy. Newer insulin analogues have not been studied.

Noninsulin Agents. The use of oral hypoglycemic agents during pregnancy to treat pre-existing type 2 diabetes or gestational

diabetes is controversial. Metformin, a biguanide and glyburide (glibenclamide), a sulphonylurea have been studied and used with good effect during pregnancy.^{84,85} Metformin transfers to the fetus with high fetal-to-maternal ratios. Although it was previously thought that glyburide did not transfer in significant quantities, more recent data suggest that it can increase expression of glucose transporter 1 in the placenta and promote fetal overgrowth.⁷⁴ In women with GDM, glyburide is associated with higher birth weights and neonatal hypoglycemia compared with insulin, and metformin resulted in less gestational weight gain but LGA at delivery.⁸⁶ Patients with GDM on glyburide are less likely to require a transition to insulin than those on metformin.⁸⁵ Small groups of children exposed to metformin in utero have been followed for up to 9 years; although there was similar total and abdominal body fat percent and metabolic variables, metformin-exposed children were larger than nonexposed children by several measures including weight and waist circumference.⁸⁷ There are no long-term studies of children exposed to glyburide.

Other members of the sulfonylurea class of medications along with thiazolidinediones, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose-cotransporter 2 inhibitors are not recommended for use during pregnancy or pregnancy planning.

Approach to Management of Hyperglycemia. During pregnancy, intensification of therapy should occur within 1 to 2 weeks if glycemic targets are not met (>15% to 20% of readings above goal). Insulin is recommended for women with pre-existing diabetes, as alternative agents will be ineffective in the case of type 1 diabetes and unable to counteract the significant increases in insulin resistance associated with type 2 diabetes. Guidelines differ in the case of GDM treatment. For example, the American Diabetes Association considers insulin to be first-line therapy for women with GDM but does not favor metformin or glyburide if an alternative is required.⁵⁶ ACOG recommends insulin as

first-line therapy with metformin (or rarely glibenclamide) to be used as a reasonable alternative,⁶⁹ and the Society for Maternal Fetal Medicine states that metformin or insulin are reasonable first-line pharmacologic therapies.⁸⁸ Until such time that further information is available, treatment must be considered on a case-by-case basis taking into account the degree of hyperglycemia, health care and financial resources, and patient preference.

Aspirin. Women with pre-existing diabetes are at increased risk of pre-eclampsia,⁸⁹ and in accordance with the US Preventive Services Task Forces,⁹⁰ low-dose aspirin (81 mg per day) is recommended after 12-weeks' gestation.^{55,56}

DKA During Pregnancy

DKA in a pregnant woman is a life-threatening emergency caused by an absolute or relative deficiency in insulin. Pregnancy is a ketogenic state, and DKA may occur even at normal blood glucose levels.⁵⁶ Although women with type 1 diabetes are at greatest risk, DKA may occur in pregnancy with any type of diabetes. If there is a suspicion or diagnosis of DKA during pregnancy, it should be treated as an emergency with immediate specialist review.⁵⁸ In the past, fetal mortality rates of up to 35% have been reported with DKA, but this has decreased in recent years with improved diagnosis and management.⁵⁵

Fetal Monitoring and Delivery Planning

Pre-existing Diabetes. Most women will undergo an ultrasound in early pregnancy to show viability. A detailed fetal anatomy scan should occur at 18- to 20-weeks' gestation and certain women may undergo fetal echocardiography, particularly if first-trimester glycemic control is not at goal or there is suspicion of a cardiac defect.⁵⁵ Ultrasound is commonly used to assess fetal growth in the third trimester but there are no recommendations on frequency. Given the risk of macrosomia, a greater fundal height, excessive maternal weight gain, and persistent poor glucose control should

prompt growth evaluation. Starting at 32-weeks' gestation, it is reasonable to initiate once- or twice-weekly monitoring such as the nonstress test, biophysical profile, or modified biophysical profile.⁵⁵ This may be started earlier or the frequency increased on an individual basis.

Women with well-controlled diabetes and reassuring fetal testing may be managed expectantly to between 39 0/7 weeks and 39 6/7 weeks of gestation, but women with diabetes-related complications, poor glycemic control, or prior stillbirth should be considered for delivery between 36 0/7 and 38 6/7 weeks of gestation.⁵⁵

During labor, women should have continuous electronic fetal monitoring. Because of the abnormal adiposity of neonates of diabetic mothers, prophylactic cesarean delivery may be recommended if the estimated fetal weight exceeds 4500 grams.⁵⁵

GDM. Women with GDM who are poorly controlled or require pharmacologic intervention should undergo fetal surveillance similar to women with pre-existing diabetes. Women whose hyperglycemia is controlled with lifestyle interventions alone should not be delivered before 39-weeks' gestation and do not require induction at later gestational ages unless otherwise indicated. In those who are well-controlled but requiring pharmacologic intervention, delivery is recommended between 39 0/7 weeks and 39 6/7 weeks of gestation. Finally, in women who are poorly controlled, delivery between 37 0/7 weeks and 38 6/7 weeks may be justified. Although there is less evidence to support such a strategy in women with GDM, cesarean delivery may be recommended if the estimated fetal weight is at least 4500 grams.⁶⁹

All women with complications will benefit from anesthesiology consultation in the third trimester of pregnancy to review the birth plan and analgesic options. If steroids are required to accelerate fetal lung maturation, an increased insulin requirement over the following 3 to 5 days is anticipated and increased glucose monitoring is

advised. In women with diabetes treated with insulin, the additional insulin is often administered intravenously with infusion rates adjusted hourly, typically targeting a glucose level of 70 to 126 mg/dL.⁵⁹

Labor and Delivery

Maternal hyperglycemia during labor and delivery is associated with neonatal hypoglycemia and fetal distress.⁵⁹ Women with diabetes who required pharmacologic intervention during pregnancy are generally managed with an intravenous insulin infusion and hourly glucose testing. With respect to the intrapartum glycemic target, there is no randomized trial evidence to support a specific goal; however, most local policies specify a range that falls between 70 and 126 mg/dL. If the appropriate expertise is available, women can continue to use their personal insulin pumps during this time.⁹¹ Women with GDM who were diet-controlled during pregnancy should also have glucose monitoring during labor with initiation of insulin if glucose levels are above 100 to 126 mg/dL.^{55,58}

On delivery, a neonatologist should review the infant, and delivery units should have the expertise to provide advanced neonatal care if required. Unless there is specific concern, neonates should remain with their mother and feeding should take place as soon as possible.⁵⁹ Two to 4 hours post-delivery, neonatal blood glucose testing should occur to exclude neonatal hypoglycemia. Clinical signs such as severe irritability or seizure-like activity should prompt earlier evaluation.⁵⁹ Measures such as tube feeding or intravenous dextrose are generally reserved for when the capillary glucose is less than 36 mg/dL despite feeding. Additional tests for polycythemia, hyperbilirubinemia, and electrolyte abnormalities should be considered based on clinical evaluation.⁵⁸

Because of a rapid increase in insulin sensitivity following placental delivery, women with pre-existing diabetes typically require a dramatic reduction in insulin doses postpartum. ACOG recommends one-third to one-half of the pre-delivery doses of long- and short-acting insulin — the latter

should be started once diet has resumed.⁵⁵

Frequent glucose monitoring is essential to reduce the risk of severe hypoglycemia. Women with GDM should discontinue all glucose-lowering medications following delivery, but postpartum glucose testing (capillary or venous) should occur before discharge from hospital to exclude persistent diabetes.⁵⁸

Postpartum Care

Breastfeeding is encouraged as it facilitates postpartum weight loss and is likely associated with lower future risk of obesity and diabetes in offspring.⁹² Women who are breastfeeding and receiving insulin frequently require additional carbohydrate snacks and lower insulin doses to prevent hypoglycemia. Based on extensive clinical experience, metformin is deemed to be safe while breastfeeding, but there are insufficient data to recommend other glucose-lowering agents except insulin.

At the 6-week postpartum follow-up, women should be counseled on the importance of planning future pregnancies. Long acting reversible contraception is ideal in this setting and may be used while breastfeeding; however, the risk of an unplanned pregnancy will likely outweigh the risk of any contraceptive option.^{51,56}

Women with GDM should have an OGTT at 4 to 12 weeks' postpartum to rule out undiagnosed pre-existing diabetes. HbA1c is not reliable, as it will be affected by changes during the recent pregnancy. Rates of attendance at postpartum glucose testing are reported to be as low as 5%, but making verbal and written contact with individual women can increase recall rates to 75%.⁹³ Women with GDM require lifelong assessment of their glucose status and other cardiovascular risks as GDM is a strong risk factor for progression to type 2 diabetes, stroke, and heart disease.⁹⁴ Testing may take the form of HbA1c, fasting plasma glucose, or a 75-g OGTT (using non-pregnant thresholds) and should take place every 1 to 3 years depending on the presence of additional risk factors for type 2 diabetes.⁵⁶ A total of 52.2% the Hyperglycemia

and Adverse Pregnancy Outcome study participants who were diagnosed with GDM using International Association of the Diabetes and Pregnancy Study Groups criteria and followed for a median duration of 11.4 years developed a disorder of glucose metabolism. This compares to 20.1% of participants who did not have GDM during pregnancy (odds ratio, 3.44; 95% CI, 2.85 to 4.14).¹¹ Data from the Diabetes Prevention Program Outcomes Study suggest that in women with a history of GDM and prediabetes, metformin can reduce progression to diabetes by 40% and lifestyle intervention by 35% over 10 years compared with placebo.⁹⁵ In this study, there was a mean interval of 12 years between the index GDM pregnancy and commencing metformin, and whether metformin would be more effective in women closer to their GDM pregnancy remains untested.

CONCLUSION

Diabetes in pregnancy poses a unique set of challenges for both the mother and her developing baby. Women with pre-existing diabetes can benefit from targeted pre-pregnancy care with optimization of glycaemic control and assessment and treatment of co-morbidities. During pregnancy, women with pre-existing diabetes and GDM benefit from a multidisciplinary approach to care with the aim of minimizing maternal complications and ensuring normal fetal development and growth. GDM confers a high risk of future type 2 diabetes and affected women should receive appropriate counseling and long-term follow-up.

Abbreviations and Acronyms: ACOG = The American College of Obstetricians and Gynecologists; DKA = diabetic ketoacidosis; GDM = gestational diabetes mellitus; LGA = large for gestational age

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Correspondence: Address to Aoife M. Egan, MB, BCh, PhD, 200 First Street SW, Rochester, MN 55905 (egan.aoife@mayo.edu; Twitter: @egan_am).

ORCID

Aoife M. Egan:  <https://orcid.org/0000-0003-0379-9279>

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