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# Management of preexisting diabetes in pregnancy: A Review

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## Abstract

**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, caesarian section, pre-term delivery, macrosomia and congenital defects. Approximately 0.9% of the 4,000,000 births in the United States are complicated by preexisting diabetes.

**Observations:** Women with diabetes have increased risk for adverse maternal and neonatal outcomes and similar risks are present for either type 1 or 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 A1c goal at conception is <6.5% and during pregnancy is <6.0%. It is also critical to screen for and optimize 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. Obese women should be screened for obstructive sleep apnea, which is often undiagnosed and can result in poor outcomes. Blood pressure goals must be considered carefully, as lower treatment thresholds may be required for women with nephropathy. During pregnancy, continuous glucose monitor use can improve glycemic control and neonatal outcomes for 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 and close contacts trained in its use. Low-dose aspirin is recommended soon after 12 weeks of gestation to minimize the risk of preeclampsia. The importance of discussing long-acting reversible contraception before and after pregnancy cannot be overstated, to allow for appropriate preconception planning.

**Conclusions and Relevance:** Preexisting diabetes in pregnancy is complex and is associated with significant maternal and neonatal risk, but 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.

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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, pre-term delivery, macrosomia, and stillbirth, among others (Box 1).

With the increasing prevalence of both type 1 and type 2 diabetes,[4,5] clinicians require greater awareness of risks associated with diabetes in pregnancy, and necessary approaches to minimize these risks. Equal emphasis should be placed on aggressive care and glycemic optimization of mothers with preexisting type 1 and type 2 diabetes, as rates of major congenital malformations, stillbirth and neonatal mortality are similar between these two groups.[6] However, type 2 diabetes confers a higher risk of perinatal mortality, whereas higher rates of diabetic ketoacidosis (DKA) and caesarian delivery are observed in mothers 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] greater risk of hospital admissions, medication use and even mortality.[14] Recent evidence also suggests influence on neurodevelopmental outcomes, as 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 to 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. Comprehensive diabetes care in pregnancy can be considered in three stages: 1) preconception, 2) pregnancy and 3) post-partum.

## 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 versus non-pregnant women, so while 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 are still unplanned.[19] Appropriate pre-pregnancy planning is one of the most important steps in reducing risk of birth defects in mothers with preexisting diabetes, because organogenesis occurs very early in pregnancy. The American Diabetes Association (ADA) recommends hemoglobin A1c (HbA1c) of <6.5% at conception, with a lower goal of

<6% during pregnancy if this can be achieved without significant hypoglycemia.[20] Targets may be relaxed to <7% if hypoglycemia occurs at lower HbA1c 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, as 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 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 type 2 diabetes with increasing prevalence in type 1 diabetes,[23] and represents an independent risk factor for congenital malformations; particularly cardiac defects.[24,25] As such, efforts should be made to optimize weight, in addition to glycemic control, prior to conception. In a recent study by Persson *et al*,[25] rate of aortic arch defects, atrial septal defect and patent ductus arteriosus increased incrementally with maternal body mass index (BMI), and rate of transposition of the great arteries was nearly double (adjusted prevalence rate ratio [PRR] 1.85, 95% CI 1.11, 3.08) in mothers with BMI above 40 $kg/m^2$ versus those with normal BMI. Furthermore, 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 since it is often underdiagnosed,[31] and 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, pre-term 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 prompt treatment with continuous positive airway pressure should be initiated 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 dietician is particularly recommended for all women with overweight or obesity, to generate a nutrition plan that accounts for pre-gestational weight, and targets at least 5–10% loss of body weight prior to conception.[34]

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

## Diabetes complications

Women should be screened for complications of diabetes including retinopathy and nephropathy prior to pregnancy. 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, though this phenomenon has been observed in non-pregnant 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 ideally prior to conception (particularly for those with preexisting diabetic retinopathy) or within the first trimester. Additional eye monitoring during pregnancy and post-partum will be guided by extent of disease.[20]

In terms of nephropathy, a urine albumin-to-creatinine ratio can be obtained for women with diabetes prior to pregnancy, though the standard measurement during pregnancy is a urine protein-to-creatinine ratio in a 24-hour urine collection. Women with nephropathy should be monitored by a multidisciplinary team including a Maternal-Fetal Medicine physician and a nephrologist before and during pregnancy. Women with baseline nephropathy have heightened perinatal risk, as they have greater odds of preeclampsia,[39,40] pre-term delivery, small for gestational age infants, and caesarian section.[40] Women with mild chronic kidney disease (estimated glomerular filtration rate of >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 have a decline in kidney function, particularly in the presence of uncontrolled hypertension. In fact, for women with end-stage renal disease, it may be helpful to delay pregnancy until after kidney transplantation since transplant recipients have a higher chance of successful pregnancies and fewer complications than women on dialysis.[41] Preexisting kidney disease also has important implications for preeclampsia monitoring, as 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 and diastolic blood pressures (BP) of 120–160 mmHg and 80–105 mmHg, respectively, 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 mmHg versus 85 mmHg; although there were more cases of severe hypertension (≥160/110 mmHg) with higher BP targets. Post-hoc analyses of this trial revealed higher risk of pregnancy loss, pre-term delivery and low birth weight for the mothers who developed severe hypertension.[43] Additionally, initiation of this ‘less-tight’ BP control before (versus after) 28 weeks gestation resulted in significantly higher rates of severe maternal hypertension, as well as pre-term delivery.[44] As a result of these studies, Canadian guidelines have adopted lower BP thresholds for anti-hypertensive initiation (start medication if diastolic BP >90 mmHg, and then target <85 mmHg).[45] Guidelines from the United Kingdom recognize end-organ damage as reason to consider lower BP goals, e.g. diastolic <90 mmHg.[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 directly 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, given 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 hypertension, potentially teratogenic medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be discontinued during pregnancy and alternative medications which are safe in pregnancy, such as labetalol, nifedipine, or clonidine should be used to control 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] though 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 60–150 mg daily (usual dose 81 mg) is recommended between 12 and 28 weeks gestation (ideally before 16 weeks) to reduce this risk.[20] Controversy exists regarding optimal dosing, as several meta-analyses have found the reduction in preeclampsia to be greatest in women taking aspirin 100 mg or higher.[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 (i.e. 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 suggests they are likely not teratogenic.[26]

For women with type 1 diabetes, thyroid-stimulating hormone (TSH) should be checked to screen for autoimmune thyroid disease when planning for pregnancy.[20,54]

## Pregnancy

### Glucose monitoring

Intensification of glucose monitoring can be a challenge for women who are pregnant. Women who are taking multiple daily injections (MDI) of insulin are advised to monitor capillary glucose in the fasting, preprandial and (1- or 2-hour) postprandial states; at least seven glucose checks daily. Recommended glucose targets are: <95 mg/dL fasting, <140 mg/dL 1-hour post-prandial and/or <120 mg/dL 2-hour post-prandial (Table 1).[20] Close glucose monitoring is essential to 1) ensure 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 recent multicenter CONCEPTT study, 215 pregnant women with type 1 diabetes were randomized to CGM or

standard capillary blood glucose monitoring.[56] CGM use resulted in a small but significantly decreased HbA1c at 34 weeks gestation (−0.19%, 95% CI −0.34, −0.03%, p=0.021) compared to HbA1c at enrollment (mean HbA1c 7.43%). CGM use also led to increased "time in target" (68% versus 61% in controls; p=0.003) and decreased incidence of babies large for gestational age (OR 0.51, 95% CI, 0.28, 0.90, p=0.0210).[56] This study had lower than expected CGM compliance in the intervention arm, which may have contributed to the modest HbA1c 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 use include discomfort, sensor accuracy and acetaminophen interference with certain sensors.[59]

## Insulin requirements during pregnancy

Women with pre-existing diabetes are most insulin sensitive 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 infants.[20] This risk is particularly notable in patients with type 1 diabetes who are typically more insulin sensitive than those with type 2 diabetes, and who are more likely to have hypoglycemic unawareness.[60] Glucagon is safe to administer in pregnancy, and close contacts 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 HbA1c. Compared with mothers during their first pregnancy, gestational insulin requirements increased by 13%, 20% and 36% in mothers with one, two, or 3–4 previous pregnancies, respectively.[61] Therefore, in multiparous women, it is reasonable to anticipate greater needs for glucose control with successive pregnancies.

While DKA occurs at higher frequency in women with type 1 diabetes, all pregnant women with diabetes are predisposed to DKA since pregnancy promotes insulin resistance, accelerated lipolysis and surplus of free fatty acids which can be shunted to ketone bodies.[62] High levels of human chorionic gonadotropin can lead to nausea, vomiting and thereby predispose 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, 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 for episodes of vomiting, inability tolerate food or drink, when otherwise ill, or if glucose remains >250

mg/dL after appropriate measures. Women with ketonuria should seek medical attention for prompt management, and to reduce maternal and neonatal risk.

## Nutrition and exercise during pregnancy

Even in non-obese 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 risk of DKA, women are advised to consume adequate carbohydrates[62]; and a daily minimum of 175 grams is recommended 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 managed with diet alone, oral agents and/or basal insulin will need education regarding intensive insulin management which may be necessary to achieve preconception targets or will need to be implemented during pregnancy.

Insulin remains the cornerstone of therapy for diabetes in pregnancy due to glucose-lowering potency as well as demonstrated safety during pregnancy, as it does not cross the placenta. Women are frequently switched to basal insulins detemir or neutral protein Hagedorn (NPH) during pregnancy as these have been more extensively studied compared to newer, basal insulin analogs. Short/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] Since insulins glargine and degludec are unlikely to cross the placenta,[68] there is no compelling evidence to suggest that women should be switched off these insulins, 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 mothers time to acclimate to the pump and ensure tight 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 either using MDI versus CSII at study inclusion. Researchers observed better glycemic outcomes and less gestational hypertension, neonatal hypoglycemia, and fewer neonatal intensive care admissions with MDI versus 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 Medtronic MiniMed

670G (Dublin, Ireland) insulin pump has an “auto-mode” commercial hybrid closed-loop system which utilizes an algorithm to target an average glucose of 120 mg/dL[71] - a glucose which is well above the fasting goal of <95 mg/dL in pregnancy, and thus likely not appropriate for use during pregnancy for most patients. Additionally, predictive low glucose suspend (PLGS) technology was recently approved for use in the Tandem Diabetes Care t:slim X2 pump with Basal-IQ technology (San Diego, CA); this system is integrated with the Dexcom sensor (San Diego, CA). PLGS technology predicts future glucose concentration, and insulin delivery is suspended if the predicted glucose in 30 minutes is <80 mg/dL, or if the current glucose declines below 70 mg/dL.[72] While PLGS 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 in some women, with less hypoglycemia,[73-76] although larger studies are needed to draw conclusions regarding their routine use in pregnancy.

## Non-insulin medications

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

There remains significant controversy about the use of metformin in pregnant women. Per the ADA guidelines, women with type 2 diabetes who are on metformin prior to pregnancy should be switched to insulin once they become pregnant.[20] However, many women with PCOS and/or obesity are continued on 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, two recent 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] In a population with gestational diabetes, children at 9 years of age exposed to metformin *in utero* were larger by several measurements compared with those exposed to insulin.[78] In women with polycystic ovarian syndrome, children exposed to metformin had higher BMI and increased prevalence of obesity (32%) compared to those exposed to placebo (18%) at 4 years of age.[80] Thus, it is possible that metformin has long-term effects on fetal and childhood development, perhaps due to its impact on mitochondrial respiration, growth inhibition, or other effects on cell metabolism and proliferation.[77] A randomized controlled trial is currently underway (MiTy trial, Clinicaltrials.gov, )[81] to investigate perinatal and neonatal outcomes in pregnant women prescribed metformin versus placebo as an adjunct to insulin for 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 use in women with preexisting diabetes in pregnancy. In a recent study by Sénat and colleagues,[82] glyburide was compared to insulin in 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 infants born to insulin-treated mothers, versus 27.6% of infants born to glyburide-treated mothers).[82] Sulfonylureas lack data to support their use in pregnancy, and in contrast to metformin, they tend to promote weight gain rather weight stability.[83] Thiazolidinediones also contribute to weight gain and lack safety data in 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 likewise not recommended in pregnancy due to lack of safety data. Women who are taking these agents should be using effective contraception, and counseled on cessation of these medications ideally three months prior to conception. Interestingly, GLP-1 receptor agonist exenatide appears to cross the placenta in only negligible amounts.[84] Since fetal exposure to GLP-1 receptor agonists is likely to be low, clinicians should be cautious of abruptly stopping these agents without concurrent initiation of other therapy (such as insulin), given 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 18–20 weeks of gestation, and fetal echocardiography can be considered (particularly if the HbA1c is >6.5%).[21] Ultrasounds are commonly performed 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). Women may need to be delivered earlier if there are issues with glycemic control or concerns about the health of the fetus. Specifically, the American College of Obstetricians and Gynecologists recommends delivery at 39 0/7 weeks to 39 6/7 weeks of 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 if women have vascular complications or poor glycemic control.[21]

## Post-partum

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

### Breastfeeding

Benefits of breastfeeding include excess weight loss 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 as carbohydrates are being 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 in 500 kcal/day above pre-pregnancy caloric intake is generally recommended for non-obese mothers 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 post-partum if not exclusively breastfeeding. Thus, the immediate post-partum period represents an opportunity to initiate LARC before women return home and develop barriers to accessing effective contraception.[88] LARC is safe post-partum and early initiation of progesterone 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 with future pregnancies, tubal ligation can be considered as a permanent form of contraception.

## Conclusion

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 including Maternal-Fetal Medicine physicians, endocrinologists, ophthalmologists, and nutritionists can help mitigate these risks, and ensure quality diabetes care before, during and after pregnancy.

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**Box 1.**

**Odd ratios of adverse maternal and child outcomes in women with preexisting diabetes in pregnancy versus those without diabetes**

Maternal outcomes

- Preeclampsia - OR 3.48 (3.01, 4.02)
- Caesarian section - OR 3.52 (2.91, 4.25)

Child outcomes

- Non-cardiac congenital defects - OR 2.34 (1,44, 3.81)
- Cardiac congenital defects - OR 4.64 (2.87, 7.51)
- Pre-term delivery (<37 weeks) - OR 3.48 (3.06, 3.96)
- Stillbirth - OR 3.52 (3.19, 3.88)
- Macrosomia (fetal weight >4 kg) - OR 1.91 (1.74, 2.10)
- Neonatal hypoglycemia - OR 26.6 (15.37, 46.11)
- Neonatal respiratory distress - OR 2.09 (1.55, 2.83)
- Neonatal jaundice - OR 2.82 (1.60, 5.00)
- Perinatal mortality - OR 3.39 (3.02, 3.81)

Odds Ratios (ORs) for congenital defects are referenced from Correa *et al*,[3] while the remaining ORs are adapted from Yu *et al*.[2] 95% CI are listed after each OR.

## 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 of pregnancy. Optimization of glycemic control prior to pregnancy is a very important step with a goal hemoglobin A1c of <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 women with diabetes in pregnancy requires careful attention to glycemic control, medication regimens and comorbidities, and planning throughout all stages of pregnancy.

**Table 1:**

ADA-recommended Glycemic Targets in Pregnancy[20]

| Timing | Glycemic target |
|---|---|
| *Preconception* | |
| HbA1c | <6.5% |
| *During pregnancy* | |
| HbA1c | <6.0% |
| Fasting glucose | ≤95 mg/dL |
| One hour after eating | ≤140 mg/dL |
| Two hours after eating | ≤120 mg/dL |

**Table 2:**

Typical pattern of insulin requirements during pregnancy [a]

| Stages of pregnancy | Insulin requirements |
|---|---|
| 0-9 weeks | Increase |
| 9-14 weeks | Decrease |
| 14-16 weeks | Low |
| 16-37 weeks | At least double |
| 37-40 weeks | Can decrease |
| Immediately post-partum | Can drop to half pre-pregnancy needs |

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

**Table 3:**

Management Considerations for Preexisting Diabetes in Pregnancy

| **Diagnostic steps** | | | | |
|---|---|---|---|---|
| | **Preconception** | **First Trimester** | **Second/Third Trimesters** | **Postpartum** |
| Laboratory studies | - HbA1c<br>- Urine ACR or PCR<br>- TSH in T1DM | | | |
| Clinical screenings | - Discuss contraception (ideally LARC)<br>- OSA screening in obesity<br>- Retinal exam<br>-consider CAD screening if multiple risk factors | - Close SMBG (7x/day) +/− CGM<br>- Retinal exam if not done preconception, and repeat evaluations as indicated | | - Discuss contraception (LARC) |
| Fetal assessment | | | -Detailed anatomical survey by US at 18-20 weeks<br>-Consider fetal echocardiography<br>-Evaluate fetal growth (third trimester)<br>-Formal fetal monitoring (often started at 32 weeks; nonstress test, biophysical profile) | |
| **Therapeutic steps** | | | | |
| | **Preconception** | **First Trimester** | **Second/Third Trimesters** | **Postpartum** |
| Non-Pharmacologic Interventions | - Weight optimization via lifestyle modifications<br>- Referral and follow-up with nutritionist to review diet +/− ICR | | | - Lactation consultation<br>- Consider ongoing nutrition support |
| Pharmacologic interventions | - Optimize glucose with HbA1c goal <6.5%<br>- May require initiation of insulin in T2DM<br>- Stop non-insulin agents including SU, TZD, DPP4i, GLP-1RA, SGLT2i [a]<br>- Initiation of daily prenatal vitamin (≥400mcg folic acid, 1000mg elemental calcium, 600IU vitamin D per day)<br>- Switch off ACEi/ARB to accepted anti-hypertensive agents[b]<br>- Stop statin | - Initiate/titrate insulin (typically period of increased insulin sensitivity) | - ASA 60-150mg (usual dose 81mg) started between 12-28 (ideally before 16) weeks to minimize risk of PET<br>-Titrate insulin (typically period of increased insulin resistance)<br>-IV insulin typically administered during labor | - Decrease insulin immediately post-partum due to high insulin sensitivity:<br>Up to 50% pre-pregnancy needs in T1DM, and consider stopping insulin in T2DM<br>- Metformin safe for breastfeeding |

**Abbreviations:** HbA1c=hemoglobin A1c; ACR=urine albumin-to-creatinine ratio; PCR=urine protein-to-creatinine ratio; CAD=coronary artery disease; CGM=continuous glucose monitoring, TSH=thyroid stimulating hormone; LARC=long-acting reversible contraception; T1DM=type 1 diabetes; OSA=obstructive sleep apnea; SMBG=self-monitoring of blood glucose; US=ultrasound; ICR=insulin-to-carbohydrate ratios; T2DM=type 2 diabetes; SU=sulfonylureas; TZD=thiazolidinediones; DPP4i=dipeptidyl peptidase 4 inhibitor; GLP-1RA=GLP-1 receptor agonist; SGLT2i=sodium glucose cotransporter 2 inhibitor; IU=international units; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; ASA=aspirin; PET=preeclampsia

[a]Metformin has been continued safely in some pregnancies, including in polycystic ovarian syndrome, although there is insufficient data to recommend use during pregnancy

[b] Accepted anti-hypertensive agents for use in pregnancy: labetalol, hydralazine, methyldopa, nifedipine