

# 14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc21-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc21-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at [professional.diabetes.org/SOC](https://professional.diabetes.org/SOC).

## DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in women of reproductive age, but there is also a dramatic increase in the reported rates of gestational diabetes mellitus. Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy may increase the risk of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

## PRECONCEPTION COUNSELING

### Recommendations

- 14.1** Starting at puberty and continuing in all women with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. **A**
- 14.2** Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until a woman’s treatment regimen and A1C are optimized for pregnancy. **A**
- 14.3** Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C <6.5% (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **B**

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All women of childbearing age with diabetes should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (3). Although observational studies are confounded by the association between elevated periconceptional A1C and other poor self-care behavior, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception, given that organogenesis occurs primarily at 5–8 weeks of gestation, with an A1C <6.5% (48 mmol/mol) being associated with the lowest risk of congenital anomalies, preeclampsia, and preterm birth (3–7).

There are opportunities to educate all women and adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (8). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (9). Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant (10–14).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all girls and women with diabetes of childbearing potential should receive education about 1) the risks of malformations associated with unplanned pregnancies and even mild hyperglycemia 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 (8). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (15).

#### Preconception Care

##### Recommendations

**14.4** Women with preexisting diabetes who are planning a pregnancy

should ideally be managed beginning in preconception in a multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**

**14.5** In addition to focused attention on achieving glycemic targets **A**, standard preconception care should be augmented with extra focus on nutrition, diabetes education, and screening for diabetes comorbidities and complications. **E**

**14.6** 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 ideally before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care provider. **B**

The importance of preconception care for all women is highlighted by the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, Prepregnancy Counseling (16). A key point is the need to incorporate a question about a woman's plans for pregnancy into routine primary and gynecologic care. The preconception care of women with diabetes should include the standard screenings and care recommended for all women planning pregnancy (16). Prescription of prenatal vitamins (with at least 400  $\mu\text{g}$  of folic acid and 150  $\mu\text{g}$  of potassium iodide [17]) is recommended prior to conception. Review and counseling on the use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications and supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus, as outlined by ACOG. See

**Table 14.1** for additional details on elements of preconception care (16,18). Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to a registered dietitian nutritionist (RD/RDN), is recommended when indicated.

Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancy and the ways to reduce risk including glycemic goal setting, lifestyle management, and medical nutrition therapy. The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs (i.e., ACE inhibitors [19,20], angiotensin receptor blockers [19], and statins [21,22]). A referral for a comprehensive eye exam is recommended. Women with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess for progression of retinopathy and provide treatment if indicated (23).

Several studies have shown improved diabetes and pregnancy outcomes when care has been delivered from preconception through pregnancy by a multidisciplinary group focused on improved glycemic control (24–27). One study showed that care of preexisting diabetes in clinics that included diabetes and obstetric specialists improved care (27). However, there is no consensus on the structure of multidisciplinary team care for diabetes and pregnancy, and there is a lack of evidence on the impact on outcomes of various methods of health care delivery (28).

#### GLYCEMIC TARGETS IN PREGNANCY

##### Recommendations

**14.7** Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve optimal glucose levels. Glucose targets are fasting plasma glucose <95 mg/dL (5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (7.8 mmol/L) or 2-h postprandial

glucose <120 mg/dL (6.7 mmol/L). Some women with preexisting diabetes should also test blood glucose preprandially. **B**

**14.8** Due to increased red blood cell turnover, A1C is slightly lower in normal pregnancy than in normal nonpregnant women. Ideally, the A1C target in pregnancy is <6% (42 mmol/mol) 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**

**14.9** When used in addition to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**

**14.10** When used in addition to self-monitoring of blood glucose targeting traditional pre- and postprandial targets, continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **B**

**14.11** Continuous glucose monitoring metrics may be used as an adjunct but should not be used as a substitute for self-monitoring of blood glucose to achieve optimal pre- and postprandial glycemic targets. **E**

**14.12** Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**

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 mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones. In patients with preexisting diabetes, glycemic targets are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic targets in pregnancy are stricter than in nonpregnant individuals, it is important that women with diabetes eat consistent

**Table 14.1—Checklist for preconception care for women with diabetes (16,18)**

**Preconception education should include:**

- Comprehensive nutrition assessment and recommendations for:
  - Overweight/obesity or underweight
  - Meal planning
  - Correction of dietary nutritional deficiencies
  - Caffeine intake
  - Safe food preparation technique
- Lifestyle recommendations for:
  - Regular moderate exercise
  - Avoidance of hyperthermia (hot tubs)
  - Adequate sleep
- Comprehensive diabetes self-management education
- Counseling on diabetes in pregnancy per current standards, including: natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in patients with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
- Supplementation
  - Folic acid supplement (400 µg routine)
  - Appropriate use of over-the-counter medications and supplements

**Medical assessment and plan should include:**

- General evaluation of overall health
- Evaluation of diabetes and its comorbidities and complications, including: DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- Evaluation of obstetric/gynecologic history, including history of: cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- Review of current medications and appropriateness during pregnancy

**Screening should include:**

- Diabetes complications and comorbidities, including: comprehensive foot exam; comprehensive ophthalmologic exam; ECG in women starting at age 35 years who have cardiac signs/symptoms or risk factors, and if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio
- Anemia
- Genetic carrier status (based on history):
  - Cystic fibrosis
  - Sickle cell anemia
  - Tay-Sachs disease
  - Thalassemia
  - Others if indicated
- Infectious disease
  - *Neisseria gonorrhoea/Chlamydia trachomatis*
  - Hepatitis C
  - HIV
  - Pap smear
  - Syphilis

**Immunizations should include:**

- Rubella
- Varicella
- Hepatitis B
- Influenza
- Others if indicated

**Preconception plan should include:**

- Nutrition and medication plan to achieve glycemic targets prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
- Contraceptive plan to prevent pregnancy until glycemic targets are achieved
- Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including: hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RD/RDN is important in order to establish a food plan and insulin-to-carbohydrate ratio and to determine weight gain goals.

### Insulin Physiology

Given that early pregnancy is a time of enhanced insulin sensitivity and lower glucose levels, many women with type 1 diabetes will have lower insulin requirements and increased risk for hypoglycemia (29). Around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly ~5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. The insulin requirement levels off toward the end of the third trimester with placental aging. A rapid reduction in insulin requirements can indicate the development of placental insufficiency (30). 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 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 when 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 (31–33). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by ACOG (upper limits are the same as for gestational diabetes mellitus [GDM], described below) (34), the ADA-recommended targets for women with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Lower limits are based on the mean of normal blood glucoses in pregnancy (35). Lower limits do not apply to diet-controlled type 2 diabetes. Hypoglycemia in pregnancy is as defined and treated in Recommendations 6.9–6.14 (Section 6 “Glycemic Targets,” <https://doi.org/10.2337/dc21-S006>). 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 hypoglycemia 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

In studies of women without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (36). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (37). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4–6,38). 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 (39,40). 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 in pregnancy, 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 (38,41,42), preterm delivery (43), and preeclampsia (1,44). Taking all of this into account, a target of <6% (42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. The A1C target in a given

patient should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (45). 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).

### Continuous Glucose Monitoring in Pregnancy

CONCEPTT (Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial) was a randomized controlled trial of continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose targets versus standard care for pregnant women with type 1 diabetes. It demonstrated the value of CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (46). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (47). Use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (48). CGM time in range (TIR) can be used for assessment of glycemic control in patients with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. There are no data to support the use of TIR in women with type 2 diabetes or GDM.

The international consensus on time in range (49) endorses pregnancy target ranges and goals for TIR for patients with type 1 diabetes using CGM as reported on the ambulatory glucose profile.

- Target range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- Time below range (<63 mg/dL [3.5 mmol/L]), goal <4%
- Time below range (<54 mg/dL [3.0 mmol/L]), goal <1%



- Time above range (>140 mg/dL [7.8 mmol/L]), goal <25%.

## MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

### Recommendations

- 14.13** Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment of many women. Insulin should be added if needed to achieve glycemic targets. **A**
- 14.14** Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.
- 14.15** Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

GDM is characterized by increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and offspring abnormal glucose metabolism in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (37,50). Offspring with exposure to untreated GDM have reduced insulin sensitivity and  $\beta$ -cell compensation and are more likely to have impaired glucose tolerance in childhood (51). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all women should be tested as outlined in Section 2 “Classification and Diagnosis of Diabetes” (<https://doi.org/10.2334/dc21-S002>). Although there is some heterogeneity, many randomized controlled trials (RCTs) suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester (52–54). There are no intervention trials in offspring of mothers with GDM.

### 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, as well as glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (54):

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

Glycemic target lower limits defined above for preexisting diabetes apply for GDM that is treated with insulin. Depending on the population, studies suggest that 70–85% of women diagnosed with GDM under Carpenter-Coustan 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 (55) diagnostic thresholds are used.

### Medical Nutrition Therapy

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the woman and an RD/RDN familiar with the management of GDM (56,57). The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote weight gain according to 2009 Institute of Medicine recommendations (58). There is no definitive research that identifies a specific optimal calorie intake for women with GDM or suggests that their calorie needs are different from those of pregnant women without GDM. The food plan should be based on a nutrition assessment with guidance from the Dietary Reference Intakes (DRI). The DRI for all pregnant women recommends a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber. The diet should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in patients with diabetes, the amount and type of carbohydrate will impact glucose levels. Simple carbohydrates will result in higher postmeal excursions.

### Pharmacologic Therapy

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large randomized studies as summarized in a U.S. Preventive Services Task Force review (59). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (60,61) and glyburide (62) in reducing glucose levels for the treatment of GDM, these agents are not recommended as first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (34). Furthermore, glyburide and metformin failed to provide adequate glycemic control in separate RCTs in 23% and 25–28% of women with GDM, respectively (63,64).

### Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (63,64). Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin in a 2015 meta-analysis and systematic review (65).

More recently, glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (66). Long-term safety data for offspring exposed to glyburide are not available (66).

### Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (65,67–69). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (70,71). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study’s analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin in the Auckland cohort for the treatment of GDM were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (72). This was not found in the Adelaide cohort. In two RCTs of metformin use in pregnancy for polycystic ovary

syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (73,74). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass (74,75). Metformin is being studied in two ongoing trials in type 2 diabetes (Metformin in Women with Type 2 Diabetes in Pregnancy Trial [MiTY] [76] and Medical Optimization of Management of Type 2 Diabetes Complicating Pregnancy [MOMPOD] [77]), but long-term offspring data will not be available for some time. A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with acceleration of postnatal growth resulting in higher BMI in childhood (74).

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 (78), and there is no evidence-based need to continue metformin in such patients (79–81).

There are some women with GDM requiring medical therapy who, due to cost, language barriers, comprehension, or cultural influences, may not be able to use insulin safely or effectively in pregnancy. Oral agents may be an alternative in these women after a discussion of the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in women with hypertension or preeclampsia or at risk for intrauterine growth restriction (82,83).

#### Insulin

Insulin use should follow the guidelines below. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy (84).

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

#### Insulin Use

##### Recommendations

**14.16** Insulin should be used for management of type 1 diabetes in

pregnancy. **A** Insulin is the preferred agent for the management of type 2 diabetes in pregnancy. **E**

**14.17** Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. **C**

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. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including maternal-fetal medicine specialist, 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 human insulin preparations have been demonstrated to cross the placenta (84–89). A recent Cochrane systematic review was not able to recommend any specific insulin regimen over another for the treatment of diabetes in pregnancy (90).

While many providers prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (91,92). Hybrid closed-loop insulin pumps that allow for the achievement of pregnancy fasting and postprandial glycemic targets may reduce hypoglycemia and allow for more aggressive prandial dosing to achieve targets. Not all hybrid closed-loop pumps are able to achieve the pregnancy targets.

#### 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.

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 (DKA) at lower blood glucose levels than in the nonpregnant state. Women with type 1 diabetes should be prescribed ketone strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Women in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (23).

#### Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for women with overweight is 15–25 lb and for women with obesity is 10–20 lb (58). There are no adequate data on optimal weight gain versus weight maintenance in women with BMI >35 kg/m<sup>2</sup>.

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 (93,94).

### PREECLAMPSIA AND ASPIRIN

#### Recommendation

**14.18** Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable; currently in the U.S., low-dose aspirin is available in 81-mg tablets. **E**

Diabetes in pregnancy is associated with an increased risk of preeclampsia (95). The U.S. Preventive Services Task Force recommends the use of low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in women who are at high risk for preeclampsia (96). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin <100 mg is not effective in reducing preeclampsia. Low-dose aspirin >100 mg is required (97–99). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (100). However, there is insufficient data regarding the benefits of aspirin in women with preexisting diabetes (98). More studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (101).

## PREGNANCY AND DRUG CONSIDERATIONS

### Recommendations

- 14.19** In pregnant patients with diabetes and chronic hypertension, a blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension **A** and minimizing impaired fetal growth. **E**
- 14.20** Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor blockers, statins) should be stopped at conception and avoided in sexually active women of childbearing age who are not using reliable contraception. **B**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, a target goal blood pressure of 110–135/85 mmHg is suggested to reduce the risk of uncontrolled maternal hypertension and minimize impaired fetal growth (102–104). The 2015 study (104) excluded pregnancies complicated by preexisting diabetes and only 6% had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight control of hypertension (104).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor

blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (19).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (20). However, ACE inhibitors and angiotensin receptor blockers should be stopped as soon as possible in the first trimester to avoid second and third trimester fetopathy (20). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other  $\beta$ -blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (105). On the basis of available evidence, statins should also be avoided in pregnancy (106).

See PREGNANCY AND ANTIHYPERTENSIVE MEDICATIONS in Section 10 “Cardiovascular Disease and Risk Management” (<https://doi.org/10.2337/dc21-S010>) for more information on managing blood pressure in pregnancy.

## POSTPARTUM CARE

### Recommendations

- 14.21** Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. **C**
- 14.22** A contraceptive plan should be discussed and implemented with all women with diabetes of reproductive potential. **A**
- 14.23** Screen women with a recent history of gestational diabetes mellitus at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**
- 14.24** Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

- 14.25** Women with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**
- 14.26** Women with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**
- 14.27** Postpartum care should include psychosocial assessment and support for self-care. **E**

## Gestational Diabetes Mellitus

### Initial Testing

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing 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” (<https://doi.org/10.2334/dc21-S002>).

### Postpartum Follow-up

The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Women of reproductive age with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–60% (107,108), women should also be tested every 1–3 years thereafter if the 4–12 weeks postpartum 75-g OGTT is normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 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 (108). Women with GDM have a 10-fold increased risk of developing type 2 diabetes compared with women without GDM (107). Absolute risk increases linearly through a woman's lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (108). In the prospective Nurses' Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns (109). Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy or postpartum weight gain is associated with increased risk of adverse pregnancy outcomes in subsequent pregnancies (110) 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 (111). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (112). 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 dramatically with delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (113,114). Insulin sensitivity 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 (115).

#### 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 (116) and offspring (117). However, lactation can

increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

#### 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 to prevent congenital malformations and reduce the risk of other complications. Therefore, all women with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to women in the immediate postpartum period. Women with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversible contraception may be ideal for many women. The risk of an unplanned pregnancy outweighs the risk of any given contraception option.

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