



13. Management of Diabetes in Pregnancy

American Diabetes Association

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For guidelines related to the diagnosis of gestational diabetes mellitus, please refer to Section 2 “Classification and Diagnosis of Diabetes.”

Recommendations

Preexisting Diabetes

- Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. **A**
- Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. **A**
- Preconception counseling should address the importance of glycemic control as close to normal as is safely possible, ideally A1C <6.5% (48 mmol/mol), to reduce the risk of congenital anomalies. **B**
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by degree of retinopathy and as recommended by the eye care provider. **B**

Gestational Diabetes Mellitus

- Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment for many women. Medications should be added if needed to achieve glycemic targets. **A**
- Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus, as it does not cross the placenta to a measurable extent. Metformin and glyburide may be used, but both cross the placenta to the fetus, with metformin likely crossing to a greater extent than glyburide. All oral agents lack long-term safety data. **A**
- Metformin, when used to treat polycystic ovary syndrome and induce ovulation, need not be continued once pregnancy has been confirmed. **A**

General Principles for Management of Diabetes in Pregnancy

- Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. **B**
- Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve glycemic control. Some women with preexisting diabetes should also test blood glucose preprandially. **B**
- Due to increased red blood cell turnover, A1C is lower in normal pregnancy than in normal nonpregnant women. The A1C target in pregnancy is 6–6.5% (42–48 mmol/mol); <6% (42 mmol/mol) may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia. **B**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. **E**

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DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. The majority is gestational diabetes mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. The rise in GDM and type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both type 1 diabetes and type 2 diabetes confer significantly greater maternal and fetal risk than GDM, with some differences according to type of diabetes as outlined below. In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. In addition, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life (1,2).

PRECONCEPTION COUNSELING

All women of childbearing age with diabetes should be counseled about the importance of tight glycemic control prior to conception. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, and caudal regression directly proportional to elevations in A1C during the first 10 weeks of pregnancy. Although observational studies are confounded by the association between elevated periconceptional A1C and other poor self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemic control prior to conception, with A1C <6.5% (48 mmol/mol) associated with the lowest risk of congenital anomalies (3,4).

There are opportunities to educate all women and adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and the opportunities for improved maternal and fetal outcomes with pregnancy planning (5). Effective preconception counseling could avert substantial health and associated cost burden in offspring (6). Family planning should be discussed, and effective contraception should be prescribed and used, until a woman is prepared and ready to become pregnant.

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all women with

diabetes of childbearing potential should receive education about 1) the risks of malformations associated with unplanned pregnancies and poor metabolic control and 2) the use of effective contraception at all times when preventing a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (5). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (7).

Preconception Testing

Preconception counseling visits should include rubella, syphilis, hepatitis B virus, and HIV testing, as well as Pap smear, cervical cultures, blood typing, prescription of prenatal vitamins (with at least 400 µg of folic acid), and smoking cessation counseling if indicated. Diabetes-specific testing should include A1C, thyroid-stimulating hormone, creatinine, and urinary albumin-to-creatinine ratio; review of the medication list for potentially teratogenic drugs, i.e., ACE inhibitors (8), angiotensin receptor blockers (8), and statins (9,10); and referral for a comprehensive eye exam. Women with preexisting diabetic retinopathy will need close monitoring during pregnancy to ensure that retinopathy does not progress.

GLYCEMIC TARGETS IN PREGNANCY

Pregnancy in women with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones.

Insulin Physiology

Early pregnancy is a time of insulin sensitivity, lower glucose levels, and lower insulin requirements in women with type 1 diabetes. The situation rapidly reverses as insulin resistance increases exponentially during the second and early third trimesters and levels off toward the end of the third trimester. In women with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain

normal glucose levels. However, in women with GDM and preexisting diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Preprandial testing is also recommended for women with preexisting diabetes using insulin pumps or basal-bolus therapy, so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (11–13). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by the American College of Obstetricians and Gynecologists (14), the ADA-recommended targets for women with type 1 or type 2 diabetes (the same as for GDM; described below) are as follows:

- Fasting ≤ 95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial ≤ 140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial ≤ 120 mg/dL (6.7 mmol/L)

These values represent optimal control if they can be achieved safely. In practice, it may be challenging for women with type 1 diabetes to achieve these targets without hypoglycemia, particularly women with a history of recurrent hyperglycemia or hypoglycemia unawareness.

If women cannot achieve these targets without significant hypoglycemia, the ADA suggests less stringent targets based on clinical experience and individualization of care.

A1C in Pregnancy

Observational studies show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4,15–17). Clinical trials have not evaluated the risks and benefits of achieving these targets, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized target of <6% (42 mmol/mol) to <7% (53 mmol/mol). Due to physiological increases in red

blood cell turnover, A1C levels fall during normal pregnancy (18,19). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic control, after self-monitoring of blood glucose.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants, whereas other adverse outcomes increase with A1C \geq 6.5% (48 mmol/mol). *Taking all of this into account, a target of 6–6.5% (42–48 mmol/mol) is recommended but <6% (42 mmol/mol) may be optimal as pregnancy progresses. These levels should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight. Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).*

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

GDM is characterized by increased risk of macrosomia and birth complications and an increased risk of maternal type 2 diabetes after pregnancy. The association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous, with no clear inflection points (20). In other words, risks increase with progressive hyperglycemia. Therefore, all women should be tested as outlined in Section 2 “Classification and Diagnosis of Diabetes.” Although there is some heterogeneity, many randomized controlled trials suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling (21,22).

Lifestyle Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, and glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (23):

- Fasting \leq 95 mg/dL (5.3 mmol/L) and either

- One-hour postprandial \leq 140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial \leq 120 mg/dL (6.7 mmol/L)

Depending on the population, studies suggest that 70–85% of women diagnosed with GDM under Carpenter-Coustan or National Diabetes Data Group (NDDG) criteria can control GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (24) diagnostic thresholds are used.

Pharmacologic Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacologic therapy. Treatment has been demonstrated to improve perinatal outcomes in two large randomized studies as summarized in a U.S. Preventive Services Task Force review (25). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual randomized controlled trials support the efficacy and short-term safety of metformin (26,27) and glyburide (28) for the treatment of GDM, both agents cross the placenta. Long-term safety data are not available for any oral agent (29).

Sulfonylureas

Concentrations of glyburide in umbilical cord plasma are approximately 70% of maternal levels (30). Glyburide may be associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin (31).

Metformin

Metformin may be associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin (31–33); however, metformin may slightly increase the risk of prematurity. Furthermore, nearly half of patients with GDM who were initially treated with metformin in a randomized trial needed insulin in order to achieve acceptable glucose control (26). Umbilical cord blood levels of metformin are higher than simultaneous maternal levels (34,35). None of these studies or meta-analyses evaluated long-term outcomes in the offspring. Patients treated with oral agents should be informed that they cross the placenta, and although no adverse effects on the fetus have been demonstrated, long-term studies are lacking.

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in women with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (36), and there is no evidence-based need to continue metformin in such patients once pregnancy has been confirmed (37–39).

Insulin

Insulin may be required to treat hyperglycemia, and its use should follow the guidelines below.

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Insulin is the preferred agent for management of both type 1 diabetes and type 2 diabetes in pregnancy.

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent self-monitoring of blood glucose. In the first trimester, there is often a decrease in total daily insulin requirements, and women, particularly those with type 1 diabetes, may experience increased hypoglycemia. In the second trimester, rapidly increasing insulin resistance requires weekly or biweekly increases in insulin dose to achieve glycemic targets. In general, a smaller proportion of the total daily dose should be given as basal insulin (<50%) and a greater proportion (>50%) as prandial insulin. In the late third trimester, there is often a leveling off or small decrease in insulin requirements. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including high-risk obstetrician, endocrinologist or other provider experienced in managing pregnancy in women with preexisting diabetes, dietitian, nurse, and social worker, as needed) is recommended if this resource is available.

None of the currently available insulin preparations have been demonstrated to cross the placenta.

Type 1 Diabetes

Women with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all women, have altered counterregulatory response in

pregnancy that may decrease hypoglycemia awareness. Education for patients and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help to prevent and manage the risks of hypoglycemia. Insulin resistance drops rapidly with delivery of the placenta. Women become very insulin sensitive immediately following delivery and may initially require much less insulin than in the perpartum period.

Pregnancy is a ketogenic state, and women with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis at lower blood glucose levels than in the nonpregnant state. Women with preexisting diabetes, especially type 1 diabetes, need ketone strips at home and education on diabetic ketoacidosis prevention and detection. In addition, rapid implementation of tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy (40).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for overweight women is 15–25 lb and for obese women is 10–20 lb (41). Glycemic control is often easier to achieve in women with type 2 diabetes than in those with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. As in type 1 diabetes, insulin requirements drop dramatically after delivery. The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better controlled and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in women with type 2 diabetes compared with the first trimester in women with type 1 diabetes (42,43).

POSTPARTUM CARE

Postpartum care should include psychosocial assessment and support for self-care.

Lactation

In light of the immediate nutritional and immunological benefits of breastfeeding for the baby, all women including

those with diabetes should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother (44) and offspring (45).

Gestational Diabetes Mellitus

Initial Testing

Because GDM may represent preexisting undiagnosed type 2 or even type 1 diabetes, women with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks' postpartum with a 75-g OGTT using nonpregnancy criteria as outlined in Section 2 "Classification and Diagnosis of Diabetes."

Postpartum Follow-up

The OGTT is recommended over A1C at the time of the 4- to 12-week postpartum visit because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy or blood loss at delivery and because the OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Reproductive-aged women with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with increased maternal risk for diabetes, women should also be tested every 1–3 years thereafter if the 4- to 12-week 75-g OGTT is normal, with frequency of testing depending on other risk factors including family history, prepregnancy BMI, and need for insulin or oral glucose-lowering medication during pregnancy. Ongoing evaluation may be performed with any recommended glycemic test (e.g., hemoglobin A1C, fasting plasma glucose, or 75-g OGTT using nonpregnant thresholds).

Gestational Diabetes Mellitus and Type 2 Diabetes

Women with a history of GDM have a greatly increased risk of conversion to type 2 diabetes over time and not solely within the 4- to 12-week postpartum time frame (46). In the prospective Nurses' Health Study II, subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns (47). Adjusting for BMI moderately, but not completely, attenuated this association. Interpregnancy or postpartum weight gain is associated with increased

risk of adverse pregnancy outcomes in subsequent pregnancies (48) and earlier progression to type 2 diabetes.

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with prediabetes and a history of GDM. Of women with a history of GDM and prediabetes, only 5–6 women need to be treated with either intervention to prevent one case of diabetes over 3 years (49). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (50). If the pregnancy has motivated the adoption of a healthier diet, building on these gains to support weight loss is recommended in the postpartum period.

Preexisting Type 1 and Type 2 Diabetes

Insulin sensitivity increases with delivery of the placenta and then returns to prepregnancy levels over the following 1–2 weeks. In women taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in women with preexisting diabetes due to the need for preconception glycemic control and preventive health services. Therefore, all women with diabetes of childbearing potential should have family planning options reviewed at regular intervals. This applies to women in the immediate postpartum period. Women with diabetes have the same contraception options and recommendations as those without diabetes. The risk of an unplanned pregnancy outweighs the risk of any given contraception option.

PREGNANCY AND DRUG CONSIDERATIONS

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, target goals for systolic blood pressure 120–160 mmHg and diastolic blood pressure 80–105 mmHg are reasonable (51). Lower blood pressure levels may

be associated with impaired fetal growth. In a 2015 study targeting diastolic blood pressure of 100 mmHg versus 85 mmHg in pregnant women, only 6% of whom had GDM at enrollment, there was no difference in pregnancy loss, neonatal care, or other neonatal outcomes, although women in the less intensive treatment group had a higher rate of uncontrolled hypertension (52).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, and intrauterine growth restriction (8). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (53). On the basis of available evidence, statins should also be avoided in pregnancy (54).

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