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Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management

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INTRODUCTION

The terms pregestational and preexisting diabetes refer primarily to type 1 or type 2 diabetes mellitus diagnosed prior to a woman's pregnancy. This topic will describe the potential maternal and fetal complications associated with pregnancy in women with preexisting diabetes and discuss preconception risk counseling, evaluation, and management of these women. Other issues related to pregnancy in women with pregestational diabetes are reviewed separately.

- (See "[Pregestational \(preexisting\) diabetes mellitus: Glycemic control during pregnancy](#)".)
- (See "[Pregestational \(preexisting\) and gestational diabetes: Intrapartum and postpartum glycemic control](#)".)
- (See "[Pregestational \(preexisting\) diabetes mellitus: Obstetric issues and management](#)".)
- (See "[Pregnancy in women with nondialysis chronic kidney disease](#)".)

PREVALENCE

The prevalence of diabetes in women of reproductive age is increasing [1,2] and, with it, the proportion of pregnancies complicated by preexisting diabetes. Data from clinical cohorts and hospital discharges suggest that pregestational diabetes complicates approximately 1 to 2 percent of all pregnancies and accounts for 13 to 21 percent of diabetes in pregnancy, with the remainder due to gestational diabetes [3,4]. The proportion of pregnant patients with type 1 and type 2 diabetes reflects their prevalence in the specific population. While rates of both pregestational type 1 and type 2 diabetes appear to be increasing, type 2 diabetes is more prevalent than type 1 diabetes in most populations [5].

GENERAL PRINCIPLES

Prior to pregnancy, all women of childbearing age with type 1 or type 2 diabetes should be counseled about the potential effects of diabetes and their medications on maternal and fetal outcomes and the potential impact of pregnancy on their diabetes control and any existing complications. The key components of preconception diabetes management are: glycemic control, proficient diabetes self-care, and medical optimization of preexisting complications and comorbidities associated with diabetes. Comprehensive and ongoing patient education is critical for shared decision-making about management goals and medication changes and for helping patients meet the considerable demands of self-care.

The intense medical and lifestyle regimen that must be undertaken before and during pregnancy and worry over pregnancy outcome can have an impact on the woman's psychological well-being. While preexisting depression does not appear to be worsened during pregnancy for women with pregestational diabetes, emotional distress (fear, worry, self-blame) can interfere with their enjoyment of pregnancy [6,7]. In the case of prior fetal loss or congenital malformation, women may also experience grief, guilt, and postpregnancy depression. For this reason, it is important that preconception counseling, evaluation, and management be conducted with a patient-centered approach that emphasizes patient support and minimizes treatment-related distress.

Type 1 and type 2 pregestational diabetes carry a significantly elevated risk of adverse maternal and fetal outcomes, including congenital malformations, miscarriage, preterm delivery, preeclampsia, macrosomia, and perinatal mortality [8-10]. Hyperglycemia is the primary driver of these risks, and studies repeatedly show that tight glycemic control in the periconceptional period and during pregnancy is associated with improved outcomes [8,11,12]. The first few weeks of pregnancy when a woman may not know she is pregnant are particularly important because congenital malformations induced by hyperglycemia develop during this time (called diabetic embryopathy) [12,13]. Studies also suggest that early pregnancy glycemia correlates with late pregnancy outcomes, including macrosomia, preeclampsia, and perinatal mortality [11,12,14,15]; however, randomized trials have not evaluated the impact of preconception control on these late outcomes.

Pregnancy-induced metabolic and vascular changes can also affect glycemic control and development or progression of diabetes complications, including development and/or progression of diabetic retinopathy and the threshold for developing diabetic ketoacidosis (DKA). Drivers in the metabolic environment other than glucose (eg, inflammation, oxidative stress) may also be associated with adverse outcomes and may explain why women with good glycemic control continue to have an excess risk of both macrosomia and preeclampsia. These pathways are not well defined and remain an area of active research.

Even though women with type 2 diabetes generally have milder glycemic disturbance, lower pregestational A1C, and shorter duration of disease than those with type 1 diabetes, a systematic review including 33 studies found that they did not have better perinatal outcomes (major congenital malformations, perinatal mortality) than those with type 1 diabetes [16]. Women with type 2 diabetes may be less likely to prepare for pregnancy and achieve good glycemic control compared with those with type 1 diabetes [17,18]. They are also likely to have a higher preconception body mass index, which carries risk of adverse pregnancy outcomes beyond hyperglycemia [19]. These factors and others (eg, higher age and parity) may account for their equivalent outcomes. While the risk of pregnancy complications may be similar for women with type 1 and type 2 diabetes, there are some important differences. Women with type 1 diabetes are more likely to have pregestational microvascular complications and are at higher risk of developing severe hypo- and hyperglycemia and DKA.

RISK COUNSELING

Risk counseling involves discussion of potential fetal, neonatal, obstetric, and maternal adverse outcomes.

Fetal and neonatal risks — Fetal and neonatal complications among women with pregestational diabetes range in severity from potentially mild (large for gestational age infant) to lethal (higher risk of miscarriage and some congenital malformations). The risk of these complications is directly related to glycemic control throughout pregnancy. Although the impact of preconception glycemic control on adverse pregnancy outcomes in women with pregestational diabetes has not been examined in randomized trials for ethical reasons, existing observational data strongly suggest that glucose control in the periconceptional period to delivery can reduce these risks. The risks for congenital malformations and some causes of perinatal mortality can be reduced to levels close to those of patients without diabetes [8,18,20].

Congenital malformations — The risk of congenital malformations (diabetic embryopathy) in women with pregestational diabetes is consistently reported to be two- to fourfold higher than that in women without diabetes (table 1) and is strongly related to the degree of hyperglycemia in the periconceptional period. Rates of major congenital malformations in women with type 1 diabetes range from 2.9 to 7.5 percent compared with 2.1 to 12.3 in women with type 2 diabetes; periconceptional hyperglycemia is associated with the high end of the range [8,21]. In an analysis of 1997 pregnancies resulting in live births from seven cohort studies, the risk of congenital abnormalities increased with increasing hemoglobin A1C: the absolute risk of a pregnancy affected by a congenital anomaly was approximately 2 percent at the nonpregnant nondiabetic population reference A1C of 5.5 percent, but increased to 2.7 percent at A1C 6.2 percent, 4 percent at A1C 7.6 percent, and 20 percent at A1C ≥ 14 percent [22]. A large population-based study of a cohort of women with type 1 or type 2 diabetes in the United Kingdom demonstrated a 30 percent reduction in risk of major congenital malformations for every 1 percent lowering of maternal A1C [23]. However in a Swedish cohort of women with type 1 diabetes, even when periconceptional A1C was < 6.3 percent, the risk of cardiac defect was two times higher than in women without diabetes [24].

The types of major congenital anomalies observed in women with pregestational diabetes are similar to those in women without diabetes and include congenital heart defects, neural tube defects, limb defects, and orofacial clefts. The most common abnormality, comprising 35 to 40 percent of major congenital anomalies, is congenital heart disease (including tetralogy of Fallot, transposition of the great arteries, septal defects, and anomalous pulmonary venous return; odds ratio [OR] 3.6, 95% CI 3.0-4.3 [25]), followed by central nervous system defects (anencephaly, spina bifida, encephalocele, hydrocephaly, anotia/microtia), and defects in the urogenital system [22,26]. Sacral agenesis/caudal dysplasia (lack of fetal development of the caudal spine and corresponding segments of the spinal cord) is rare in the general population but highly associated with maternal diabetes (adjusted OR 80, 95% CI 46-139 [27]), which accounts for 15 to 25 percent of all cases [28].

In animal models, the pathogenesis of embryopathy from hyperglycemia appears to be related to induction of high levels of oxidative stress, which leads to dysregulation of gene expression and excess apoptosis in developing organs [29]. The cardiovascular, central nervous, and skeletal systems are particular targets of this process.

Prematurity — Women with pregestational diabetes mellitus are at significantly higher risk of both medically/obstetrically indicated preterm delivery and spontaneous preterm delivery compared with women without diabetes. (See ['Preterm delivery'](#) below.)

Preterm infants are at increased risk of respiratory distress syndrome and a variety of other complications related to prematurity, especially in the setting of poor maternal glycemic control. (See ["Short-term complications of the preterm infant"](#) and ["Long-term outcome of the preterm infant"](#) and ["Infants of women with diabetes"](#).)

Macrosomia — Macrosomia (variously defined as fetal/newborn weight above 4000 grams, 4500 grams, or 10 pounds) occurs in 40 to 60 percent of pregnancies of women with pregestational diabetes versus 6 to 10 percent of pregnancies in the general obstetric population [9,12,17]. (See ["Fetal macrosomia"](#) and ["Large for gestational age newborn"](#).)

Macrosomic fetuses are at increased risk of shoulder dystocia and birth trauma (brachial plexus injury, fracture) if delivered vaginally. Many are delivered by cesarean either electively or because of abnormal labor progress. (See ["Shoulder dystocia: Risk factors and planning delivery of high-risk pregnancies"](#) and ["Pregestational \(preexisting\) diabetes mellitus: Obstetric issues and management"](#), section on 'Route of delivery'.)

The pathogenetic factors leading to macrosomia appear to be triggered in early pregnancy. Tight glucose control periconceptionally and in the first trimester seems to have a greater impact on reducing the risk of macrosomia than late pregnancy glycemic control. The reasons for this have yet to be fully elucidated but a growing body of research suggests that genetic factors, maternal glycemic load in early pregnancy, placental nutrient metabolism, and factors influencing fetal islet development and subsequent fetal hyperinsulinemia (the fetal pancreas is functional by 14 weeks of gestation) contribute to the role of early glycemic control [30].

Nevertheless, glycemic control throughout pregnancy is important for reducing risk of macrosomia [31,32]. Glycemic variability, gestational weight gain, prepregnancy obesity, and maternal lipid levels also to play a role in development of macrosomia. (See ["Fetal macrosomia"](#), section on 'Pathogenesis'.)

The body composition of macrosomic infants of mothers with pregestational diabetes differs from those born to women without diabetes. They are more likely to have a higher percentage of body fat, larger shoulders and extremity circumferences, and a lower head-to-shoulder ratio than infants of similar weight and length. The reasons for these differences in body composition are unclear but are thought to be caused by increased maternal transfer of substrates (glucose, amino acids), leading to fetal hyperinsulinemia and subsequent effects of insulin on target tissues to promote growth and store excess nutrients as adipose [33].

Growth restriction — Pregestational diabetes is associated with failure of the fetus to achieve its genetic growth potential, which is termed intrauterine growth restriction and variously defined as fetal/neonatal weight <3rd, 5th, or 10th percentile (see ["Fetal growth restriction: Screening and diagnosis"](#)). This risk is higher in women with type 1 versus type 2 diabetes. Women with type 1 diabetes with preexisting microvascular complications or hypertension have a 6- to 10-fold higher risk of growth restriction compared with women without preexisting vascular disease [34,35]. Growth restriction is associated with increased mortality and short-term and long-term morbidity. (See ["Infants with fetal \(intrauterine\) growth restriction"](#).)

Neonatal medical complications — Neonatal medical complications associated with pregestational diabetes include neonatal hypoglycemia, erythrocytosis, hyperbilirubinemia, hypocalcemia, respiratory distress, and cardiomyopathy. These outcomes are discussed separately. (See ["Infants of women with diabetes"](#).)

Perinatal mortality — Perinatal mortality is increased among women with pregestational diabetes, and the risk begins to increase at A1C levels between 6 and 6.9 percent [11,12]. The perinatal mortality rates are similar (3 to 4 percent) for women with type 1 and type 2 diabetes [11,20]; however, the underlying causes of death may differ. In a prospective study of fetal loss in women with type 1 and type 2 diabetes, perinatal deaths associated with type 2 diabetes were more likely to be due to stillbirth, birth asphyxia, or intraamniotic infection versus congenital abnormality or complications of prematurity in type 1 diabetes [20].

Rates of perinatal mortality in type 2 diabetes do not appear to vary with duration of disease [16], and women with type 2 diabetes first recognized in pregnancy appear to have rates similar to those with longstanding diabetes [20,36].

Improvements in perinatal mortality overtime in some studies (eg, stillbirth decreased from approximately 26 to 29/1000 births in 2002/2003 to 11/1000 births in 2015 in the United Kingdom [37]) have probably been related to improvements in the provision and uptake of prepregnancy care and tighter glycemic targets [38]. If glucose and risk factor control are optimal, perinatal death rates may approach those of women without diabetes [39]; however, a small excess risk of perinatal death has been observed even among women with good glycemic control [11,12,20].

Long-term outcomes — Maternal diabetes has potential long-term impact on offspring health. Offspring of mothers with diabetes are at increased risk of developing diabetes, obesity, and other adverse cardiometabolic outcomes [40-43]. The diabetes type (1 or 2) in offspring is related, in part, to maternal and paternal diabetes status. Increasingly, however, studies suggest an increased risk of obesity and type 2 diabetes in offspring of women with pregestational diabetes independent of genetic factors and possibly due to the effects of the uterine environment on neonatal programming [40,44-46]. It is unclear whether cognitive and other neurodevelopmental outcomes of offspring are affected by maternal diabetes. Pregestational diabetes and gestational diabetes have been linked with an increased risk for autism in offspring [47,48]. (See ["Infants of women with diabetes"](#), [section on 'Long-term outcome'](#) and ["Autism spectrum disorder: Terminology, epidemiology, and pathogenesis"](#).)

Obstetric complications

Miscarriage — Rates of miscarriage are two- to threefold higher in women with pregestational diabetes than among women without diabetes. Possible reasons for this higher risk include an increased rate of congenital malformations, toxic effects of hyperglycemia, and maternal vascular disease leading to utero-placental insufficiency [11,17,21].

Aneuploidy, a common cause of miscarriage, does not appear to be a factor because the risk of having an aneuploid fetus seems to be the same in women with and without diabetes. However, it is possible that epigenetic changes in gene expression may be influenced by pregestational diabetes; this is an area of ongoing investigation [8]. (See ["Pregnancy loss \(miscarriage\): Risk factors, etiology, clinical manifestations, and diagnostic evaluation"](#).)

Preeclampsia and gestational hypertension — The risks of both preeclampsia and gestational hypertension are three- to fourfold higher in women with pregestational diabetes than those without (for preeclampsia: 12 to 20 percent versus 5 to 7 percent) [49,50]. The risk may be higher in women with type 1 diabetes due to their higher risk of preexisting microvascular disease. A systematic review of 11 cohort studies in type 1 diabetes found that 17 percent of women experienced preeclampsia, a rate that is five to six times higher than the background population [51]. The risk of preeclampsia is magnified in women with chronic hypertension, preexisting microvascular complications, vascular disease, or renal disease, where it occurs in approximately 50 percent of patients [21,34]. The role of hyperglycemia in mediating preeclampsia is unclear; however, evidence suggests that glycemic control decreases the risk of developing preeclampsia [14,50]. (See "[Preeclampsia: Clinical features and diagnosis](#)" and "[Preeclampsia: Management and prognosis](#)".)

The risk of preeclampsia may be reduced by use of low-dose [aspirin](#) during pregnancy, beginning at the end of the first trimester. (See "[Preeclampsia: Prevention](#)" and "[Preeclampsia: Prevention](#)", [section on 'Low-dose aspirin'](#)".)

Polyhydramnios — Polyhydramnios (excessive amniotic fluid) occurs more frequently in pregnancies associated with pregestational diabetes, especially those with poor glycemic control or a large for gestational age fetus [52]. The mechanism for polyhydramnios in these pregnancies is unclear. Fetal hyperglycemia leading to polyuria is one likely etiology and is supported by the observation that polyhydramnios is often associated with high maternal A1C levels and fetal macrosomia [52,53]. Decreased fetal swallowing or an imbalance of water movement between the maternal and fetal compartments are other possible mechanisms. Polyhydramnios has been associated with a variety of adverse obstetric outcomes. (See "[Polyhydramnios](#)".)

Preterm delivery — Compared with women without diabetes, women with pregestational diabetes mellitus have significantly higher rates of both indicated and spontaneous preterm delivery [10,54,55].

In a Swedish population-based cohort study, the overall incidence of preterm birth in women with type 1 diabetes (n = 2474) and those without diabetes was 22.3 and 4.7 percent, respectively [55]. The incidence was higher at every level of A1C, progressively increasing from 13 percent at A1C <6.5 percent to 37.5 percent at A1C ≥9.1 percent, for A1C measured any time from 90 days before to 91 days after conception. Compared with women without diabetes, the adjusted relative risks for indicated and spontaneous preterm birth in women with diabetes were 9.1 and 2.6, respectively. Secondary outcomes, including large for gestational infant, macrosomia, neonatal hypoglycemia or respiratory distress, low Apgar score, and stillbirth or neonatal death, were also increased, but the relationship was not linear. Although these findings affirm and expand upon previous data on the association between type 1 diabetes and adverse pregnancy outcomes, questions remain regarding the role of periconceptional glucose control versus other factors (eg, maternal obesity, second- and third-trimester glucose control, nonglucose mediated effects) in this association and whether a target A1C <6.5 percent is adequate.

Cesarean delivery — Maternal diabetes is not an indication for cesarean birth in the absence of the usual obstetric indications. However, women with pregestational diabetes are at higher risk of undergoing cesarean delivery than women in the general obstetric population, in part because of their higher rates of macrosomia, preeclampsia, induction of labor, and obesity [20]. Women with type 2 diabetes are also at high risk of cesarean delivery, but appear to be at lower risk than those with type 1 diabetes (in one meta-analysis: OR 0.80, 95% CI

0.59-0.94 [16]). (See ["Pregestational \(preexisting\) diabetes mellitus: Obstetric issues and management", section on 'Route of delivery'.](#))

Maternal medical risks — Pregnant women with pregestational diabetes treated with insulin are at increased risk for severe hypoglycemia in early pregnancy, due in part to the lower glucose targets in pregnancy, and possibly to the contribution of erratic meals due to morning sickness. In addition, pregnant patients are at higher risk for diabetic ketoacidosis (DKA) and exacerbation of preexisting diabetes complications later in pregnancy. The emotional impact of diabetes in pregnancy is an additional concern.

Progression of microvascular disease — The likelihood of worsening microvascular complications in pregnancy is related to duration of diabetes and prepregnancy glycemic control [56]. Although two large prospective studies of women with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) [57] and the EURODIAB Prospective Complications Study (PCS) [58], suggest that pregnancy alone is not a risk factor for the de novo development of microvascular complications, pregnancy can exacerbate preexisting microvascular disease, and this effect varies by type of complication.

Diabetic retinopathy — The majority of women with diabetic retinopathy will not experience worsening of retinopathy in or following pregnancy. However, for some, particularly those with proliferative retinopathy (marked by new retinal vessel growth), retinopathy may worsen during pregnancy ("transient worsening") because of pregnancy-related vascular and volume changes. For a small subset of women with severe pregestational retinopathy, visual changes may persist postdelivery.

The likelihood of retinopathy progression is related to maternal duration of diabetes, presence and severity of existing retinopathy, and to the degree of glycemic control prior to and during pregnancy. Hypertension, smoking, hyperlipidemia, and hypoglycemia have also been associated with acceleration of retinopathy in pregnancy [59]. Rarely, retinopathy first develops in pregnancy. (See ["Diabetic retinopathy: Classification and clinical features", section on 'Natural history'.](#))

As in nonpregnant patients, rapid tightening of glycemic control has been associated with worsening retinopathy in women with pregestational diabetes [56,60]. Worsening of retinopathy in this setting is thought to be mediated by closure of small retinal blood vessels, which were narrowed but patent prior to tightening of glucose control. Correction of hyperglycemia may lower intravascular volume, leading to vessel closure. In most women, the benefits of normoglycemia for the fetus far outweigh the modest and generally transient deterioration in retinopathy from improved glycemic control, as milder forms of diabetic retinopathy typically improve after delivery. However, some women with severe proliferative retinopathy or with macular edema may experience persistence or even further progression of retinopathy postpregnancy [60].

These relationships were illustrated by the Diabetes in Early Pregnancy (DIEP) study, a prospective study of 140 women with pregestational diabetes and no proliferative retinopathy at periconceptional baseline examination [61]. At follow-up examination one month postpartum, progression of retinopathy was noted in 20 percent of women with microaneurysms or mild nonproliferative retinopathy at baseline and 55 percent of those with moderate to severe nonproliferative retinopathy [61]. Proliferative retinopathy developed in 6 percent of women with mild baseline retinopathy and 29 percent of women with moderate to severe baseline retinopathy. Ten

percent of women without retinopathy at baseline had signs of retinopathy postpartum on fundoscopic examination.

Data on impact of antepartum progression of retinopathy on the clinically meaningful outcome of postpartum vision are scant. One study reported postpartum women with diabetes had worse visual acuity as measured by letter recognition at nine weeks after delivery compared with nonpregnant women with diabetes followed for the same interval; however, the vision decrement was small, suggesting the impact of pregnancy in most women with pregestational diabetes is minimal [62]. The vision change was reported for all subjects with diabetes and pregnancy, without correlation to progression or severity of retinopathy; thus, impact of pregnancy on vision in higher risk subgroups remains unclear.

Diabetic kidney disease — Women with diabetes and normal albumin excretion are at low risk for development of kidney disease in pregnancy. Women with diabetes, moderately increased albuminuria (formerly microalbuminuria), and normal kidney function appear to be at low risk for loss of kidney function during pregnancy, but may have a transient increase in albuminuria. Among women with overt proteinuria at baseline, urinary protein excretion can rise dramatically as pregnancy progresses, but after delivery, protein excretion decreases in most women.

By contrast, women with poorly controlled hypertension or reduced glomerular filtration rate and heavy proteinuria (serum creatinine level >1.5 mg/dL, proteinuria >3 grams in 24 hours) at the onset of pregnancy are at risk of permanent kidney damage, including end-stage kidney disease. As many as 40 percent of women with serum creatinine >3 mg/dL or creatinine clearance <50 mL/minute will develop permanent worsening of renal function with pregnancy [63]. (See "[Pregnancy in women with nondialysis chronic kidney disease](#)".)

Diabetic kidney disease also carries risks for the pregnancy. Both moderately increased albuminuria (formerly microalbuminuria) and overt nephropathy are associated with an increased rate of preterm birth, primarily due to preeclampsia. Hypertension and preeclampsia are associated with fetal growth restriction and (rarely) fetal or maternal death. (See "[Pregnancy in women with nondialysis chronic kidney disease](#)".)

Cardiovascular disease — Pregnant women with pregestational diabetes are at increased risk of macrovascular cardiac disease (coronary artery disease, heart failure, stroke) and microvascular cardiovascular disease (microvascular angiopathy, cardiac autonomic neuropathy). The risk is related both to diabetes and to the frequent presence of other cardiovascular and renal risk factors, such as hypertension and nephropathy [64-66]. In addition, pregnancy-related volume expansion may unmask previously subclinical disease, such as asymptomatic diastolic dysfunction. (See "[Overview of general medical care in nonpregnant adults with diabetes mellitus](#)", [section on 'Screening for coronary heart disease'](#)".)

Peripheral and autonomic neuropathy — Pregnancy does not appear to affect the course of peripheral or autonomic neuropathy. However, autonomic neuropathy can complicate pregnancy as affected women are at increased risk of hyperemesis gravidarum (related to gastroparesis), hypoglycemia unawareness, and orthostatic hypotension.

Diagnosis of gastroparesis is important because it may strongly influence dietary approach, insulin regimen, and other medical therapies. In addition, the clinical manifestations of gastroparesis may be confused with

hyperemesis of pregnancy. Severe gastroparesis is one of the few relative contraindications to pregnancy in women with pregestational diabetes as it can lead to extreme hypo- and hyperglycemia, increased risk of DKA, weight loss, and malnutrition [64,67]. Women with significant gastroparesis who become pregnant often have frequent hospitalizations and may require parenteral nutrition [49].

Diabetic ketoacidosis — DKA is more common, occurs at lower levels of glycemia, and carries a higher risk of mortality in pregnant women with type 1 diabetes compared with nonpregnant women with type 1 diabetes. It can occur at glucose values ≤ 250 mg/dL (13.9 mmol/L) because the increased insulin resistance and lipolytic state of pregnancy, coupled with compensated respiratory alkalosis with decreased ability to buffer ketoacids, render pregnant women more prone to ketoacidosis [64,68,69].

DKA has been reported in 1 to 10 percent of pregnant women with type 1 diabetes and may be fatal. The risk of fetal demise is substantial: rates of 9 to 35 percent have been reported [70,71]. Other complications include sequelae of fetal hypoxia and acidosis, preterm delivery, and maternal and/or neonatal intensive care unit admission [72].

DKA can occur in ketosis-prone type 2 diabetes, but is rare in pregnancy [73]. (See ["Pregestational \(preexisting\) diabetes mellitus: Obstetric issues and management", section on 'Diabetic ketoacidosis'.](#))

In addition to the usual precipitants of DKA, potential pregnancy-related causes include treatment with beta-mimetic tocolytics and antenatal corticosteroids. (See ["Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Precipitating factors'.](#))

PRECONCEPTION EVALUATION AND MANAGEMENT

Overview — Preconception planning is the foundation for a successful outcome of pregnancy in women with pregestational diabetes. In a 2010 systematic review and meta-analysis of 12 cohort studies that evaluated the effectiveness and safety of preconception care in improving maternal and fetal outcomes for women with preexisting diabetes mellitus, preconception care was associated with significantly reduced rates of congenital malformation (relative risk [RR] 0.25, 95% CI 0.15-0.42), preterm delivery (RR 0.70, 95% CI 0.55-0.90), and perinatal mortality (RR 0.35, 95% CI 0.15-0.82) and a lower first-trimester A1C level (average reduction 2.43 percent, 95% CI 2.27-2.58) [74]. However, women who participate in preconception planning are likely to be different from those who did not and therefore the improvement ascribed to prepregnancy care may be reflective of differences in populations [75]. No randomized trials of preconception care versus no care have been performed.

Preconception counseling should be delivered in a culturally appropriate manner, tailored to the patient's type of diabetes (type 1, type 2), and her personal history of diabetic complications. Preconception care should include:

- Counseling about the impact of glycemic status on maternal-fetal outcome, the risk of development or progression of preexisting complications of diabetes, and the types and risks of adverse maternal, fetal, and neonatal outcomes (see ["Risk counseling"](#) above)
- Helping the patient achieve good glucose control, with A1C in the normal range if safely achievable

- Adjusting medications as needed for fetal safety
- Beginning [folic acid](#) supplementation
- Evaluating for comorbidities and complications of diabetes
- Initiating treatment of comorbidities and complications or optimizing status of existing medical conditions
- Discussion and provision of effective contraception to avoid unplanned pregnancy

In women with advanced complications of diabetes, weighing the risk of a pregnancy to their health versus the desire for childbearing is particularly important. For example, women at risk of deteriorating renal function leading to dialysis may decide not to pursue becoming pregnant.

The following text describes issues of preconception evaluation and management specific to women with diabetes. Routine aspects of preconception care applicable to all women are reviewed separately. (See ["The preconception office visit"](#).)

Glycemic control — Our primary preconception A1C goal for all women with diabetes is <6.5 percent, but we attempt to achieve A1C <6 percent if this is possible without inducing significant hypoglycemia. The American Diabetes Association (ADA) recommends aiming for an A1C <6.5 percent (48 mmol/mol) and the Endocrine Society recommends aiming for an A1C level "as close to normal as possible" (ie, <6.5 percent [48 mmol/mol]) without causing undue hypoglycemia [\[76,77\]](#).

Since it takes two to three months to turn over A1C, women with diabetes should be encouraged to allow a minimum of six months to achieve optimal glucose control before trying to conceive, if they are not already well controlled. A1C goals during pregnancy are lower than in nonpregnant women because increased blood volume and red blood cell turnover during pregnancy cause a physiologic fall in A1C levels and because lower A1C levels are associated with better outcomes (see ["Risk counseling"](#) above). There are limited high-quality clinical trial data on the effects and risk/benefits of very low A1C levels during pregnancy.

The following preconception glucose targets are reasonable to attempt to achieve:

- A1C <6.5 percent
- Fasting capillary blood glucose concentration 80 to 110 mg/dL (4.4 to 6.1 mmol/L)
- Two hour postprandial glucose concentration <155 mg/dL (8.6 mmol/L)

Glucose self-monitoring is an important tool for achieving the tight glucose control needed in pregnancy. All women contemplating pregnancy should be instructed how to perform self-monitoring of blood glucose. (See ["Self-monitoring of glucose in management of nonpregnant adults with diabetes mellitus"](#) and ["Patient education: Self-monitoring of blood sugar in diabetes \(Beyond the Basics\)"](#).)

It is important to review signs and symptoms of hypoglycemia with the patient, as well as actions she (and close contacts) should take if she develops hypoglycemia. She should be instructed to carry a snack at all times. Those who have a history of hypoglycemia or who begin to experience hypoglycemia when tightening their glucose control should be given a prescription for glucagon and taught or retaught how to administer it. Reinforcement of hypoglycemia management is particularly important prepregnancy so the patient is prepared in early pregnancy

when the frequency of hypoglycemia may increase due to tightened glucose control, changes in hormone levels, nausea and vomiting of pregnancy, and reduction in physical activity. Hypoglycemia is more likely to occur in women with type 1 diabetes due to autoimmune destruction of the alpha cells that produce glucagon.

The risk of diabetic ketoacidosis (DKA) is increased in pregnancy, primarily in women with type 1 diabetes, but also in women with longstanding type 2 diabetes. Women should be aware of this risk and the symptoms, management, and consequences of DKA. They should have ketone strips at home and instructed to use them when blood glucose levels are >200 mg/dL (11.1 mmol/L) [64]. They should contact their care provider if ketone results are positive.

Diet, weight, and exercise — Diet is one of the most important behavioral aspects of diabetes treatment. Referral to a registered dietitian is usually of benefit for women with diabetes who are planning pregnancy. Understanding how different food intakes affect glycemia and developing a food plan of meals and snacks helps women reduce glucose fluctuations and manage fluctuations that occur. Nutritional considerations for women with type 1 and type 2 diabetes are discussed in detail separately. (See "[Nutritional considerations in type 1 diabetes mellitus](#)" and "[Nutritional considerations in type 2 diabetes mellitus](#)".)

Women who are overweight or obese should be encouraged to lose weight prior to conception. In addition to improving prepregnancy glycemic control and potential benefits on metabolic profile (hypertension, hyperlipidemia, fatty liver disease), weight reduction prior to pregnancy may decrease the risk of pregnancy complications associated with obesity (eg, preeclampsia, some congenital anomalies, cesarean delivery, macrosomia). (See "[Obesity in pregnancy: Complications and maternal management](#)".)

In adults with diabetes, regular exercise is important to improve glycemic control, assist with weight maintenance, and reduce the risk of cardiovascular disease and overall mortality. An appropriate exercise program for nonpregnant women with diabetes is described separately (see "[Effects of exercise in adults with diabetes mellitus](#)", [section on 'A program for physical activity'](#)). Exercise can be maintained in pregnancy. (See "[Exercise during pregnancy and the postpartum period](#)".)

Folic acid and iodide supplementation

- [Folic acid](#) 400 micrograms/day is recommended for most reproductive-age women to decrease the occurrence of neural tube defects (NTDs). (See "[Folic acid supplementation in pregnancy](#)".)

Because women with pregestational diabetes are at increased risk of having a child with a neural tube defect, some authorities have opined that they may benefit from a higher dose of [folic acid](#); however, the optimum dose of folic acid in this population has not been studied and recommendations vary. We agree with the ADA's recommendation for a minimum dose of at least 400 micrograms/day [77], which was effective in at least two case-control studies [78,79] and in at least one study in animals [80]. The American College of Obstetricians and Gynecologists (ACOG) recommend at least 400 micrograms/day folic acid for women with diabetes contemplating pregnancy and states that higher doses (800 to 1000 mcg) may be beneficial in high risk women, such as those with other risk factors for NTDs [81]. The Society of Obstetricians and Gynaecologists of Canada recommends 1 mg per day [82]. The Endocrine Society suggests 5 mg/day beginning three months before discontinuing contraception or otherwise trying to conceive, and reducing the

dose to 0.4 to 1.0 mg/day at 12 weeks of gestation through the completion of breastfeeding [76]. (See ["Folic acid supplementation in pregnancy", section on 'Preexisting diabetes'.](#))

- Women who are planning pregnancy or are currently pregnant should supplement their diet with a daily oral supplement that contains 150 mcg of iodine in the form of potassium iodide [77,83].

Medication management

Glucose control — We recommend insulin for women with type 1 or type 2 diabetes planning to conceive. Insulin remains the standard drug for glucose management during pregnancy and should be started prior to conception in women taking oral antihyperglycemic agents to provide continuity [81].

We suggest using insulins with a good fetal safety profile, such as NPH, regular, lispro, aspart, and levemir, and avoiding premixed insulins. [Insulin glargine](#), a long-acting insulin, has greater mitogenic potential and higher affinity binding to the IGF-1 receptor than other insulins [84]. Theoretically this could lead to increased fetal growth and macrosomia, but small observational studies in humans do not support this concern [85-87]. Given the availability of better-studied and effective alternatives, we substitute NPH insulin or insulin levemir for insulin glargine prior to pregnancy. If this is not possible due to patient preference or inability to achieve optimal glucose control on an alternative regimen, we discuss the theoretic risks of insulin glargine on pregnancy and help her make an informed decision. Some authorities, however, continue insulin glargine before and during pregnancy [76]. For a short-acting insulin, we generally use a rapid-acting insulin, lispro or aspart, instead of [regular insulin](#). These insulins have a rapid onset, which improves control of the postprandial increase in glucose, and have a rapid offset, which may decrease hypoglycemia. A randomized trial of rapid-acting aspart versus regular insulin in pregnancy demonstrated less of a glucose rise postprandially with aspart than regular insulin, but no significant difference in hypoglycemia rates [88]. (See ["Pregestational \(preexisting\) diabetes mellitus: Glycemic control during pregnancy", section on 'Insulin'.](#))

For women with type 2 diabetes on an oral antihyperglycemic agent, we suggest switching to insulin therapy prior to conception for better glucose control and to avoid transplacental passage of the drug to the fetus. Although there are limited data suggesting that [metformin](#) and [glyburide](#) are effective and safe in the management of gestational diabetes, these data primarily reflect use in the third trimester when organogenesis is mostly complete, so they do not apply to the management of women with preexisting diabetes. Importantly, long-term outcomes of the infants of pregnancies treated with oral agents are sparse. Thus, insulin remains the first choice of therapy for women who are pregnant. (See ["Pregestational \(preexisting\) diabetes mellitus: Glycemic control during pregnancy", section on 'Oral anti-hyperglycemic agents'.](#))

Women already using insulin pumps can continue to use them as they attempt to conceive and during pregnancy. However, we avoid switching women to pump therapy during pregnancy because of the risks for significant hypo- or hyperglycemia (including DKA) during the transition period. Therefore, if a nonpregnant woman is considering switching to insulin pump therapy, initiation should ideally occur prior to attempts at conception to allow ample time for training, acclimatization to pump use, and troubleshooting before pregnancy. Of note, at least one study suggested multiple daily injections of insulin were superior to pump therapy in achieving lower A1C levels [89]. There may be individual exceptions (eg, women with poor glucose control on multiple dose injections), with some patients obtaining better glucose control with pump therapy initiated during pregnancy.

One group that ran two parallel trials of continuous glucose monitoring (CGM), one in pregnant women with type 1 diabetes and the other in women with type 1 diabetes planning pregnancy, reported that pregnancy outcomes were not significantly improved for women who began CGM during pregnancy planning, possibly due to the small sample size [90]. However, CGM during pregnancy resulted in improved pregnancy outcomes. Nevertheless, CGM may be helpful to some women trying to achieve glucose control preconception, and this decision should be made on a case-by-case basis.

Blood pressure control — Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) should be discontinued and replaced with another class of antihypertensive drug (eg, [labetalol](#) or a long-acting calcium channel blocker) when women with diabetes and hypertension are planning pregnancy and before stopping contraception (see "[Management of hypertension in pregnant and postpartum women](#)"). Although ACEIs and ARBs are commonly used for management of hypertension and may be recommended for management of moderately increased albuminuria (formerly microalbuminuria) in nonpregnant individuals with diabetes, both classes of drugs are contraindicated in the second and third trimesters of pregnancy as they have been associated with fetal renal injury and neonatal renal failure [91]. Whether first-trimester exposure to these drugs is also teratogenic is controversial, but switching to an agent(s) with a better safety profile is prudent [92,93]. If not already discontinued, ACEIs and ARBs should be stopped when pregnancy is confirmed. (See "[Adverse effects of angiotensin converting enzyme inhibitors and receptor blockers in pregnancy](#)".)

Lipid control — Statins are contraindicated in pregnancy because of limited and contradictory data suggesting an increased risk of birth defects with first-trimester exposure. This discordance may reflect confounding by indication. We suggest discontinuing statins in women who are planning pregnancy and resuming these drugs after delivery/breast feeding. (See "[Statins: Actions, side effects, and administration](#)", [section on 'Risks in pregnancy and breastfeeding'](#).)

Evaluation of and approach to complications of diabetes mellitus — Evaluation for complications of diabetes should be up to date before women attempt to conceive. We perform both physical examination ([table 2](#)) and laboratory evaluation (A1C, serum creatinine, estimated glomerular filtration rate, aspartate aminotransferase and alanine aminotransferase, thyroid stimulating hormone [TSH], urine albumin-to-creatinine ratio on a spot urine or 24 urine collection for protein and creatinine).

A baseline evaluation is important because some diabetes-related complications should be treated prior to conception (eg, retinopathy). In addition, this information is important for counseling and pregnancy management since some complications, such as diabetic kidney disease, are associated with an increased risk of pregnancy complications, may worsen during pregnancy, and may make the diagnosis of pregnancy complications (eg, preeclampsia) more difficult.

Diabetic kidney disease — As discussed above (see '[Diabetic kidney disease](#)' above), pregnancy does not appear to increase the risk of developing diabetic kidney disease if not present before pregnancy, but women with established nephropathy can develop permanent worsening of renal functioning during pregnancy. The risk of permanent loss of renal function is significant in women with uncontrolled hypertension, baseline serum creatinine >1.5 mg/dL, or protein ≥3 grams in a 24-hour urine collection [64,67].

Women with significant diabetic kidney disease should be referred to a nephrologist skilled in the care of pregnant women to assist them in balancing their desire for pregnancy and the risks and consequences of deterioration of renal function. (See ["Pregnancy in women with nondialysis chronic kidney disease"](#).)

Major treatment options for preservation of renal function in nonpregnant women (angiotensin-converting enzyme inhibitors [ACEI] or angiotensin II receptor blockers [ARBs]) are contraindicated in pregnancy. However, control of hypertension with medications such as calcium channel blockers is safe and may be beneficial. (See ["Treatment of diabetic kidney disease"](#) and ["Adverse effects of angiotensin converting enzyme inhibitors and receptor blockers in pregnancy"](#).)

Retinopathy — As discussed above (see ["Diabetic retinopathy"](#) above), retinopathy can worsen during pregnancy, sometimes rapidly, and result in permanent loss of vision, although generally only in persons who started with advanced retinopathy in the pregravid state. To reduce this risk, women with diabetes should have a dilated eye examination before pregnancy [76,77], and if proliferative retinopathy is detected, it should be treated prior to attempts at conception. Since exacerbation of retinopathy can occur with rapid control of glucose levels, improvement in glucose control should be made gradually over months prior to pregnancy, when possible. (See ["Diabetic retinopathy: Prevention and treatment"](#), section on 'Pregnancy'.)

Gastroparesis — Evaluation for gastroparesis (see ["Peripheral and autonomic neuropathy"](#) above) is performed by history and physical examination after a meal. A report of nausea, vomiting, early satiety, postprandial fullness, abdominal pain, or bloating and presence of succussion splash suggests the diagnosis. In some cases, evaluation of gastric emptying by scintigraphy is performed to make a definitive diagnosis. (See ["Gastroparesis: Etiology, clinical manifestations, and diagnosis"](#).)

Initial management of gastroparesis consists of dietary modification, optimization of glycemic control, and hydration. In patients with continued symptoms, pharmacologic therapy with prokinetic and antiemetic medications with a good fetal safety profile may be needed (eg, [metoclopramide](#)). (See ["Treatment of gastroparesis"](#).)

Cardiovascular disease — Women with type 1 or type 2 diabetes of long duration may have cardiovascular disease. Extended evaluation should be based on the patient's history and physical examination ([table 2](#)). For example, a carotid bruit can be an indicator of ischemic cardiac disease and angina may present as atypical chest pain or shortness of breath. Women with abnormal cardiac findings on examination or by history should be referred to a cardiologist for further evaluation (such as exercise tolerance testing), management, and counseling. (See ["Acquired heart disease and pregnancy"](#).)

The Pregnancy Summary of Evidence and Consensus Recommendations for Care [64] recommend a resting electrocardiogram (ECG) for women with diabetes who are ≥ 35 years of age and a stress ECG or echocardiogram for women in this age group who have had diabetes > 10 years, especially if there are signs of cardiovascular disease on physical examination (eg, carotid bruits). We agree with these recommendations except that we do not solely use age cut offs (as explained above) and we generally reserve stress ECGs for women with abnormal resting ECGs or echocardiograms or any symptoms suggestive of angina.

Thyroid disease — Although not caused by diabetes, autoimmune thyroid dysfunction is frequently associated with type 1 diabetes; hypothyroidism is more common than hyperthyroidism. ADA, ACOG, and the Endocrine Society recommend screening women with type 1 diabetes prior to pregnancy with a thyroid stimulating hormone (TSH) level [64,76,81]. Hypothyroidism is treated with [levothyroxine](#). The TSH should be <2.5 milliunits/mL before pregnancy is attempted [94,95]. (See "[Diagnosis of and screening for hypothyroidism in nonpregnant adults](#)" and "[Overview of thyroid disease and pregnancy](#)".)

If the TSH is low, a thyroxine (T4) level should be obtained. Goals and medications for the treatment of hyperthyroidism prior to and during pregnancy are complex and should be managed by an endocrinologist or other clinician experienced in the management of hyperthyroidism during pregnancy. (See "[Diagnosis of hyperthyroidism](#)" and "[Hyperthyroidism during pregnancy: Treatment](#)".)

Women with type 2 diabetes also have a higher prevalence of hypothyroidism than the general population. Whether this is a true association or confounding by indication due to increased testing is unclear; however, the ADA [64] recommends checking the TSH level prior to pregnancy in women with type 2 diabetes, and initiating treatment when indicated.

Routine measurement of antithyroid antibodies is not necessary for the assessment of thyroid function. Whether to treat euthyroid thyroid peroxidase antibody (TPO) positive women to improve pregnancy outcome is controversial, and reviewed separately. (See "[Overview of thyroid disease and pregnancy](#)", [section on 'Thyroid peroxidase antibodies in euthyroid women'](#)".)

Contraception and timing of pregnancy — Family planning with use of effective contraception until glucose control is achieved should be a key feature in the management of all women with diabetes and should be discussed at regular intervals. Given the importance of optimization of glucose control at conception, evaluation for and management of diabetes complications, and change in medication prior to conception, it is crucial that women with prepregnancy diabetes plan their pregnancies to optimize the likelihood for a healthy pregnancy both for the mother and the baby.

Guidelines from the [United States Centers for Disease Control \(CDC\) Medical Eligibility Criteria for Contraceptive Use](#) are helpful for advising women with diabetes about the safety of contraceptive methods [96]. Estrogen-progestin and progestin-only contraceptives are safe and effective for many women with type 1 or type 2 diabetes. However, women with nephropathy, retinopathy, neuropathy, other vascular disease, or diabetes >20 years duration have conditions where the theoretical or proven risks of using an estrogen-progestin method or depot [medroxyprogesterone acetate](#) (DMPA) usually outweigh the advantages of using the method or represent an unacceptable health risk if the contraceptive method is used. Other progestin-only methods (pill, implant, intrauterine device [IUD]) and the copper-releasing IUD are preferable methods for women with these conditions as they are associated with a lower rate of thromboembolic events than estrogen-progestin contraceptives [97].

The selection of a contraceptive method for an individual patient should be based on the same guidelines that apply to women without diabetes. Considerations of potential side effects of contraceptive agents should be weighed against the risk of an unplanned pregnancy.

Types of hormonal and nonhormonal contraception and important factors in choosing a contraceptive method are reviewed separately. (See ["Contraceptive counseling and selection for women".](#))

Multidisciplinary programs — Prior to and during pregnancy, women with preexisting diabetes may benefit from being followed in a multidisciplinary care program with providers that include an obstetrician, an endocrinologist (or other clinician with expertise in diabetes management in pregnancy), a dietitian, and a diabetes educator (with other health professionals as needed). Data supporting the benefit of these programs in improving pregnancy outcomes are limited by the lack of randomized trials and the caveat that women who are more motivated to manage their diabetes are likely to be those who attend these programs. Nevertheless, observational data, including a prospective cohort including both type 1 and type 2 diabetes, suggest that women who attend preconception programs have better pregnancy outcomes, including decreased congenital malformation, stillbirth, and neonatal mortality [[18,98](#)].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Diabetes mellitus in pregnancy".](#))

SUMMARY AND RECOMMENDATIONS

Prior to pregnancy, all women of childbearing age with type 1 or type 2 diabetes should be counseled about the potential effects of diabetes on maternal and fetal outcomes and the potential impact of pregnancy on their diabetes control and any existing complications. The key components of preconception diabetes management are: glycemic control, proficient diabetes self-care, and medical optimization of preexisting complications and comorbidities associated with diabetes. Patient education also includes insulin management, prevention and identification of hypoglycemia and diabetic ketoacidosis (DKA), and diet and exercise counseling. (See ['General principles'](#) above.)

Risks

- The risk of adverse pregnancy outcome is increased in women with diabetes, but appears to be similar for women with type 1 and type 2 diabetes. Women with type 1 diabetes are more likely to have microvascular disease-related complications than women with type 2 diabetes, and they are at higher risk of developing severe hypo- and hyperglycemia. (See ['General principles'](#) above.)
- Adverse pregnancy outcomes include miscarriage, congenital anomaly, macrosomia, preeclampsia, preterm birth, cesarean delivery, and perinatal mortality. Short- and long-term morbidity in offspring is also a concern. Maternal medical risks include progression of retinopathy and nephropathy, DKA, and complications related to gastroparesis. (See ['Risk counseling'](#) above.)
- Hyperglycemia in the periconception period and during the course of pregnancy is the single most important determinant of excess risk of adverse fetal outcome in women with pregestational diabetes. Achieving

preconception glycemic control as close to normal as possible while avoiding hypoglycemia is of critical importance. (See '[General principles](#)' above and '[Risk counseling](#)' above.)

Evaluation and management

- Contraception is recommended until glycemic control is achieved, management of complications or comorbidities is optimized, and pregnancy is desired. (See '[Contraception and timing of pregnancy](#)' above.)
- Preconception evaluation includes physical examination ([table 2](#)) and laboratory evaluation (A1C, serum creatinine, estimated glomerular filtration rate, aspartate aminotransferase and alanine aminotransferase, thyroid stimulating hormone [TSH], urine albumin-to-creatinine ratio on a spot urine or 24 urine collection for protein and creatinine). Further evaluation may be indicated based on patient's history and examination. (See '[Evaluation of and approach to complications of diabetes mellitus](#)' above.)
- Our primary A1C goal for all women is A1C <6.5 percent, but we attempt to achieve A1C <6 percent if this is possible without inducing significant hypoglycemia. Glucose targets are fasting capillary blood glucose concentration 80 to 110 mg/dL (4.4 to 6.1 mmol/L) and two-hour postprandial glucose concentration <155 mg/dL (8.6 mmol/L). (See '[Glycemic control](#)' above.)
- We agree with the American Diabetes Association (ADA) recommendation for supplemental [folic acid](#) 400 mcg/day and potassium iodide 150 mcg/day. (See '[Folic acid and iodide supplementation](#)' above.)
- We prescribe insulin for women with type 1 and type 2 diabetes planning to conceive. (See '[Glucose control](#)' above.)
- Angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and statins should be discontinued before pregnancy is attempted. (See '[Blood pressure control](#)' above and '[Lipid control](#)' above.)
- Women with significant diabetic kidney disease should be referred to a nephrologist skilled in the care of pregnant women to assist them in balancing their desire for pregnancy and the risks and consequences of deterioration of renal function. Women with established nephropathy may develop permanent worsening of renal functioning during pregnancy. (See '[Diabetic kidney disease](#)' above.)
- A dilated eye examination should be performed before pregnancy and, if proliferative retinopathy is detected, it should be treated prior to attempts at conception. Diabetic retinopathy can worsen during pregnancy. (See '[Retinopathy](#)' above.)
- Gastroparesis may influence dietary approach, insulin regimen, and other medical therapies. Severe gastroparesis is one of the few relative contraindications to pregnancy. (See '[Gastroparesis](#)' above.)
- Signs and symptoms of cardiovascular disease on history or physical examination (eg, carotid bruits, absent peripheral pulse) is an indication for further cardiac evaluation and possible referral to a cardiologist. (See '[Cardiovascular disease](#)' above.)

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GRAPHICS

Rate of congenital anomalies among offspring of 1677 women with pre-existing diabetes mellitus in the north of England

Group (subtype)*	Pregnancies with diabetes		Pregnancies without diabetes		Relative risk (95% CI)
	n	Rate (95% CI)	n	Rate (95% CI)	
Nervous system	16	9.5 (5.4, 15.4)	769	1.9 (1.8, 2.1)	5.0 (3.0, 8.1)
Neural tube defects	10	6.0 (2.9, 10.9)	443	1.1 (1.0, 1.2)	5.4 (2.9, 10.1)
Hydrocephalus	2		115		
Microcephaly	1		55		
Holoprosencephaly	1		31		
Eye	2		98		
Cardiovascular system	44	26.2 (19.1, 35.1)	2919	7.3 (7.0, 7.6)	3.6 (2.7, 4.8)
Transposition of great vessels	3	1.8 (0.4, 5.2)	130	0.3 (0.3, 0.4)	5.5 (1.8, 17.2)
Single ventricle	1		13		
Ventricular septal defect	21	12.5 (7.8, 19.1)	1285	3.2 (3.0, 3.4)	3.9 (2.6, 6.0)
Atrial septal defect	1		217		
Atrioventricular septal defect	2		69		
Tetralogy of Fallot	4	2.4 (0.7, 6.0)	95	0.24 (0.2, 0.3)	10.0 (3.7, 27.2)
Pulmonary valve stenosis	3	1.8 (0.4, 5.2)	244	0.6 (0.5, 0.7)	2.9 (0.9, 9.1)
Hypoplastic left heart	1		78		
Coarctation of aorta	2		101		
Total anomalous pulmonary venous return	1		35		
Orofacial clefts	1		437		
Digestive system	10	6.0 (2.9, 10.9)	421	1.05 (0.95, 1.15)	5.7 (3.0, 10.6)
Oesophageal atresia	2		43		
Duodenal atresia or stenosis	1		36		
Hirschsprung's disease	1		51		
Atresia of bile ducts	1		15		
Diaphragmatic hernia	2		91		
Urinary	12	7.2 (3.7, 12.5)	974	2.4 (2.3, 2.6)	2.9 (1.7, 5.2)
Cystic kidney disease	2		200		
Congenital hydronephrosis	1		20		
Bladder exstrophy	1		14		
Genital	2		76		
Limb	2		234		
Musculoskeletal	3	1.8 (0.4, 5.2)	55	0.14 (0.1, 0.2)	13.0 (4.1, 41.5)
Syndrome (monogenic or unknown)	11	6.6 (3.2, 11.7)	439	1.1 (1.0, 1.2)	6.0 (3.1, 10.9)
Laterality syndrome (right/left atrial isomerism, situs inversus)	6	3.6 (1.3, 7.8)	25	0.06 (0.04, 0.09)	57.2 (23.5, 139.2)
Angelman syndrome	1		6		
Blepharophimosis-ptosis syndrome	1		3		

Laurence-Moon syndrome	1		2		
Prader-Willi syndrome	1		10		
Incontinentia pigmenti	1		6		
Associations	1		34		
Sequence	7	4.2 (1.6, 8.6)	139	0.35 (0.3, 0.4)	12.0 (5.6, 25.6)
Caudal dysplasia sequence	5	3.0 (0.9, 6.9)	7	0.02 (0.01, 0.03)	170.2 (54.1, 535.6)
Sirenomelia	1		6		
Partial urorectal septum malformation sequence	1		21		
Multiple anomalies	9	5.4 (2.5, 10.2)	440	1.1 (1.0, 1.2)	4.9 (2.5, 9.4)
Total nonchromosomal	120	71.6 (59.6, 84.9)	7613	19.1 (18.6, 19.5)	3.8 (3.2, 4.5)
Chromosomal anomalies	9	5.4 (2.5, 10.2)	1747	4.4 (4.2, 4.6)	1.2 (0.6, 2.4)
Grand total	129	76.9 (64.6, 90.8)	9359	23.4 (23.0, 23.9)	3.3 (2.8, 3.9)

Rates (95% CI) of major groups and selected subtypes of congenital anomalies* in pregnancies of women with and without pre-existing diabetes per 1000 singleton pregnancies and relative risk (95% CI).

* European Surveillance of Congenital Anomalies (EUROCAT) coding.

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Targeted preconception physical examination for women with diabetes

Dilated funduscopy examination by an ophthalmologist
Examination for thyromegaly
Cardiac auscultation
Evaluation for carotid bruits and pulses present to the periphery
Blood pressure measurement in both arms and pulse, lying and standing to check for orthostasis
Lung auscultation
Check for succussion splash if patient not fasting
Check sensation and check for tremor, hypo- or hyper-reflexia

Graphic 97118 Version 1.0

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