JAMA | Review | WOMEN'S HEALTH

Management of Preexisting Diabetes in Pregnancy
A Review

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IMPORTANCE The presence of preexisting type 1 or type 2 diabetes in pregnancy increases the risk of adverse maternal and neonatal outcomes, such as preeclampsia, cesarean delivery, preterm delivery, macrosomia, and congenital defects. Approximately 0.9% of the 4 million births in the United States annually are complicated by preexisting diabetes.

OBSERVATIONS Women with diabetes have increased risk for adverse maternal and neonatal outcomes, and similar risks are present with type 1 and type 2 diabetes. Both forms of diabetes require similar intensity of diabetes care. Preconception planning is very important to avoid unintended pregnancies and to minimize risk of congenital defects. Hemoglobin A_{1c} goals are less than 6.5% at conception and less than 6.0% during pregnancy. It is also critical to screen for and manage comorbid illnesses, such as retinopathy and nephropathy. Medications known to be unsafe in pregnancy, such as angiotensin-converting enzyme inhibitors and statins, should be discontinued. Women with obesity should be screened for obstructive sleep apnea, which is often undiagnosed and can result in poor outcomes. Blood pressure goals must be considered carefully because lower treatment thresholds may be required for women with nephropathy. During pregnancy, continuous glucose monitoring can improve glycemic control and neonatal outcomes in women with type 1 diabetes. Insulin is first-line therapy for all women with preexisting diabetes; injections and insulin pump therapy are both effective approaches. Rates of severe hypoglycemia are increased during pregnancy; therefore, glucagon should be available to the patient and close contacts should be trained in its use. Low-dose aspirin is recommended soon after 12 weeks' gestation to minimize the risk of preeclampsia. The importance of discussing long-acting reversible contraception before and after pregnancy, to allow for appropriate preconception planning, cannot be overstated.

CONCLUSIONS AND RELEVANCE Preexisting diabetes in pregnancy is complex and is associated with significant maternal and neonatal risk. Optimization of glycemic control, medication regimens, and careful attention to comorbid conditions can help mitigate these risks and ensure quality diabetes care before, during, and after pregnancy.

JAMA. 2019;321(18):1811-1819. doi:10.1001/jama.2019.4981

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Preexisting diabetes complicates 0.9% of pregnancies in the United States and increases the risk of adverse maternal and neonatal outcomes.[1-3] Specific risks of uncontrolled diabetes in pregnancy include preeclampsia, congenital defects, preterm delivery, macrosomia, and stillbirth (**Box**).

With the increasing prevalence of type 1 and type 2 diabetes,[4,5] clinicians require greater awareness of risks associated with diabetes in pregnancy and approaches to minimize these risks. Equal emphasis should be placed on aggressive care and glycemic optimization of pregnant women with preexisting type 1 and type 2 diabetes because rates of major congenital malformations, stillbirth, and neonatal mortality are similar between these 2 groups.[6] However, type 2 diabetes confers a higher risk of perinatal mortality, whereas higher rates of diabetic ketoacidosis (DKA) and cesarean delivery are observed in pregnant women with type 1 diabetes.[6]

Fetal exposure to diabetes during pregnancy may also lead to long-term developmental programming in offspring and may manifest as higher rates of diabetes and obesity in adulthood,[7,8] adverse cardiometabolic profiles,[8-13] and greater risk of hospital admissions, medication use, and mortality.[14] Evidence also suggests diabetes during pregnancy may have an influence on neurodevelopmental outcomes; offspring of mothers with diabetes may have lower long-term cognitive function with worse school performance[15,16] as well as heightened risk of autism[17] and attention-deficit/hyperactivity disorder[18] compared with offspring of mothers without preexisting diabetes.

Appropriate planning and optimization of glycemic control prior to pregnancy can help mitigate risks associated with diabetes. The purpose of this review is to provide an evidence-based update to the management of preexisting diabetes in pregnancy.

Box. Odd Ratios (ORs) of Adverse Maternal and Child Outcomes in Women With Preexisting Diabetes in Pregnancy vs Women Without Diabetes

Maternal Outcomes, OR (95% CI)

Preeclampsia: 3.48 (3.01-4.02)

Cesarean delivery: 3.52 (2.91-4.25)

Child Outcomes, OR (95% CI)

Noncardiac congenital defects: 2.34 (1.44-3.81)

Cardiac congenital defects: 4.64 (2.87-7.51)

Preterm delivery (<37 wk): 3.48 (3.06-3.96)

Stillbirth: 3.52 (3.19-3.88)

Macrosomia (fetal weight >4 kg): 1.91 (1.74-2.10)

Neonatal hypoglycemia: 26.6 (15.37-46.11)

Neonatal respiratory distress: 2.09 (1.55-2.83)

Neonatal jaundice: 2.82 (1.60-5.00)

Perinatal mortality: 3.39 (3.02-3.81)

ORs for congenital defects are derived from Correa et al,[3] while the remaining ORs are adapted from Yu et al.[2]

Key Points

Question What are evidence-based approaches to managing preexisting diabetes in pregnancy?

Findings Management considerations vary depending on whether women are in the preconception, pregnancy, or postpartum stage. Optimization of glycemic control prior to pregnancy is a very important step, with a target hemoglobin A_{1c} of less than 6.5% at conception. Insulin is the cornerstone of pharmacotherapy for women with type 1 and type 2 diabetes. Attention to nutrition as well as comorbidities, including obesity, nephropathy, and hypertension, is essential.

Meaning Management of diabetes in pregnant women requires careful attention to glycemic control, medication regimens, and comorbidities and planning throughout all stages before, during, and after pregnancy.

Comprehensive diabetes care in pregnancy can be considered in the preconception, pregnancy, and postpartum stages.

Methods

We searched the PubMed database from January 1, 2000, to January 31, 2019, for English-language studies related to the management of preexisting diabetes in pregnancy. There are few randomized clinical trials of pregnant vs nonpregnant women, so, although such studies were included, the search was not limited to these studies. Guidelines of major professional societies, meta-analyses, and observational studies were also reviewed. Selected articles were mutually agreed upon by the authors.

Preconception

Preconception Counseling and Glycemic Targets

While rates of unintended pregnancy have decreased in recent years, nearly half of pregnancies in the United States are still unplanned.[19] Appropriate prepregnancy planning is one of the most important steps in reducing the risk of birth defects for women with preexisting diabetes because organogenesis occurs very early in pregnancy. The American Diabetes Association (ADA) recommends hemoglobin A_{1c} (HbA_{1c}) of less than 6.5% at conception, with a lower goal of less than 6% during pregnancy if it can be achieved without significant hypoglycemia.[20] Targets may be relaxed to less than 7% if hypoglycemia occurs at lower HbA_{1c} levels.[20] Discussions regarding the risks of congenital anomalies with unplanned pregnancy and the importance of effective contraception should be initiated at the onset of diabetes or puberty and continued thereafter. Long-acting reversible forms of contraception (LARC), such as implantable progestin or intrauterine devices, should be recommended as first-line therapy for women who do not desire fertility in the near future because these are the most effective forms of contraception.[21,22] Patients should alert their clinicians before ceasing contraception and, ideally, this step would be preceded by monthly meetings between the patient and care team to optimize glycemic control.

Women with diabetes should ideally be referred to a maternal-fetal medicine specialist (high-risk obstetrician) prior to conception. These specialists can counsel women on possible maternal and fetal complications and the need for intensified fetal surveillance during pregnancy.

Weight and Nutrition

Obesity is common in individuals with type 2 diabetes, with increasing prevalence in individuals with type 1 diabetes,[23] and represents an independent risk factor for congenital malformations, particularly cardiac defects.[24,25] Efforts should be made to optimize weight in addition to glycemic control prior to conception. In a 2019 study by Persson et al,[25] the rate of aortic arch defects, atrial septal defect, and patent ductus arteriosus increased incrementally with maternal body mass index (BMI), and the rate of transposition of the great arteries was nearly double (adjusted prevalence rate ratio, 1.85 [95% CI, 1.11-3.08]) in mothers with BMI above 40 vs mothers with normal BMI. Furthermore, pregnant women who are obese are more likely to have comorbid illnesses that can affect outcomes, such as hyperlipidemia,[26,27] hypertension,[28] and obstructive sleep apnea (OSA).[29,30] OSA is particularly notable because it is often underdiagnosed,[31] and the prevalence of OSA in pregnancy may be as high as 5% in Europe and 20% in the United States.[30] OSA has been linked to higher rates of gestational hypertension, preeclampsia, preterm birth, low infant Apgar scores, and greater need for neonatal intensive unit care.[29,30] It is also correlated with worse glycemic profiles and insulin resistance.[32] Therefore, clinicians should screen for OSA in overweight or obese women planning pregnancy, and treatment with continuous positive airway pressure should be initiated promptly for all confirmed cases.[33]

All women with diabetes should be referred to a dietician prior to or early in pregnancy. Referral to a registered dietitian is particularly recommended for all women with overweight or obesity to generate a nutrition plan that accounts for pregestational weight and targets at least 5% to 10% loss of body weight prior to conception.[34]

To prevent neural tube defects, prospective mothers should take at least 400 µg of folic acid daily for at least 1 month prior to conception.[35] They should also take 1000 mg of elemental calcium and 600 IU of vitamin D daily while pregnant to support bone health in the neonate[36,37]; these nutrients can be prescribed in the form of a prenatal multivitamin and/or consumed via diet.

Diabetes Complications

Prior to pregnancy, women should be screened for complications of diabetes, including retinopathy and nephropathy. Diabetic retinopathy can worsen during pregnancy and with brisk improvement in glycemic control. Worsening of retinopathy with rapidly improved glycemic control is not well understood, although this phenomenon has been observed in nonpregnant populations and is often transient.[38] While pregnancy-induced retinopathy (or worsening of preexisting disease) is unlikely to be permanent, retinopathy progression can threaten vision during pregnancy. All women with type 1 and type 2 diabetes should undergo retinal examination prior to conception, ideally, (particularly women with preexisting diabetic retinopathy) or within the first trimester. Additional ophthalmologic monitoring during and after pregnancy will be guided by extent of the disease.[20]

In terms of nephropathy, a urine albumin:creatinine ratio can be obtained for women with diabetes prior to pregnancy, although the standard measurement during pregnancy is a urine protein:creatinine ratio from a 24-hour urine collection. Women with nephropathy should be monitored by a multidisciplinary team that includes a maternal-fetal medicine physician and a nephrologist before and during pregnancy. Women with baseline nephropathy have heightened perinatal risk because they have greater risk of preeclampsia,[39,40] preterm delivery, infants who are small for gestational age, and cesarean delivery.[40] Women with mild chronic kidney disease (estimated glomerular filtration rate >60 mL/min/1.73 m^2) are unlikely to have significant worsening of kidney disease during pregnancy.[40] In contrast, women with more severe kidney disease or with proteinuria can experience a decline in kidney function, particularly in the presence of uncontrolled hypertension. For women with end-stage renal disease, it may be helpful to delay pregnancy until after kidney transplantation because transplant recipients have a higher chance of successful pregnancies and fewer complications than women undergoing dialysis.[41] Preexisting kidney disease also has important implications for preeclampsia monitoring because preeclampsia detection relies on urine protein screening. Therefore, it is critical to monitor blood pressure closely in the presence of diabetic nephropathy.

For women with chronic hypertension and diabetes, systolic blood pressure (BP) of 120 mm Hg and diastolic BP of 80 to 105 mm Hg are recommended by the ADA as reasonable targets to avoid impairment of fetal growth,[20] although there is controversy regarding accepted BP targets. In 2015, the CHIPS study[42] demonstrated no difference in pregnancy loss or neonatal outcomes in pregnant women whose diastolic BP was targeted to 100 mm Hg vs 85 mm Hg, although there were more cases of severe hypertension (≥160/110 mm Hg) in the group with the higher BP target. Post hoc analyses of this trial revealed higher risk of pregnancy loss, preterm delivery, and low birth weight for the women who developed severe hypertension.[43] Additionally, initiation of this "less tight" BP control before 28 weeks' gestation resulted in significantly higher rates of severe maternal hypertension as well as preterm delivery compared with this BP control after 28 weeks.[44] As a result of these studies, Canadian guidelines have adopted lower BP thresholds for antihypertensive initiation (start medication if diastolic BP >90 mm Hg and target BP <85 mm Hg).[45] Guidelines from the United Kingdom recognize end-organ damage as reason to consider lower BP goals (eg, diastolic BP <90 mm Hg).[46] The CHIPS study did not include any women with preexisting diabetes or proteinuria and only 6% of study participants had gestational diabetes, thus, these data are not generalizable to women with preexisting type 1 or type 2 diabetes.[42] However, it is reasonable to consider women with preexisting diabetes at particularly high risk of poor outcomes related to hypertension because they are more likely to have baseline nephropathy. While this concern has yet to be reflected in ADA guidelines, it is sensible for clinicians to consider lower BP targets for pregnant women with diabetic nephropathy.

When treating women with hypertension, potentially teratogenic medications, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, should be discontinued during pregnancy and alternative medications that are considered safe in pregnancy, such as labetalol, nifedipine, or clonidine, should be used to manage blood pressure.[47,48] Studies have suggested that nondihydropyridine calcium channel blockers, such as diltiazem, decrease proteinuria and thus diltiazem could be considered for women with hypertension and proteinuria during pregnancy,[49] although there are limited studies of this agent in pregnancy.[50,51]

Diabetes in pregnancy increases the risk of preeclampsia, so initiation of low-dose aspirin (60 mg to 150 mg daily; usual dose, 81 mg) is recommended between 12 and 28 (ideally before 16) weeks' gestation to reduce this risk.[20] Controversy exists regarding optimal dosing; several meta-analyses have found the reduction in preeclampsia to be greatest in women taking at least 100 mg of aspirin per day.[52,53] While coronary artery disease (CAD) is uncommon in pregnancy, it is associated with high maternal mortality.[20] Therefore, clinicians should consider CAD risk factors (ie, advanced maternal age, chronic renal disease, hypertension, smoking, family history of premature CAD) and screen high-risk mothers with an electrocardiogram and/or exercise echocardiogram. Statins should be discontinued when planning pregnancy, although data suggest they are likely not teratogenic.[26]

For women with type 1 diabetes who are planning for pregnancy, thyroid-stimulating hormone levels should be checked to screen for autoimmune thyroid disease.[20,54]

During Pregnancy

Glucose Monitoring

Intensification of glucose monitoring can be a challenge for women who are pregnant. Women receiving multiple daily injections (MDI) of insulin are advised to monitor capillary glucose in the fasting, preprandial, and (1- or 2-hour) postprandial states and to undergo at least 7 glucose checks daily. Recommended targets are less than 95 mg/dL for fasting glucose, less than 140 mg/dL for 1-hour postprandial glucose, and less than 120 mg/dL for 2-hour postprandial glucose (**Table 1**).[20] Close glucose monitoring is essential to (1) ensure

Table 1. American Diabetes Association-Recommended Glycemic Targets in Pregnancy[20]

Timing	Glycemic Target
Before Pregnancy	
HbA_{1c}, %	<6.5
During Pregnancy	
HbA_{1c}, %	<6.0
Glucose, mg/dL	
Fasting	≤95
1 h after eating	≤140
2 h after eating	≤120

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

glycemic goals are being met, (2) inform adjustments to the medication and nutrition plan, and (3) preempt and detect physiologic changes in insulin requirements during pregnancy.

Improvements in glycemic control and outcomes have been reported with use of continuous glucose monitoring (CGM) systems as an adjunct to capillary glucose monitoring in pregnancy, although some data are conflicting.[55-58] As part of the 2017 multicenter CONCEPTT study, 215 pregnant women with type 1 diabetes were randomized to receive CGM or standard capillary blood glucose monitoring.[56] There was a small but significant between-group difference in the mean decrease in HbA_{1c} at 34 weeks' gestation (difference, 0.19% [95% CI, −0.34% to −0.03%]; P = .02) compared with HbA_{1c} at enrollment (mean HbA_{1c}, 7.43%), favoring CGM. CGM also led to higher "time in target" than in the standard monitoring group (68% vs 61% ; P = .003) and lower incidence of newborns who were large for gestational age (odds ratio, 0.51 [95% CI, 0.28-0.90]; P = .0210).[56] This study had lower than expected CGM adherence in the intervention group, which may have contributed to the modest HbA_{1c} response to CGM. Nonetheless, the CONCEPTT trial highlights CGM as a useful tool in pregnancies complicated by preexisting diabetes, with the potential to improve neonatal outcomes. Limitations to consider with CGM include discomfort, sensor accuracy, and acetaminophen interference with certain sensors.[59]

Insulin Requirements During Pregnancy

Women with preexisting diabetes are most sensitive to insulin during early stages of pregnancy. Close glucose monitoring is therefore essential to avoid hypoglycemia, which, in addition to altered consciousness, seizures, and maternal injury,[60] can lead to low birth weight.[20] This risk is particularly notable in patients with type 1 diabetes, who are typically more insulin sensitive than patients with type 2 diabetes and who are more likely to have hypoglycemic unawareness.[60] Glucagon is safe to administer during pregnancy, and close contacts to the patient should be taught administration in case of severe hypoglycemia.

As pregnancy progresses past 16 weeks' gestation, women with preexisting diabetes become more insulin resistant, and insulin needs may change on a weekly basis (**Table 2**), so close glucose monitoring is critical. Insulin requirements also may increase from pregnancy to pregnancy. Skajaa et al[61] demonstrated incremental increases in daily insulin requirements of mothers with type 1 diabetes with increasing parity, adjusted for age, BMI, and HbA_{1c}. Compared with women during their first pregnancy, gestational insulin requirements increased by 13% in women with 1 previous pregnancy, 20% for 2 previous pregnancies, and 36% for 3 to 4 previous pregnancies.[61] Therefore, in multiparous women, it is reasonable to anticipate greater need for glucose control with successive pregnancies.

Table 2. Typical Pattern of Insulin Requirements During Pregnancy[a]

Stages of Pregnancy, wk	Insulin Requirements
0-9	Increase
9-14	Decrease
14-16	Low
16-37	At least double
37-40	Can decrease
Immediately after pregnancy	Can drop to half of prepregnancy needs

[a] Adapted from Skajaa et al.[61]

Although DKA occurs at a higher frequency in women with type 1 diabetes, all pregnant women with diabetes are predisposed to DKA because pregnancy promotes insulin resistance, accelerated lipolysis, and surplus of free fatty acids that can be shunted to ketone body production.[62] High levels of human chorionic gonadotropin can lead to nausea and vomiting and thereby predispose women to DKA early in pregnancy. In contrast, insulin resistance and metabolic demands increase significantly by the third trimester, which can precipitate DKA via hyperglycemia and relative starvation.[62] Additionally, a major reason for earlier acidosis in pregnancy is lower acid buffering capacity; women who are pregnant have respiratory alkalosis with compensatory metabolic acidosis and, thus, lower bicarbonate levels.[63] Pregnant women can develop DKA with normal glucose values, which may be partially attributed to glomerular hyperfiltration resulting in glucosuria,[64] so euglycemia should not provide false reassurance to patients and clinicians.[65] Women who are pregnant or planning pregnancy should be educated regarding ketone testing and supplied with urine or serum ketone testing supplies. Women (particularly with type 1 diabetes) should measure urine ketones after episodes of vomiting or inability tolerate food or drink, when otherwise ill, or if glucose remains greater than 250 mg/dL after appropriate measures. Women with ketonuria should seek medical attention for prompt treatment to reduce maternal and neonatal risk.

Nutrition and Weight During Pregnancy

Even in nonobese women, weight gain exceeding recommended targets during pregnancy can be associated with worse perinatal outcomes, including macrosomia, shoulder dystocia, and neonatal hypoglycemia.[66] Thus, pregnancy requires close attention to food intake to ensure strict glycemic control and avoid excess weight gain. However, care should be taken to avoid inadequate carbohydrate intake, which can lead to starvation and ketosis in pregnancy. To minimize the risk of DKA, women are advised to consume adequate carbohydrates[62]; a daily minimum of 175 g of carbohydrates is recommended for pregnant women by the Dietary Reference Intakes,[20] although nutrition plans should be individualized.

Approach to Insulin Management

Women with preexisting diabetes commonly require basal-bolus regimens to achieve glycemic targets. Specifically, women with

type 2 diabetes who are treated with diet alone, oral agents, or basal insulin will need education regarding intensive insulin management that may be necessary to achieve preconception targets or that will need to be implemented during pregnancy.

Insulin remains the cornerstone of therapy for pregnant women with diabetes because of glucose-lowering potency as well as demonstrated safety during pregnancy because insulin does not cross the placenta. Women are frequently switched to basal insulins detemir or neutral protamine Hagedorn during pregnancy because these have been more extensively studied than newer, basal insulin analogues. Short-acting/rapid-acting insulins regular, lispro, and aspart have also been well studied. There are reports of safe and successful pregnancies in women taking insulin glargine during pregnancy.[67] Because insulins glargine and degludec are unlikely to cross the placenta,[68] there is no compelling evidence to suggest that women should be switched off of these insulins when pregnant, particularly when they are already achieving excellent glycemic control.

MDI and insulin pump therapy, also called continuous subcutaneous insulin infusion (CSII), are both effective approaches in pregnancy. While insulin pumps offer obvious advantages in terms of flexibility of bolusing, there is insufficient evidence to recommend one method over the other.[69] However, if CSII is to be initiated, it should be started well before conception to allow women time to acclimate to the pump and ensure glycemic control before pregnancy. Also, women using CSII require a subcutaneous insulin plan in case of pump malfunction. A prespecified analysis of the CONCEPTT trial was to compare glycemic control and pregnancy outcomes in women with type 1 diabetes who were using MDI vs CSII at study inclusion. Researchers observed better glycemic outcomes, less gestational hypertension and neonatal hypoglycemia, and fewer neonatal intensive care unit admissions with MDI vs CSII, although women were not randomized to method of insulin delivery in this trial.[70]

Closed-loop insulin delivery systems that integrate CGM data with CSII may hold promise in the management of diabetes in pregnancy but, currently, glucose targets are not customizable and are typically too high for pregnancy. For instance, the MiniMed 670G (Medtronic) insulin pump has an "auto-mode" commercial hybrid closed-loop system that utilizes an algorithm to target an average glucose of 120 mg/dL,[71] a glucose value that is well above the fasting goal of less than 95 mg/dL in pregnancy, and thus likely not appropriate for use during pregnancy for most patients. Additionally, predictive low glucose suspend technology was recently approved for use in the t:slim X2 Insulin Pump with Basal-IQ Technology (Tandem Diabetes Care), which is integrated with the Dexcom sensor. This technology predicts future glucose concentration and suspends insulin delivery if the predicted glucose in 30 minutes is less than 80 mg/dL or if the current glucose is less than 70 mg/dL.[72] While predictive low glucose suspend technology protects against hypoglycemia, it also does not account for lower glucose goals in pregnancy. Despite the caveat of inflexible glucose targets, closed-loop systems may still result in comparable glycemic control with less hypoglycemia in some women,[73-76] although larger studies are needed to draw conclusions regarding their routine use in pregnancy.

Noninsulin Medications

Oral agents are not recommended as first-line therapy for pregnant women with diabetes because they are typically not capable of overcoming the insulin resistance of pregnancy in women with type 2 diabetes and are not effective in individuals with type 1 diabetes. Furthermore, metformin and sulfonylureas cross the placenta whereas insulin does not.

There remains significant controversy about the use of metformin among pregnant women. Per the ADA guidelines, women with type 2 diabetes who are prescribed metformin prior to pregnancy should be switched to insulin when they become pregnant.[20] However, many women with polycystic ovary syndrome and/or obesity continue receiving metformin through the first trimester, and not all professional organizations agree on the use of metformin during pregnancy.[77] Studies have shown an association of metformin treatment with less maternal weight gain, primarily in women with gestational diabetes[20,78] as well as women with type 2 diabetes.[79] However, 2 studies that examined children of women who were treated with metformin during pregnancy suggest that metformin may have long-term effects on offspring.[78,80] At 9 years of age, children of women with gestational diabetes who were exposed to metformin in utero had larger measures of subcutaneous fat compared with children exposed to insulin.[78] At 4 years of age, children of women with polycystic ovarian syndrome who were exposed to metformin had higher BMI and increased prevalence of obesity (32%) compared with children exposed to a placebo (18%).[80] Thus, it is possible that metformin has long-term effects on fetal and childhood development, perhaps due to its effects on mitochondrial respiration, growth inhibition, or cell metabolism and proliferation.[77] A randomized clinical trial is currently under way (the MiTy Trial; NCT01353391)[81] to investigate perinatal and neonatal outcomes in pregnant women prescribed metformin vs placebo as an adjunct to insulin to manage type 2 diabetes. Additional studies will still be needed to determine long-term effects of metformin on offspring. For women who decline insulin, metformin can be continued, although the safety data and high likelihood of treatment failure necessitating insulin should be fully discussed with the patient.[20]

Sulfonylureas are not recommended for pregnant women with preexisting diabetes. In a 2018 study by Sénat and colleagues,[82] glyburide was compared with insulin in pregnant women with gestational diabetes and there was a failure to demonstrate noninferiority of glyburide for the composite outcome of macrosomia, neonatal hypoglycemia, and hyperbilirubinemia (outcome occurred in 23.4% of neonates born to women treated with insulin vs 27.6% of neonates born to women treated with glyburide).[82] Sulfonylureas lack data to support their use in pregnancy and, in contrast to metformin, they tend to promote weight gain rather than weight stability.[83] Thiazolidinediones also contribute to weight gain and lack safety data regarding pregnancy.

Newer glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium glucose-cotransporter 2 inhibitors, are also not recommended in pregnancy because of a lack of safety data. Women who are prescribed these agents should be using effective contraception and counseled on cessation of these medications ideally 3 months prior to conception. Interestingly, the GLP-1 receptor agonist exenatide appears to cross the placenta in only negligible amounts.[84] Because fetal exposure to GLP-1 receptor agonists is likely to be low, clinicians should be cautious of abruptly stopping these agents without concurrent initiation

Table 3. Management Considerations for Preexisting Diabetes in Pregnancy

Diabetes Management	Before Conception	First Trimester	Second and Third Trimesters	After Pregnancy
Diagnostic Steps				
Laboratory studies	• HbA_{1c} • Urine ACR or PCR • TSH in women with type 1 diabetes			
Clinical screenings	• Discuss contraception (ideally LARC) • OSA screening in women with obesity • Retinal examination • Consider CAD screening if multiple risk factors are present	• Close SMBG (7 times/d) with or without CGM • Retinal examination if not done before pregnancy, and repeat evaluations as indicated		• Discuss contraception (LARC)
Fetal assessment			• Detailed anatomical survey via ultrasonography at 18-20 weeks' gestation • Consider fetal echocardiography • Evaluate fetal growth (third trimester) • Formal fetal monitoring (often started at 32 weeks' gestation; nonstress test, biophysical profile)	
Therapeutic Steps				
Nonpharmacologic interventions	• Weight optimization via lifestyle modifications • Referral and follow-up with nutritionist to review diet with or without ICR			• Lactation consultation • Consider ongoing nutrition support
Pharmacologic interventions	• Optimize glucose with HbA_{1c} goal <6.5% • May require initiation of insulin in women with type 2 diabetes • Stop noninsulin agents, including sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1RA, and SGLT-2 inhibitors[a] • Initiation of daily prenatal vitamin (≥400 mcg folic acid, 1000 mg elemental calcium, 600 IU vitamin D per day) • Discontinue use of ACE inhibitors/ARBs and initiate use of accepted antihypertensive agents[b] • Stop use of statins	• Initiate/titrate insulin (typically a period of increased insulin sensitivity)	• Initiate 60 to 150 mg of aspirin per day (usual dose, 81 mg) started between 12 to 28 (ideally before 16) weeks' gestation to minimize the risk of preeclampsia • Titrate insulin (typically aa period of increased insulin resistance) • Intravenous insulin typically administered during delivery	• Decrease insulin immediately after delivery because of high insulin sensitivity (up to 50% of the prepregnancy dose for women with type 1 diabetes, and consider stopping insulin for women with type 2 diabetes) • Metformin is safe for women who are breastfeeding

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin:creatinine ratio; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CGM, continuous glucose monitoring; TSH, thyroid-stimulating hormone; HbA_{1c}, hemoglobin A_{1c}; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide 1 receptor agonist; ICR, insulin:carbohydrate ratios; LARC, long-acting reversible contraception; OSA, obstructive sleep apnea; PCR, protein:creatinine ratio; SGLT-2, sodium glucose cotransporter 2; SMBG, self-monitoring of blood glucose.

[a] Metformin has been continued safely in some pregnancies, including in cases of women with polycystic ovarian syndrome, although there are insufficient data to recommend use during pregnancy.

[b] Accepted antihypertensive agents for use during pregnancy include labetalol, hydralazine, methyldopa, and nifedipine.

of other therapy, such as insulin, because the risk of uncontrolled hyperglycemia may exceed fetal risk of the drug.

Fetal Monitoring and Delivery Planning

Women with diabetes who become pregnant require increased fetal monitoring (**Table 3**). Women should have a detailed anatomy scan at 18 to 20 weeks' gestation and fetal echocardiography can be considered (particularly if HbA_{1c} is >6.5%).[21] Ultrasonography is commonly used to assess fetal growth in the third trimester, though a specific approach to timing and frequency has not been demonstrated as superior. Most clinicians obtain formal fetal monitoring, such as the nonstress test, the biophysical profile, or the modified biophysical profile, starting at 32 weeks' gestation (often once or twice weekly). The American College of Obstetricians and Gynecologists recommends delivery at 39 0/7 to 39 6/7 weeks' gestation in women without vascular complications and with well-controlled blood glucose values, but recommends earlier delivery at 36 0/7 to 38 6/7 weeks' gestation for women who have vascular complications or poor glycemic control.[21]

Postpartum

During delivery, most cases of diabetes are managed with intravenous insulin, although this is dependent on local institutional policies. Women become exquisitely sensitive to insulin with delivery of the placenta. Insulin requirements may decrease to as low as 50% of prepregnancy needs, particularly in patients with type 1 diabetes (Table 2). Therefore, it is prudent to administer 50% to 90% of prepregnancy insulin doses, and this decision can be guided by immediate postpartum glucose values, intravenous insulin needs, and food intake. It is helpful for outpatient clinicians to document prepregnancy insulin doses leading up to delivery.

Breastfeeding

Benefits of breastfeeding include loss of excess weight in mothers, infant bonding, and lower future risk of obesity and type 2 diabetes in offspring.[85,86] Women who breastfeed are predisposed to hypoglycemia because carbohydrates are expelled into breast milk,

so insulin doses may need to be lowered during this time and/or women can be counseled to consume a snack with lactation to avoid hypoglycemia. An increase of 500 kcal per day from prepregnancy caloric intake is generally recommended for nonobese women who are breastfeeding.[21,87]

Contraception

Most women do not plan on conceiving within 1 year of giving birth,[88] but fertility may return as soon as 6 weeks after delivery in women who are not exclusively breastfeeding. Thus, the immediate postpartum period represents an opportunity to initiate LARC before women return home and develop barriers to accessing effective contraception.[88] LARC is safe in the postpartum period and early initiation of progestogen does not appear to negatively affect glycemic control, breastfeeding, or infant growth.[88] For women who do not plan to have children in the future or who have end-organ complications resulting in high-risk future pregnancies, tubal ligation can be considered as a permanent form of contraception.

Conclusions

Preexisting diabetes in pregnancy is complex and is associated with significant maternal and neonatal risk. Optimization of glycemic control, medication regimens, and careful attention to comorbid conditions by a multidisciplinary team that includes maternal-fetal medicine physicians, endocrinologists, ophthalmologists, and nutritionists can help mitigate these risks and ensure quality diabetes care before, during, and after pregnancy.

ARTICLE INFORMATION

Accepted for Publication: April 3, 2019.

Author Contributions: Dr Peters had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Alexopoulos, Peters.
Acquisition, analysis, or interpretation of data: Alexopoulos, Blair.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Alexopoulos, Blair.
Supervision: Peters.

Conflict of Interest Disclosures: Dr Peters reported grants from AstraZeneca, Dexcom, and MannKind and consulting for Abbott Diabetes Care, Eli Lilly, Livongo, MannKind, Medscape, Novo Nordisk, Omada Health, Sanofi and Zafgen. No other disclosures were reported.

Funding/Support: This work was supported by the National Institutes of Health awards T32DK007012 (Dr Alexopoulos) and T32HL007609 (Dr Blair).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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