



15. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2022*

American Diabetes Association
Professional Practice Committee*

Diabetes Care 2022;45(Suppl. 1):S232–S243 | <https://doi.org/10.2337/dc22-S015>

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/dc22-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/dc22-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at 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 (GDM). 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

- 15.1** Starting at puberty and continuing in all women with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. **A**
- 15.2** 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**
- 15.3** Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C <6.5%

*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at <https://doi.org/10.2337/dc22-SPPC>.

Suggested citation: American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45(Suppl. 1):S232–S243

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(48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **A**

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 preconceptional 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). A systematic review and meta-analysis of observational studies of preconception care for women with preexisting diabetes demonstrated lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admission (8).

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 (9). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (10). 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 (11–15).

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 (9). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (16).

Preconception Care

Recommendations

- 15.4** 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**
- 15.5** 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**
- 15.6** 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, “Pregnancy Counseling” (17). 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 (17). Prescription of prenatal vitamins (with at least 400 µg of folic acid and 150 µg of potassium iodide [18]) 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 15.1** for additional details on elements of preconception care (17,19). 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 and behavioral 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 [20,21], angiotensin receptor blockers [20], and statins [22,23]). 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 (24).

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 (25–28). One study showed that care of preexisting diabetes in clinics that included diabetes

and obstetric specialists improved care (28). 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 (29).

GLYCEMIC TARGETS IN PREGNANCY

Recommendations

15.7 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**

15.8 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**

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

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

15.11 Continuous glucose monitoring metrics may be used in addition to but should not be used as a substitute for

Table 15.1—Checklist for preconception care for women with diabetes (17,19)

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.

self-monitoring of blood glucose to achieve optimal pre- and postprandial glycemic targets. **E**

15.12 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 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 an increased risk for hypoglycemia (30). 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 pre-pregnancy 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 (31). 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 a lower risk of preeclampsia (32–34). 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 GDM, described below) (35), 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 glucose in pregnancy (36). 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/dc22-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 (37). In the Hyperglycemia and Adverse Pregnancy Outcome

(HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (38). 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 (4–6,39). 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 (40,41). 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 blood glucose monitoring.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants (39,42,43), preterm delivery (44), and preeclampsia (1,45). 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 (46). 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 (RCT) of real-time 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 real-time 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 (47). 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 (48). 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 (49). 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 (50) endorses pregnancy target ranges and goals for TIR for patients with type 1 diabetes using CGM as reported on the ambulatory glucose profile; however, it does not specify the type or accuracy of the device or need for alarms and alerts. Selection of CGM device should be individualized based on patient circumstances.

- 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

15.13 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**

15.14 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.

15.15 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

15.16 Telehealth visits for pregnant women with gestational diabetes mellitus improve outcomes compared with standard in-person care. **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 (38,51). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β -cell compensation and are more likely to have impaired glucose tolerance in childhood (52). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all women should be screened as outlined in Section 2, “Classification and Diagnosis of Diabetes” (<https://doi.org/10.2337/dc22-S002>). Although there is some heterogeneity, many RCTs and a Cochrane review 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 (53–55). There are no intervention trials in offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk women with obesity, polycystic ovary syndrome, or preexisting insulin resistance (56). A meta-analysis of 32 RCTs evaluating the effectiveness of telehealth visits for GDM demonstrated reduction of incidences of cesarean delivery, neonatal hypoglycemia, premature rupture of membranes, macrosomia, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhy-

dramnios compared with standard in-person care (57).

Lifestyle and Behavioral 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 (58):

- 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 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 (59) 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 (60,61). 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 (62). 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. The current recommended amount of carbohydrate is 175 g, or ~35% of a 2,000-calorie diet. Liberalizing higher quality, nutrient-dense carbohydrates results in controlled fasting/postprandial glucose, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity. Mothers who substitute fat for carbohydrate may unintentionally enhance lipolysis, promote elevated free fatty acids, and worsen maternal insulin resistance (63,64). Fasting urine ketone testing may be useful to identify women who are severely restricting carbohydrates to control blood glucose. Simple carbohydrates will result in higher post-meal excursions.

Physical Activity

A systematic review demonstrated improvements in glucose control and reductions in need to start insulin or insulin dose requirements with an exercise intervention. There was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity) (65).

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 (66). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (67,68) and glyburide (69) 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 (35). Furthermore, glyburide and metformin failed to provide adequate glycemic control in separate RCTs in 23% and 25–28% of women with GDM, respectively (70,71).

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 (70,71). Glyburide was associated with a higher rate of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference than insulin or metformin in meta-analyses and systematic reviews (72,73).

Glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (74). Long-term safety data for offspring exposed to glyburide are not available (74).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (72,75–77). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (78,79). 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 for the treatment of GDM in the Auckland cohort were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (80). This difference 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 (81,82). 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 (82,83). A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood (82).

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

(84), and there is no evidence-based need to continue metformin in such patients (85–87).

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 (88,89).

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 (90).

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

Insulin Use

Recommendations

15.17 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. **B**

15.18 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 blood glucose monitoring. 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 (90–95). Insulins studied in RCTs are preferred (96–99) over those studied in cohort studies (100), which are preferred over those studied in case reports only.

While many providers prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (101,102). 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. None of the current hybrid closed-loop insulin pump systems achieve pregnancy targets. However, predictive low glucose suspend (PLGS) technology has been shown in nonpregnant people to be better than sensor augment technology (SAP) for reducing low glucoses (103). It may be suited for pregnancy because the predict low glucose threshold for suspending insulin is in the range of premeal and overnight glucoses targets in pregnancy and may allow for more aggressive prandial dosing.

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 (24).

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 (62). There are no adequate data on optimal weight gain versus weight maintenance in women with BMI >35 kg/m².

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. Insulin is the preferred treatment for type 2 diabetes in pregnancy. An RCT of metformin added to insulin for the treatment of type 2 diabetes found less maternal weight gain and fewer cesarean births. There were fewer macrosomic neonates, but there was a doubling of small-for-gestational-age neonates (104). 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 (105,106).

PRECLAMPSIA AND ASPIRIN

Insulin Use

Recommendation

15.19 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 **E**; currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Diabetes in pregnancy is associated with an increased risk of preeclampsia (107). 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 (108). 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 (109–111). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (112). However, there are insufficient data regarding the benefits of aspirin in women with preexisting diabetes (110). More studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (113).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

15.20 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**

15.21 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 child-bearing 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 (114–116). The 2015 study (116) 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 (116).

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 (20).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (21). 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 (21). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β -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 (117). On the basis of available evidence, statins should also be avoided in pregnancy (118).

See pregnancy and antihypertensive medications in Section 10, "Cardiovascular Disease and Risk Management" (<https://doi.org/10.2337/dc22-S010>), for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

- 15.22** 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**
- 15.23** A contraceptive plan should be discussed and implemented with all women with diabetes of reproductive potential. **A**
- 15.24** 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**

- 15.25** Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**
- 15.26** 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**
- 15.27** 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**
- 15.28** 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 fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, "Classification and Diagnosis of Diabetes" (<https://doi.org/10.2337/dc22-S002>), specifically **Table 2.2**. In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥ 126 mg/dL [7.0 mmol/L]) and 2-h plasma glucose (≥ 200 mg/dL [11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists.

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% (119,120), 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 (120). Women with GDM have a 10-fold increased risk of developing type 2 diabetes compared with women without GDM (119). 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 (120). 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 (121). 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 (122) 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 (123). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (124). 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 (125). 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 (126).

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 (127) and offspring (128). 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.

References

- Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000;49:2208–2211
- Holmes VA, Young IS, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, pre-

eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care* 2011;34:1683–1688

- Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care* 2007;30:1920–1925
- Jensen DM, Korsholm L, Ovesen P, et al. Periconceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009;32:1046–1048
- Nielsen GL, Møller M, Sørensen HT. HbA_{1c} in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes Care* 2006;29:2612–2616
- Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia* 2000;43:79–82
- Ludvigsson JF, Neovius M, Söderling J, et al. Maternal glycemic control in type 1 diabetes and the risk for preterm birth: a population-based cohort study. *Ann Intern Med* 2019;170:691–701
- Wahabi HA, Fayed A, Esmail S, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. *PLoS One* 2020;15:e0237571
- Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. *Diabetes Care* 2013;36:3870–3874
- Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. *Am J Obstet Gynecol* 2015;212:74.e1–74.e9
- Britton LE, Hussey JM, Berry DC, Crandell JL, Brooks JL, Bryant AG. Contraceptive use among women with prediabetes and diabetes in a US national sample. *J Midwifery Womens Health* 2019;64:36–45
- Morris JR, Tepper NK. Description and comparison of postpartum use of effective contraception among women with and without diabetes. *Contraception* 2019;100:474–479
- Goldstuck ND, Steyn PS. The intrauterine device in women with diabetes mellitus type i and ii: a systematic review. *ISRN Obstet Gynecol* 2013;2013:814062
- Wu JP, Moniz MH, Ursu AN. Long-acting reversible contraception—highly efficacious, safe, and underutilized. *JAMA* 2018;320:397–398
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 201: Pregestational diabetes mellitus. *Obstet Gynecol* 2018;132:e228–e248
- Charron-Prochownik D, Downs J. Diabetes and Reproductive Health for Girls. Alexandria, VA, American Diabetes Association, 2016
- American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice; American Society for Reproductive Medicine. ACOG Committee Opinion No. 762: Prepregnancy counseling. *Obstet Gynecol* 2019;133:e78–e89

- Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;27:315–389
- Ramos DE. Preconception health: changing the paradigm on well-woman health. *Obstet Gynecol Clin North Am* 2019;46:399–408
- Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. *Hypertension* 2012;60:444–450
- Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol* 2017;129:174–184
- Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. *Reprod Toxicol* 2008;26:175–177
- Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ* 2015;350:h1035
- Chew EY, Mills JL, Metzger BE, et al.; National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Metabolic control and progression of retinopathy. *The Diabetes in Early Pregnancy Study*. *Diabetes Care* 1995;18:631–637
- McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med* 2000;9:14–20
- Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. *Diabetes Care* 2010;33:2514–2520
- Elixhauser A, Weschler JM, Kitzmiller JL, et al. Cost-benefit analysis of preconception care for women with established diabetes mellitus. *Diabetes Care* 1993;16:1146–1157
- Owens LA, Avalos G, Kirwan B, Carmody L, Dunne F. ATLANTIC DIP: closing the loop: a change in clinical practice can improve outcomes for women with pregestational diabetes. *Diabetes Care* 2012;35:1669–1671
- Taylor C, McCance DR, Chappell L, et al. Implementation of guidelines for multidisciplinary team management of pregnancy in women with pre-existing diabetes or cardiac conditions: results from a UK national survey. *BMC Pregnancy Childbirth* 2017;17:434
- García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia* 2010;53:446–451
- Padmanabhan S, Lee VW, Mclean M, et al. The association of falling insulin requirements with maternal biomarkers and placental dysfunction: a prospective study of women with preexisting diabetes in pregnancy. *Diabetes Care* 2017;40:1323–1330
- Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR. Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized

- controlled clinical trial. *Am J Obstet Gynecol* 2003;189:507–512
33. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 1995;333:1237–1241
34. Jovanovic-Peterson L, Peterson CM, Reed GF, et al.; National Institute of Child Health and Human Development—Diabetes in Early Pregnancy Study. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991;164:103–111
35. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational diabetes mellitus. *Obstet Gynecol* 2018;131:e49–e64
36. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? *Diabetes Care* 2011;34:1660–1668
37. Ho Y-R, Wang P, Lu M-C, Tseng S-T, Yang C-P, Yan Y-H. Associations of mid-pregnancy HbA_{1c} with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. *PLoS One* 2017;12:e0177563
38. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
39. Maresh MJA, Holmes VA, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* 2015;38:34–42
40. Nielsen LR, Ekbohm P, Damm P, et al. HbA_{1c} levels are significantly lower in early and late pregnancy. *Diabetes Care* 2004;27:1200–1201
41. Mosca A, Paleari R, Dalfrà MG, et al. Reference intervals for hemoglobin A_{1c} in pregnant women: data from an Italian multicenter study. *Clin Chem* 2006;52:1138–1143
42. Hummel M, Marienfeld S, Huppmann M, et al. Fetal growth is increased by maternal type 1 diabetes and HLA DR4-related gene interactions. *Diabetologia* 2007;50:850–858
43. Cyganek K, Skupien J, Katra B, et al. Risk of macrosomia remains glucose-dependent in a cohort of women with pregestational type 1 diabetes and good glycemic control. *Endocrine* 2017;55:447–455
44. Abell SK, Boyle JA, de Courten B, et al. Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes. *Aust N Z J Obstet Gynaecol* 2017;57:308–314
45. Temple RC, Aldridge V, Stanley K, Murphy HR. Glycaemic control throughout pregnancy and risk of pre-eclampsia in women with type 1 diabetes. *BJOG* 2006;113:1329–1332
46. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 1992;15:1251–1257
47. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPT): a multicentre international randomised controlled trial. *Lancet* 2017;390:2347–2359
48. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. *Diabetologia* 2019;62:1143–1153
49. Law GR, Gilthorpe MS, Secher AL, et al. Translating HbA_{1c} measurements into estimated average glucose values in pregnant women with diabetes. *Diabetologia* 2017;60:618–624
50. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42:1593–1603
51. Scholtens DM, Kuang A, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group; HAPO Follow-Up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal glycemia and childhood glucose metabolism. *Diabetes Care* 2019;42:381–392
52. Lowe WL Jr, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care* 2019;42:372–380
53. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational diabetes mellitus can be prevented by lifestyle intervention: the Finnish Gestational Diabetes Prevention Study (RADIEL): a randomized controlled trial. *Diabetes Care* 2016;39:24–30
54. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol* 2017;216:340–351
55. Griffith RJ, Alsweller J, Moore AE, et al. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2020;6:CD012394
56. Doi SAR, Furuya-Kanamori L, Toft E, et al. Metformin in pregnancy to avert gestational diabetes in women at high risk: meta-analysis of randomized controlled trials. *Obes Rev* 2020;21:e12964
57. Xie W, Dai P, Qin Y, Wu M, Yang B, Yu X. Effectiveness of telemedicine for pregnant women with gestational diabetes mellitus: an updated meta-analysis of 32 randomized controlled trials with trial sequential analysis. *BMC Pregnancy Childbirth* 2020;20:198
58. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 2007;30(Suppl. 2):S251–S260
59. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the International Association of Diabetes in Pregnancy Study Group criteria for the screening and diagnosis of gestational diabetes. *Am J Obstet Gynecol* 2015;212:224.e1–224.e9
60. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. *Cochrane Database Syst Rev* 2013;3:CD009275
61. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. *Diabetes Care* 2014;37:3345–3355
62. Institute of Medicine and National Research Council. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, D.C., National Academies Press, 2009
63. Hernandez TL, Mande A, Barbour LA. Nutrition therapy within and beyond gestational diabetes. *Diabetes Res Clin Pract* 2018;145:39–50
64. Hernandez TL, Van Pelt RE, Anderson MA, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. *Diabetes Care* 2014;37:1254–1262
65. Laredo-Aguilera JA, Gallardo-Bravo M, Rabanales-Sotos JA, Cobo-Cuenca AI, Carmona-Torres JM. Physical activity programs during pregnancy are effective for the control of gestational diabetes mellitus. *Int J Environ Res Public Health* 2020;17:E6151
66. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med* 2013;159:123–129
67. Rowan JA, Hague WM, Gao W, Battin MR; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358:2003–2015
68. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2013;8:e64585
69. Langer O, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343:1134–1138
70. Hebert MF, Ma X, Naraharisetty SB, et al.; Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther* 2009;85:607–614
71. Malek R, Davis SN. Pharmacokinetics, efficacy and safety of glyburide for treatment of gestational diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2016;12:691–699
72. Balsells M, Garcia-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015;350:h102
73. Tarry-Adkins JL, Aiken CE, Ozanne SE. Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: a systematic review and meta-analysis. *PLoS Med* 2020;17:e1003126
74. Sénat M-V, Affres H, Letourneau A, et al.; Groupe de Recherche en Obstétrique et Gynécologie (GROG). Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. *JAMA* 2018;319:1773–1780
75. Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet* 2010;111:37–40

76. Nachum Z, Zafran N, Salim R, et al. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. *Diabetes Care* 2017;40:332–337
77. Jiang Y-F, Chen X-Y, Ding T, Wang X-F, Zhu Z-N, Su S-W. Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2015;100:2071–2080
78. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril* 2005;83:1575–1578
79. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006;28:67–72
80. Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. *BMJ Open Diabetes Res Care* 2018;6:e000456
81. Hanem LGE, Stridsklev S, Júlíusson PB, et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs. *J Clin Endocrinol Metab* 2018;103:1612–1621
82. Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: a systematic review and meta-analysis. *PLoS Med* 2019;16:e1002848
83. Hanem LGE, Salvesen Ø, Júlíusson PB, et al. Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5–10 year follow-up of the PregMet randomised controlled trial. *Lancet Child Adolesc Health* 2019;3:166–174
84. Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010;95:E448–E455
85. Legro RS, Barnhart HX, Schlaff WD, et al.; Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356:551–566
86. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:4068–4074
87. Palomba S, Orio F Jr, Nardo LG, et al. Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:4801–4809
88. Barbour LA, Scifres C, Valent AM, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol* 2018;219:367.e1–367.e7
89. Barbour LA, Feig DS. Metformin for gestational diabetes mellitus: progeny, perspective, and a personalized approach. *Diabetes Care* 2019;42:396–399
90. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst Rev* 2016;6:CD005542
91. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care* 2010;33:29–33
92. Holcberg G, Tsadkin-Tamir M, Sapir O, et al. Transfer of insulin lispro across the human placenta. *Eur J Obstet Gynecol Reprod Biol* 2004;115:117–118
93. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. *Diabetes Care* 2003;26:1390–1394
94. McCance DR, Damm P, Mathiesen ER, et al. Evaluation of insulin antibodies and placental transfer of insulin aspart in pregnant women with type 1 diabetes mellitus. *Diabetologia* 2008;51:2141–2143
95. Suffecool K, Rosenn B, Niederkofler EE, et al. Insulin detemir does not cross the human placenta. *Diabetes Care* 2015;38:e20–e21
96. Mathiesen ER, Hod M, Ivanisevic M, et al.; Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care* 2012;35:2012–2017
97. Hod M, Mathiesen ER, Jovanović L, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med* 2014;27:7–13
98. Hod M, Damm P, Kaaja R, et al.; Insulin Aspart Pregnancy Study Group. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008;198:186.e1–186.e7
99. Persson B, Swahn M-L, Hjertberg R, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2002;58:115–121
100. Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *Ann Pharmacother* 2011;45:9–16
101. Carta Q, Meriggi E, Trossarelli GF, et al. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabetes Metab* 1986;12:121–129
102. Kernaghan D, Farrell T, Hammond P, Owen P. Fetal growth in women managed with insulin pump therapy compared to conventional insulin. *Eur J Obstet Gynecol Reprod Biol* 2008;137:47–49
103. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. *Diabetes Care* 2018;41:2155–2161
104. Feig DS, Donovan LE, Zinman B, et al.; MiTy Collaborative Group. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020;8:834–844
105. Clausen TD, Mathiesen E, Ekblom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005;28:323–328
106. Cundy T, Gamble G, Neale L, et al. Differing causes of pregnancy loss in type 1 and type 2 diabetes. *Diabetes Care* 2007;30:2603–2607
107. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;330:565
108. Henderson JT, Whitlock EP, O’Conner E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville, MD, Agency for Healthcare Research and Quality, 2014. (Evidence Syntheses, No. 112). Accessed 17 October 2021. Available from <https://www.ncbi.nlm.nih.gov/books/NBK196392/>
109. Roberge S, Bujold E, Nicolaidis KH. Aspirin for the prevention of preeclampsia and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2018;218:287–293.e1
110. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;377:613–622
111. Hoffman MK, Goudar SS, Kodkany BS, et al.; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet* 2020;395:285–293
112. Werner EF, Hauspurg AK, Rouse DJ. A Cost-benefit analysis of low-dose aspirin prophylaxis for the prevention of preeclampsia in the United States. *Obstet Gynecol* 2015;126:1242–1250
113. Voutetakis A, Pervanidou P, Kanaka-Gantenbein C. Aspirin for the prevention of preeclampsia and potential consequences for fetal brain development. *JAMA Pediatr* 2019;173:619–620
114. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018;72:24–43
115. American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic hypertension in pregnancy. *Obstet Gynecol* 2019;133:e26–e50
116. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:407–417
117. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–265
118. Kazmin A, Garcia-Bournissen F, Koren G. Risks of statin use during pregnancy: a systematic review. *J Obstet Gynaecol Can* 2007;29:906–908
119. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ* 2020;369:m1361

120. Li Z, Cheng Y, Wang D, et al. Incidence rate of type 2 diabetes mellitus after gestational diabetes mellitus: a systematic review and meta-analysis of 170,139 women. *J Diabetes Res* 2020;2020:3076463
121. Tobias DK, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. *Arch Intern Med* 2012;172:1566–1572
122. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* 2006;368:1164–1170
123. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
124. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646–1653
125. Achong N, Duncan EL, McIntyre HD, Callaway L. Peripartum management of glycemia in women with type 1 diabetes. *Diabetes Care* 2014;37:364–371
126. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. *Endocr Pract* 2009;15:187–193
127. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA* 2005;294:2601–2610
128. Pereira PF, Alfenas R de CG, Araújo RMA. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. *J Pediatr (Rio J)* 2014;90:7–15