12. Management of Diabetes in Pregnancy

American Diabetes Association

Diabetes Care 2016;39(Suppl. 1):S94–S98 | DOI: 10.2337/dc16-S015

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

Recommendations

Pregestational Diabetes

- Provide preconception counseling that addresses 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**
- Family planning should be discussed and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant. **A**
- 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. Eye examinations should occur before pregnancy or in the first trimester and then be monitored every trimester and for 1 year postpartum as indicated by degree of retinopathy. **B**

Gestational Diabetes Mellitus

- Lifestyle change is an essential component of management of gestational diabetes mellitus and may suffice for treatment for many women. Medications should be added if needed to achieve glycemic targets. **A**
- Preferred medications in gestational diabetes mellitus are insulin and metformin; glyburide may be used but may have a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin. Other agents have not been adequately studied. Most oral agents cross the placenta, and all lack long-term safety data. **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, preprandial, and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and pregestational diabetes in pregnancy to achieve glycemic control. **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**

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 pregestational type 1 diabetes and type 2 diabetes. The rise in GDM and pregestational type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both pregestational type 1 diabetes and type 2 diabetes confer significantly greater maternal and fetal risk than GDM, with some differences according to type as outlined below. In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, intrauterine 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).

Suggested citation: American Diabetes Association. Management of diabetes in pregnancy. Sec. 12. In Standards of Medical Care in Diabetes—2016. *Diabetes Care 2016;39(Suppl. 1):S94–S98*

PRECONCEPTION COUNSELING

All women of childbearing age with diabetes should be counseled about the importance of near-normal 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.

Preconception Testing

Preconception counseling visits should address rubella, rapid plasma reagin, 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 testing; review of the medication list for potentially teratogenic drugs (i.e., ACE inhibitors, statins); and referral for a comprehensive eye exam.

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 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 pregestational type 2 diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, preprandial and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (7). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Nevertheless, the American College of Obstetricians and Gynecologists (ACOG) (8) recommends the following targets for women with pregestational type 1 or type 2 diabetes:

- Fasting ≤90 mg/dL (5.0 mmol/L)
- One-hour postprandial ≤130–140 mg/dL (7.2–7.8 mmol/L)
- 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 severe hypoglycemia or hypoglycemia unawareness.

If women cannot achieve these targets without significant hypoglycemia, the American Diabetes Association (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 (4,9–11). 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 (12). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, while A1C may be useful, it should be used as a secondary measure, after self-monitoring of blood glucose.

In the second and third trimester, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants, whereas other adverse outcomes increase with A1C ≥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 diabetes after pregnancy. The association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous, with no clear inflection points (13). In other words, risks increase with progressive hyperglycemia. Therefore, all women should be screened 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 (14,15).

Lifestyle Management

After diagnosis, treatment starts with medical nutrition therapy, physical

activity, and weight management depending on pregestational weight, as outlined in the section on pregestational type 2 diabetes below, and glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (16):

- 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)

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 increase using the lower International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (17) diagnostic thresholds.

Pharmacological Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacological 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 (18). Insulin is the first-line agent recommended for treatment of GDM in the U.S. Individual randomized controlled trials support the efficacy and short-term safety of metformin (19,20) (pregnancy category B) and glyburide (21) (pregnancy category B) for the treatment of GDM. However, both agents cross the placenta, and long-term safety data are not available for either agent (22).

Sulfonylureas

More recently, several meta-analyses and large observational studies examining maternal and fetal outcomes have suggested that sulfonylureas, such as glyburide, may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia with this class.

Metformin

Metformin, which is associated with a lower risk of hypoglycemia and potential lower weight gain, may be preferable to insulin for maternal health if it suffices to control hyperglycemia (23–25); however, metformin may slightly increase the risk of prematurity. None of these studies or meta-analyses evaluated long-term outcomes in the offspring. Thus, patients treated with oral agents should be informed that they cross the placenta and, while no adverse effects on the fetus have been demonstrated, long-term studies are lacking.

Insulin

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

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

Insulin Use

Insulin is the preferred agent for management of pregestational type 1 diabetes and type 2 diabetes that are not adequately controlled with diet, exercise, and metformin.

The physiology of pregnancy requires frequent titration of insulin to match changing requirements. 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, dietitian, nurse, and social worker, as needed) is recommended if this resource is available.

All insulins are pregnancy category B except for glargine, glulisine, and degludec, which are labeled category C.

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. Hypoglycemia education for patients and family members is important before and during early pregnancy and throughout 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 prepartum 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. All insulin-deficient women 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 (26).

Type 2 Diabetes

Pregestational 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. Glycemic control is often easier to achieve in type 2 diabetes than in 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. Associated hypertension and other comorbidities often render pregestational type 2 diabetes as high or higher risk than pregestational type 1 diabetes, even if the diabetes is better controlled and of shorter duration, with pregnancy loss appearing to be more prevalent in the third trimester in type 2 diabetes compared with the first trimester in type 1 diabetes (27,28).

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 (29) and offspring (30).

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 6–12 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 6- 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. Because GDM is associated with increased maternal risk for diabetes, women should also be tested every 1–3 years thereafter if 6- to 12-week 75-g OGTT is normal, with frequency of screening depending on other risk factors including family history, prepregnancy BMI, and need for insulin or oral glucose-lowering medication during pregnancy. Ongoing screening 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 6- to 12-week postpartum time frame (31). 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 (32). 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 (33) 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 impaired glucose tolerance, only 5–6 individuals need to be treated with either intervention to prevent one case of diabetes over 3 years (34). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (35).

Pregestational 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 is needed to hypoglycemia prevention in the setting of erratic sleep and eating schedules. 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.

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 pregestational diabetes due to the need for preconception glycemic control and preventive health services. Therefore, all women with diabetes of childbearing age 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 ANTIHYPERTENSIVE DRUGS

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, target goals of systolic blood pressure 110–129 mmHg and diastolic blood pressure 65–79 mmHg are reasonable. 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 (36).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated, because they may cause fetal renal dysplasia, oligohydramnios, and intrauterine growth restriction. 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 (37).

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