

# PREGESTATIONAL DIABETES MELLITUS

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#### ABSTRACT

The physiological changes which occur during pregnancy with diabetes are vast and involve every body system. In this chapter, we will review the metabolic changes that occur during normal pregnancies and those affected by pregestational diabetes. Due to the significant overlap in maternal and perinatal risks secondary to pregestational diabetes and obesity, we will review the risks of maternal obesity and hyperglycemia on maternal, fetal, and infant outcomes. The management of pregestational diabetes in pregnancy will be reviewed in detail including up-to-date medications and diabetes technologies. Postpartum issues including insulin sensitivity, changes in breastfeeding, and contraception for individuals with pregestational diabetes will be discussed.

## ROLE OF PRECONCEPTION AND INTERPREGNANCY COUNSELING/CARE

In recent years, increasing focus has been placed on improving preconception and inter-pregnancy care for reproductive-age individuals (1,2).Obstetric and perinatal outcomes are improved when an individual with pregestational diabetes enters pregnancy in a medically-optimized state (3-6). Since roughly 50% of pregnancies are unplanned, it is in the individual's best interest if their team begins discussing contraception and family planning during adolescence and early adulthood, as recommended by the American Diabetes Association (ADA) (7). Among those with pregestational diabetes, emphasis on strict glycemic control, folic acid supplementation, nutrition and physical activity, encouraging weight overweight/obese loss in individuals. discontinuation of potentially harmful medications (such as statins, angiotensin converting enzyme [ACE] inhibitors), and optimization of associated medical conditions, are all important components of preconception care. Those with pregestational diabetes mellitus (DM) who are planning pregnancy should ideally be engaged in multidisciplinary care in the preconception timeframe with a team that includes an endocrinology health care professional,

maternal fetal medicine specialist, registered dietician, and diabetes care and education specialist (7). Counseling should include a review of diabetes-related short- and long-term risks to the pregnant individual and fetus and the relationship of such risk to glycemic control in the peripartum period.

Hyperglycemia in the months leading up to conception and through the first trimester confers a significant "dose-dependent" risk of congenital anomalies, including fetal cardiac and skeletal defects. as well as miscarriage (8-10). A glycosylated hemoglobin (A1c) value ≤6.0% around the time of conception is associated with a risk for congenital anomalies of 1-3%, similar to the baseline population risk (9). Hence, the ADA recommends achieving an A1c <6.5% prior to conception, while the American College of Obstetricians and Gynecologists (ACOG) recommends an even stricter target of an A1c <6.0% (7,11). Furthermore, if diabetes is poorly controlled or sequelae such as renal and cardiac

disease are present at the time of conception, obstetric risks of hypertensive disorders of pregnancy (HDP), preterm delivery, and stillbirth are also increased (12,13).

We encourage health care providers to view every encounter with an individual of reproductive age as a pre-conception visit, in particular because nearly half of pregnancies in the US are not planned (Figure 1). Socio-economic barriers including poor health literacy, smoking, being unmarried, lower family income, and poor relationship with their provider are associated with an absence of prepregnancy care, so increased efforts must be made to provide avenues to discuss family planning among these individuals (14). Some suggested solutions include app-based platforms to engage individuals and provide education on diet and lifestyle as well as pharmacy-based surveys to identify individuals who require folic acid supplements or other medication adjustments (15, 16).



Figure 1. Adapted from Wilkie, G. & Leftwich, H. (2020). Optimizing Care Preconception for Individuals With Diabetes and Obesity. Clinical Obstetrics and Gynecology.

#### NORMAL GLUCOSE LEVELS IN PREGNANCY

Understanding normative glucose levels in pregnancy is important for setting glycemic targets in pregnant individuals with pregestational diabetes. The first change that happens is a fall in fasting glucose levels, which occurs early in the first trimester. In the second and third trimesters, glucose levels rise slightly due to insulin resistance. A review of the literature including all available trials using continuous glucose monitors (CGM), plasma glucose samples, and self-monitored blood glucose (SMBG) demonstrated that pregnant individuals without diabetes and obesity during the third trimester (~34 weeks) have on average a fasting blood glucose (FBG) of 71 mg/dl; a 1 hour postprandial (PP) glucose of 109 mg/dl; and a 2 hour value of 99 mg/dl, which are all much lower than the current targets for glycemic control for pregnant individuals

with diabetes (17) (Figure 2). Increasing gestational age affects "normal" glucose levels. A longitudinal study of 32 healthy, normal weight pregnant individuals between 16 weeks' gestation to 6 weeks postpartum demonstrated a rise in mean glucose levels using CGM from 16 weeks (82.3 mg/dl) to 36 weeks (94.0 mg/dl) which was maintained at 6 weeks postpartum (93.7 mg/dl) (18). Two-hour postprandial levels were increased rising from 95.7 mg/dl at 16 weeks to a peak of 110.6 mg/dl at 36 weeks. Although fasting blood glucose levels are lower in pregnancy, postprandial glucose levels are slightly elevated, which is likely related to the many impaired insulin action. altered ß cell secretion, hepatic gluconeogenesis, and placentally-derived circulating hormones (19). Among those without pregestational or gestational diabetes, many CGM parameters are higher in individuals with obesity compared to those with a normal BMI (20).



Figure 2. Glucose Levels During Pregnancy not affected by diabetes. A. Patterns of glycemia in normal pregnancy (gestational week  $33.8 \pm 2.3$ ) across 11 studies published between 1975 and 2008. B. Mean pattern of glycemia across 12 studies.

# REDUCING THE RISK OF CONGENITAL ANOMALIES

Hyperglycemia is a teratogen and can result in complex cardiac defects, central nervous system (CNS) anomalies such as anencephaly and spina bifida, skeletal malformations, and genitourinary abnormalities (21–23). A systematic review of 13 observational studies of pregnant individuals with pregestational diabetes demonstrated that poor glycemic control resulted in a pooled odds ratio of 3.44 (95%CI 2.3-5.15) of a congenital anomaly, 3.23 (CI 1.64- 6.36) of spontaneous loss and 3.03 (1.87-4.92) of perinatal mortality compared to individuals with

optimal glycemic control (24). Individuals with a normal A1c at conception and during the first trimester have no increased risk while individuals with an A1c of 10-12% or a fasting blood glucose >260 mg/dl have up to a 25% risk of major congenital malformations (25,26). A recent analysis of 1,676 deliveries to individuals with pregestational diabetes between 2009-2018 found a similar significant rate of congenital anomalies especially with increasing A1c at the first prenatal visit: individuals with an A1c of 10% had a major congenital anomaly rate of 10% while individuals with an A1c of 13% had a 20% major anomaly rate. The overall anomaly rate was 8% in this contemporary cohort of whom 91% had type 2

diabetes (T2DM) (27). The offspring of individuals with type 1 diabetes T1DM have higher prevalence of neonatal death as well as infant death compared with individuals offspring of without diabetes. >6.5%, Periconception A1c preconception retinopathy, and lack of preconception folic acid supplementation were all independently associated with risk of neonatal and infant death (28). A recent systematic review and meta-analysis also showed an increased risk of neonatal mortality and stillbirth in pregnancies affected by T2DM compared with those without diabetes (29). Most organizations recommend pregnant individuals with pregestational diabetes achieve an A1c of less than 6.5% prior to conception (30,31). For individuals with hypoglycemia unawareness, less stringent glycemic targets may need to be used such as an A1c <7.0%. The A1C falls in pregnancy and if it is possible without significant hypoglycemia, an A1c of less than 6% is recommended.

The mechanism of glucose-induced congenital anomalies has not been fully elucidated (32). It has been shown that diabetes-induced fetal abnormalities may be mediated by a number of metabolic disturbances, including elevated superoxide dismutase activity, reduced levels of myoinositol and arachidonic acid, and inhibition of the pentose phosphate shunt pathway. Oxidative stress appears to be involved in the etiology of fetal dysmorphogenesis and neural tube defects in the embryos of diabetic mice and are also associated with altered expression of genes which control development of the neural tube (33).

Individuals with T2DM are more likely to be treated for dyslipidemia and hypertension. Chronic hypertension occurs in 13-19% of individuals with T2DM and many of these individuals will be prescribed an ACE inhibitor or Angiotensin receptor blocker (ARB) (34). The data on risk for first trimester exposure to ACE inhibitors is conflicting (see nephropathy section). Depending on the indication for use, an informed discussion on the benefits and risks of stopping these agents before pregnancy must occur but they should certainly be stopped as soon as a missed period occurs. The data on teratogenicity of statins for treatment of hypercholesterolemia is also conflicting and is based on animal, not human, studies (35). Pravastatin has had favorable effects on vascular endothelial growth factor in animal studies (36-38). A small multicenter pilot study examining pravastatin in prevention of HDP in high-risk pregnant individuals found that pravastatin was safe when started between 12-16 weeks gestation (39). There is a large randomized clinical trial of 1,550 pregnant individuals evaluating pravastatin to prevent HDP that is ongoing currently (ClinicalTrials.gov ID NCT03944512). At this time, current guidelines recommend that statins be stopped prior to pregnancy, but definitely at diagnosis of pregnancy, for most individuals (7). Continuation of statins preconception and during pregnancy may be warranted through shared decision making and risk/benefit discussions in high-risk individuals (40).

# INFLUENCE OF METABOLIC CHANGES IN PREGNANCY

Pregnancy is a complex metabolic state that involves dramatic alterations in the hormonal milieu in addition to changes in adipocytes and inflammatory cytokines. There are high levels of estrogen, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone, human chorionic somatomammotropin (human placental lactogen), leptin, TNF $\alpha$ , and oxidative stress biomarkers. In addition, decreases in adiponectin worsen maternal insulin resistance in the second trimester to facilitate fuel utilization by the fetus (41).

Metabolically, the first trimester is characterized by increased insulin sensitivity, which promotes adipose tissue accretion in early pregnancy. What mediates this increased insulin sensitivity remains unclear. Pregnant individuals are at an increased risk for hypoglycemia, especially if accompanied by nausea and vomiting in pregnancy. Although most pregnant individuals show an increase in insulin sensitivity between 6-20 weeks' gestation and report more frequent episodes of hypoglycemia, especially at night, there is a transient increase in insulin resistance very early in pregnancy (prior to 10 weeks), usually followed by increased insulin sensitivity up until 14-20 weeks (42).

In the fasting state, pregnant individuals deplete stores their glycogen quickly due to the fetoplacental glucose demands, and switch from carbohydrate to fat metabolism within 12 hours. resulting in increased lipolysis and ketone production (43–45). In pregnant individuals without diabetes, the second and third trimesters are characterized by insulin resistance with a 200-300% increase in the insulin response to glucose (46). This serves to meet the metabolic demands of the fetus, which requires 80% of its energy as glucose, while maintaining euglycemia in the mother. The placental and fetal demands for glucose are considerable and approach the equivalent of ~150 grams per day of glucose in the third trimester (44). In addition, the maternal metabolic rate increases by ~150-300 kcal/day in the third trimester, depending on the amount of gestational weight gain. These increased nutritional needs place the pregnant individual at risk for ketosis, which occurs much earlier than usual without adequate oral or intravenous nutrients, frequently referred to as "accelerated starvation of pregnancy" (43). See "Diabetic Ketoacidosis in Pregnancy" section for further details.

## DIABETES COMPLICATIONS AND TREATMENT OPTIONS IN INDIVIDUALS WITH PREGESTATIONAL DIABETES AND THE ROLE OF PRECONCEPTION COUNSELING

Although historically, T1DM has been more prevalent than T2DM in individuals of child-bearing age, this is changing with increased obesity rates worldwide. The prevalence of prediabetes and diabetes is a burgeoning global epidemic (47,48). In the United States, the prevalence of diabetes among adults between 1980 and 2020 has quadrupled with an estimated 21.9 million adults living with diabetes, including reproductive aged individuals (48). There was higher prevalence of diabetes among non-Hispanic blacks and Mexican Americans (49). Similar temporal trends, as well as racial and ethnic disparities, have been observed in the rate of pregestational diabetes among pregnant individuals in the US (Figures 3 and 4) (50).



Figure 3. Rate of pregestational diabetes in the United States, 2016-2021.



Figure 4. Rate of pregestational diabetes by race and Hispanic origin in the United States, 2021.

Both pregnant individuals with T1DM and T2DM are at increased risk of poor obstetrical outcomes, and both can have improved outcomes with optimized care (5,51). The White Classification (Table 1) was developed decades ago by Priscilla White at the Joslin Clinic to stratify risk of adverse pregnancy outcomes in individuals with T1DM according to the age of the individual, duration of diabetes, and presence of vascular complications of diabetes. Although recent evidence suggests that the classification does not predict adverse pregnancy outcomes better than taking into account the increased risk of micro- and macrovascular disease retinopathy, (e.g. nephropathy, hypertension, coronary artery disease, etc.), it is still often used in the U.S. to indicate level of risk for adverse pregnancy outcomes (52). Although it was developed for use in individuals with T1DM rather than T2DM, given the very low prevalence of T2DM in individuals of childbearing age decades ago when it was first established in 1949, many also apply

it to this group of individuals. ACOG further modified it in 1986, and gestational diabetes (GDM) was added to the classification and designated as A1 (controlled by diet alone) and A2 (controlled by medication). Pregnant individuals with T2DM are at least as high of a risk of pregnancy complications as individuals with T1DM. The reasons for this may include older age, a higher incidence of obesity, a lower rate of preconception counselina. disadvantaged socioeconomic backgrounds, and the co-existence of the metabolic syndrome including hyperlipidemia, inflammation chronic hypertension, and (34). Furthermore, the causes of pregnancy loss appear to differ in individuals with T1DM versus T2DM. In one series comparing outcomes, >75% of pregnancy losses in individuals with T1DM were due to major congenital anomalies or prematurity (53). In individuals with T2DM, >75% were attributable to stillbirth or chorioamnionitis, suggesting that obesity may play a role.

Table 1. Modified White Classification of Pregnant Diabetic Individuals						
Class	Diabetes onse	Duration (year)	Type of Vascular	Medication Need		
	age (year)		Disease			
Gestational Diabetes (GDM)						
A1	Any	Pregnancy	None	None		
A2	Any	Pregnancy	None	Yes		
Pregestational Diabetes						
В	20	<10	None	Yes		
С	10-19 OR	10-19	None	Yes		
D	<10 OR	20	Benign	Yes		
			Retinopathy			
F	Any	Any	Nephropathy	Yes		
R	Any	Any	Proliferative	Yes		
			Retinopathy			
Т	Any	Any	Renal Transplant	Yes		
Н	Any	Any	Coronary Artery	Yes		
			Disease			

## MANAGEMENT OF PREGESTATIONAL DIABETES DURING PREGNANCY

## **Treatment Options in Achieving Glycemic Control**

All pregnant individuals with T1DM and T2DM should target an A1c of <6.5% preconception and <6.0% during pregnancy when possible. For pregnant individuals with T2DM on oral or noninsulin injectable agents, consider switching to insulin prior to pregnancy, even in individuals with goal glycemic control. Insulin should be used for management of T1DM and is the preferred agent for management of T2DM in pregnancy.

# ORAL AND NON-INSULIN INJECTABLE GLYCEMIC LOWERING AGENTS

No oral hypoglycemics, including metformin and glyburide, are approved for pregestational diabetes in pregnancy. There is no evidence that exposure to glyburide or metformin in the first trimester are teratogenic, but both do cross the placenta, metformin substantially more than glyburide (54–56). Both of these agents have been used in multiple randomized controlled trials (RCTs) for GDM and T2DM. Please see Endotext Gestational Diabetes chapter.

#### Metformin

Early studies on metformin use in pregnancy for individuals with pregestational diabetes found high failure rates of monotherapy and mixed results on the impact on pregnancy outcomes (57,58). Recent randomized trials have evaluated the safety and efficacy of metformin in pregnancy for individuals with T2DM (59,60). The Metformin in Women with Type 2 Diabetes in Pregnancy Trial (MiTy) enrolled 502 individuals with T2DM and randomized them to metformin 1000 mg twice daily or placebo, added to insulin (60). They found no difference in their primary outcome which was a composite of serious neonatal outcomes. They found that individuals treated with metformin achieved better glycemic control, required less insulin, had less gestational weight gain (GWG), and were less likely to deliver via cesarean. Neonates exposed to metformin were more likely to be SGA and had reduced adiposity. The Medical Optimization and Management of Pregnancies with Overt Type 2 Diabetes (MOMPOD) trial enrolled 794 pregnant individuals with a diagnosis of T2DM prior to pregnancy or a diagnosis of diabetes early in pregnancy and randomized them to metformin 1000 mg twice daily or placebo (59). They found no difference in their primary composite neonatal outcome. Metformin exposed neonates were less likely to be LGA.

Data on long term outcomes for offspring exposed to metformin come from trials in both GDM and pregestational diabetes. Follow up from the Metformin in Gestational Diabetes (MiG) trial followed 208 children (28% of original trial) and found no differences in body composition or metabolic outcomes at 7 years (61). At 9 years the metformin offspring were slightly larger by measures of BMI and skinfolds. In 24 month follow up of the MiTy trial, 263 children (61% of original trial) were assessed and no differences in BMI Z score or mean sum of skinfolds was found (62). A systematic review and meta-analysis of neonatal and childhood outcomes following treatment with metformin versus insulin for GDM, demonstrated that while offspring exposed to metformin had lower birth weights, they were heavier as infants and had higher BMIs as children.

Metformin has historically been used preconception and throughout the first trimester in individuals with polycystic ovary syndrome (PCOS) to improve fertility and prevent early miscarriage. However, trials have not shown benefit in use of metformin for preventing spontaneous abortion and have demonstrated letrozole as the preferred agent for ovulation induction (63–65). Current guidelines therefore recommend the use of metformin in those with PCOS who demonstrate glucose intolerance but not as a primary agent to improve fertility or pregnancy outcomes (66). Per ADA recommendations, metformin prescribed for the purpose of ovulation induction should be discontinued by the completion of the first trimester (7).

When used in pregnancy, metformin is typically prescribed with a starting dose of 500 mg once or twice daily for 5-7 days. If well tolerated, the dose can subsequently be up titrated to a maximum dose of 2500 mg daily in divided doses with meals. The most common reported side effects are gastrointestinal complaints (67). Metformin should be avoided in those with renal insufficiency.

## Glyburide

Data on glyburide in pregnancy comes from studies on its use in individuals with GDM. Briefly, meta-analyses have demonstrated increased risk of adverse neonatal outcomes such as neonatal hypoglycemia, macrosomia and increased neonatal abdominal circumference.(68,69) There is a dearth of evidence on long term outcomes of offspring exposed to glyburide.

# Other Agents

There is minimal data on thiazolidinediones, metiglinides, dipeptidyl peptidase IV (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and sodium-glucose transport protein 2 (SGLT-2) inhibitors. A 2023 review of the evidence on GLP-1 agonist and SGLT-2 inhibitors found potential teratogenicity and adverse pregnancy outcomes based largely on animal data and more limited human data (70). Additional data on SGLT-2 inhibitors and DPP-4 inhibitors is reassuring but extremely limited (71).

GLP-1 agonist use, in particular, has increased in the general population over the last decade (72). Outside of pregnancy, these agents are approved for use in individuals with obesity and T2DM with HbA1c above goal, atherosclerotic cardiovascular disease, or chronic renal disease (73-75). Studies have shown their use can lead to a reduction in HbA1c, weight loss. and a decrease in athero-thrombotic events in nonpregnant individuals (73,74,76). Animal studies of exposure to GLP-1 agonists during pregnancy have shown associations with congenital anomalies, decreased fetal growth, and embryonic death (70,73,77). Two recent observational studies on periconceptual use of GLP-1 agonists in humans have not demonstrated an association between GLP-1 agonist use and major congenital malformations (71,78). However, these studies have limited data on maternal glycemic control and on other important adverse pregnancy outcomes such as HDP, preterm birth, and fetal growth restriction (73).

At this time, the use of these agents in pregnancy should ideally occur only in the context of approved clinical trials.

#### INSULIN USE IN PREGNANCY

## **Overall Approach**

Both ADA and ACOG recommend insulin as first line therapy for pregnant individuals with pregestational diabetes while trying to conceive and during pregnancy (7,11). Unlike oral agents, insulin preparations commonly utilized in pregnancy do not cross the placenta (79-81). It is recommended that individuals with T2DM who are actively trying to become pregnant should be switched from oral or noninsulin injectable hypoglycemic agents to insulin prior to conception if possible. This rationale is based on the fact that it may take some time to determine the ideal insulin dose prior to the critical time of embryogenesis. However, individuals who conceive on any oral agents should not stop them until they can be switched effectively to insulin because hyperglycemia is potentially more dangerous than any of the current available therapies to treat diabetes. Following a review of risks and benefits, oral agents, such as metformin, may be considered as a reasonable adjunct or alternative therapy for those unable or unwilling to use insulin while attempting to conceive or during pregnancy.

## Basal Insulin

Basal insulin is given 1-2 times daily or via a continuous insulin infusion pump. Intermediate-acting insulin, such as neutral protamine Hagedorn (NPH), and long-acting insulin analogues, such as detemir and glargine may be used. Compared to NPH, both detemir and glargine have a flatter, more consistent insulin activity (82). Studies have shown no difference in pregnancy and neonatal outcomes when comparing glargine to NPH (83). Despite a lack of trial data, both U100 and U300 glargine are commonly used in pregnancy given a reassuring safety profile in observational studies (84,85). Trials of detemir, compared to NPH, have demonstrated improved glycemic control as well as lower rates of adverse pregnancy and neonatal outcomes (86-88). However, as of 2024, detemir has been discontinued on the US market. Limited data exists on the ultralong-acting insulin analog, degludec. A 2023 trial showed degludec was noninferior to determir when used in a basal-bolus regimen with respect to glycemic control and pregnancy outcomes (89). There have been no studies looking at the safety of newer basal insulins such as biosimilar glargine (Basaglar), however these are commonly used in pregnancy due to constraints of availability and insurance coverage.

Basal insulin may be provided as two doses of NPH or with one or two doses of a long-acting analogue. Fasting hyperglycemia may be best targeted by the use of NPH before bedtime to take advantage of its 8hour peak. The evening dose of NPH should be administered at bedtime, rather than dinner, to avoid nocturnal hypoglycemia and prevent fasting hyperglycemia (81).

#### Bolus Insulin

Bolus insulin dosing is provided with short- or rapidacting insulin with doses calculated based on pre-meal glucose and carbohydrate intake using a correction factor and insulin to carbohydrate ratio (90). Alternatively, fixed meal-time insulin dosing can be prescribed. Rapid-acting insulins, lispro and aspart, have been used in multiple trials in pregnancy, and their safety and efficacy are well-established. Lispro and aspart are preferred to short-acting regular insulin due to improvement in postprandial glycemia and reduced hypoglycemia, with equivalent fetal outcomes (91,92). Patient satisfaction has also been higher for individuals using lispro or aspart compared to regular insulin (87). Lispro or aspart insulin may be especially helpful in pregnant individuals with hyperemesis or gastroparesis because they can be dosed after a successful meal and still be effective. It has been demonstrated that rapid acting insulins may take longer to reach maximal concentrations (49 [37-55] vs 71 [52-108] min) in late gestation (93). Thus, for some pregnant individuals it may be necessary to take mealtime insulin 15-30 minutes prior to the start of a meal (termed pre-bolusing). If used in conjunction with NPH, due to its longer duration of action, regular insulin should be taken twice a day with a second dose no sooner than 5 hours after the initial dose (94). Regular insulin should generally be given 30-60 minutes prior to starting a meal. Despite limited data, both ultra rapid-acting aspart (Fiasp) and lispro

(Lyumjev) are approved for use in Europe given similarities to their rapid-acting versions (95). A recent trial in pregnant individuals comparing rapid-acting aspart to ultra rapid-acting aspart found no difference in A1c or mean birthweight (96).

An understanding of behavior and lifestyle including mealtimes, sleep, work schedules, and physical activity, in conjunction with blood glucose data, may aid in the selection of an appropriate basal and bolus regimen. Pharmacologic therapy should occur in conjunction with ongoing nutritional therapy and lifestyle changes.

# Continuous Subcutaneous Insulin Infusion (CSII) or Insulin Pump Therapy

Many pregnant individuals with T1DM or long-standing T2DM require multiple daily injections (MDI, 4-5 injections per day) or a continuous subcutaneous insulin infusion pump (CSII) to achieve optimal glycemic control during pregnancy. Many individuals with T1DM use CSII and CGM during pregnancy (97). CGM will be reviewed in detail below. There have been several studies showing CSII use is safe in pregnancy. In a large multicenter trial of individuals with T1DM during pregnancy, individuals using CSII had improved A1c both in the first trimester as well as in the third trimester and there was no difference in rates of diabetic ketoacidosis (DKA) or severe hypoglycemia compared with individuals using MDI (98). An analysis of data from 248 individuals with T1DM enrolled in the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) showed that pregnant individuals using MDI therapy versus CSII therapy had similar first trimester glycemia but MDI users had lower glycemia at 34 weeks and were more likely to achieve target A1c than CSII users. In this analysis, CSII users had an increased risk of NICU admission, neonatal hypoglycemia, hypertensive and disorders of pregnancy compared with MDI users (99). Several additional studies and a Cochrane review of MDI

versus CSII generally have shown equivalent glycemic control, as well as maternal and perinatal outcomes (100–105). CSII can be especially useful for individuals with nocturnal hypoglycemia, gastroparesis, or a prominent dawn phenomenon (99).

Disadvantages of CSII include cost and the risk for hyperglycemia or DKA as a consequence of insulin delivery failure from a kinked catheter or from infusion site problems, although rare (106). Pregnant individuals should be educated on how to quickly recognize and manage insulin pump failure. Therefore, it may be optimal to begin pump therapy before pregnancy due to the steep learning curve involved with its use and the need to continually adjust basal and bolus settings due to the changing insulin resistance in pregnancy. However, in motivated pregnant individuals with a multidisciplinary team of diabetes education specialists and pump trainers, insulin pump initiation is safe in pregnancy. Several studies demonstrate significant changes in bolus more than basal insulin requirements during pregnancy which should be understood to achieve optimal glycemic control(107,108).

## Automated Insulin Delivery

Automated insulin delivery (AID) systems are comprised of a CGM, an insulin pump, and an algorithm that uses CGM data to calculate insulin (109). Diabetes technology use in general, and AID use specifically, has become increasingly prevalent and is expected to continue to increase in the coming years (110,111). The existing data on AID use in pregnancy have shown improved or equivalent CGM metrics when compared with MDI (112-114). The Automated insulin Delivery Among Pregnant Women with TIDM (AiDAPT) trial was a multicenter, randomized controlled trial of 124 pregnant individuals with T1DM comparing MDI to AID with a pregnancyspecific target glucose range (112). Those using AID spent more time in range, spent less time above range, and had lower A1c levels. There were no safety concerns, including severe hypoglycemia or DKA associated with AID use. Other trials of AID use in pregnancy have not used pregnancy-specific glucose targets and participants in these studies have used assistive techniques that override algorithms such as 'fake' carbohydrate insulin boluses and use of mode with stricter ranges such as sleep mode. This includes CRISTAL, a randomized controlled trial of 95 pregnant individuals with T1DM comparing AID to MDI (113). There was no difference in the primary outcome of time in range, however those using AID had more overnight time in range and had less time below range. Studies have not yet demonstrated improvements in other pregnancy outcomes with AID use; however, several trials are ongoing (115,116). In 2024, the CamAPS FX algorithm, used in the AiDAPT trial was Food and Drug Administration (FDA) approved for use in pregnancy. There are several additional AID systems that are FDA approved for use outside of pregnancy. In the interim, pregnant individuals are also using do-it-yourself AID systems and while no observational study or trial data exist, case reports to date have shown positive outcomes and patient experiences (117-119).

Few studies have evaluated patient perspectives and psychosocial implications of AID use in pregnancy. Those that do exist suggest both benefits and burdens of these systems (120–122). Benefits include improved well-being, greater flexibility, and more positive collaboration between pregnant individuals and their healthcare team. Burdens include technical failures, device maintenance, system bulk/visibility, and access to an overwhelming amount of data. Ongoing education and support for both patients and providers are necessary to optimize the balance of these positive and negative aspects of AID use in pregnancy (120,123).

The ADA recommends that AID systems with pregnancy specific targets are preferred for use in pregnancy; however, those without pregnancy specific targets may be considered for use in collaboration with

experienced health care teams (7). Glycemic control, comfort with technology, social determinants of health, and individual preference should all be considered when evaluating individuals for AID use in pregnancy.

#### Importance of Glycemic Control

Failure to achieve optimal control in early pregnancy may have teratogenic effects in the first 3-10 weeks of gestation or lead to early fetal loss. Poor glycemic control later in pregnancy increases the risk of intrauterine fetal demise, macrosomia, cardiac septal enlargement in the fetus, perinatal death, and metabolic complications such as hypoglycemia in the newborn. Target glucose values for fasting and postprandial times should be discussed with the pregnant individual. Current guidelines are that fasting and pre-meal blood glucose should be 70-95 mg/dl, the 1-hour postprandial glucose should be 110-140 mg/dl and the 2-hour postprandial glucose should be 100-120 mg/dl (7,11). Although a review of the literature suggests that the mean fasting plasma glucose (FPG), 1 hour PP, and 2 hour PP +/- 1 SD glucose values are significantly lower in normal weight individuals in the 3rd trimester (FPG ~71 +/- 8 mg/dl; 1 hour PP ~109 +/- 13 mg/dl; 2 hour PP 99 +/- 10 mg/dl) than current therapeutic targets (19), no RCTs have been completed to determine whether lowering the therapeutic targets results in more favorable pregnancy outcomes. A prospective study in pregnant individuals with T1DM showed less HDP with glucose targets of fasting <92 mg/dl, preprandial <108 mg/dl and 1 hour postprandial <140 mg/dl (124). An A1c should be done at the first visit and every 1-3 months thereafter depending on if at target or not (<6% if possible, with minimal hypoglycemia) (11,30). Additional labs and exams recommended for individuals with pregestational diabetes during pregnancy are summarized in Table 2.

Table 2. Evaluation of Pregnant Individuals with Pregestational Diabetes				
Initially and every 1 – 3 months				
TSH every trimester if + TPO antibodies				
Cr; Urine albumin or If abnormal, obtain 24-hour urine for protein and estimated CrCl Repeat				
inuria				
AST,				
uation				
uation				

Abbreviations: glycosylated hemoglobin (A1c), thyroid stimulating hormone (TSH), thyroid peroxidase (TPO), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), metabolic dysfunction-associated steatotic liver disease (MASLD), creatinine (Cr), electrocardiogram (EKG).

The risk of maternal hypoglycemia needs to be weighed against the risk of maternal hyperglycemia. Maternal hypoglycemia is common and often severe in pregnancy in individuals with T1DM. During the first trimester, before the placenta increases the production of hormones, nausea and increased insulin sensitivity may place the mother at risk for hypoglycemia. Pregnant individuals must be counseled that their insulin requirements in the first trimester are likely to decrease by 10-20% (125). This is especially true at night when prolonged fasting and continuous fetal-placental glucose utilization places the pregnant individual at even higher risk for hypoglycemia. One of the highest risk periods for severe hypoglycemia is between midnight and 8:00 a.m. Pregnant individuals with diabetes complicated by gastroparesis or hyperemesis gravidarum are at the greatest risk for daytime hypoglycemia. In a series of 84 pregnant individuals with T1DM, hypoglycemia requiring assistance from another person occurred in 71% of individuals with a peak incidence at 10-15 weeks gestation (126). One third of individuals had at least one severe episode resulting in seizures, loss of consciousness, or injury. There are also data to suggest that the counterregulatory hormonal responses to hypoglycemia, particularly growth hormone and epinephrine, are diminished in pregnancy (127,128). This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control in the preconception period, by the use of analogue insulins, and with the use of CGM (128,129). Insulin pumps with or without CGM may help achieve glycemic targets without increasing hypoglycemia (98,131,132).

Use of CGM especially with real-time sensor glucose data shared with a partner has been shown to reduce fear of hypoglycemia in pregnancy. The risk of hypoglycemia is also present in pregnant individuals with T2DM but tends to be less so than in individuals with T1DM (133). The risk of hypoglycemia to the fetus is difficult to study but animal studies indicate that hypoglycemia is potentially teratogenic during organogenesis (134). Exposure to hypoglycemia in utero may have long-term effects on the offspring including neuropsychological defects (134). To help reduce risk of nocturnal hypoglycemia, individuals with T1DM may need a small bedtime snack and/or reduce overnight basal insulin doses. Every pregnant individual should have a glucagon emergency kit (intramuscular injection or intranasal) and carry easily absorbed carbohydrate at all times. Education of individuals and care providers to avoid hypoglycemia reduce the incidence of hypoglycemia can unawareness. The incidence of severe hypoglycemia in pregnant individuals with T1DM can be reduced without significantly increasing A1c levels and is a priority given hypoglycemic unawareness worsens with repeated episodes and can result in maternal seizures and rarely maternal death (135).

By 18-20 weeks of gestation, peripheral insulin resistance increases resulting in increasing insulin requirements so that it is not unusual for a pregnant individual to require 2-3 times as much insulin as she did prior to pregnancy depending on baseline insulin resistance, carbohydrate intake, and body mass index. In a study of 27 individuals with T1DM on an insulin pump, the carbohydrate-to-insulin ratio intensified 4-fold from early to late pregnancy (e.g. 1 unit for every 20 grams to 1 unit for every 5 grams), and the basal insulin rates increased 50% (107).

## **Glucose Monitoring Timing and Frequency**

Pregnant individuals with diabetes must frequently self-monitor their glucose to achieve tight glycemic

control. Since fetal macrosomia (overgrowth) is related to both fasting and postprandial glucose excursions, pregnant individuals with diabetes need to monitor their post-meal and fasting glucoses regularly and those using a flexible intensive insulin regimen also need to monitor their pre-meal glucose values (136).

Postprandial glucose measurements determine if the insulin to carbohydrate ratios is effective in meeting glycemic targets as optimal control is associated with less macrosomia, metabolic complications in the fetus, and possibly HDP (124,137). Due to the increased risk of nocturnal hypoglycemia with intensive insulin therapy, glucose monitoring during the night is often necessary given the frequent occurrence of recurrent hypoglycemia and resulting hypoglycemic unawareness with the achievement of tight glycemic control.

## **Continuous Glucose Monitoring**

CGM may help identify periods of hyper- or hypoglycemia and certainly confirm glycemic patterns and variability (138,139). In pregnancy, the mean sensor glucose may be better at estimating glycemic control than A1c (140). The previously mentioned CONCEPTT trial was a large multicenter trial that examined CGM use in individuals planning pregnancy as well as pregnant individuals with T1DM using either MDI or insulin pump therapy (139). This study found statistically significantly lower incidence of LGA infants, less neonatal intensive care unit stays, and less neonatal hypoglycemia with CGM used compared to capillary glucose monitoring. There was a small difference in A1c among the pregnant individuals using CGM, less time spent in hyperglycemia range, and more time spent in range. Importantly this was the first study to show improvement in non-glycemic clinical outcomes for CGM use in pregnancy (139). A follow-up study to the CONCEPTT trial found that pregnant individuals using real-time CGM compared to capillary glucose monitoring were more likely to

achieve ADA and NICE (National Institute of Clinical Excellence) guidelines for A1c targets by 34 weeks Similar to CONCEPTT. gestation. additional observational studies have demonstrated that modest increases (5%) in TIR are associated with improved glycemic control and reduced neonatal morbidity (141,142). Data on the use of CGM for pregnant individuals with T2DM is more limited and has not consistently demonstrated improved outcomes (143-145). There are multiple ongoing trials investigating the impact of CGM on pregnancy outcomes in individuals with T2DM (146,147).

Given the improvement demonstrated in outcomes, the ADA recommends CGM for use in pregnant individuals with T1DM. However, due to insufficient data in pregnant individuals with T2DM, use of CGM in this population may be considered on an individualized basis. For pregnant individuals with T1DM, the International Consensus on Time in Range recommends increasing time in range in pregnancy quickly and safely with a pregnancy goal sensor glucose range of 63 to 140 mg/dl with >70% time in range, <25% time above range (>140 mg/dl), <4% of time below 63 mg/dl, and <1% time below 54 mg/dl (148). The expert guidance recommends the same glucose goal ranges for pregnant individuals with T2DM or GDM but do not specify goals for time spent in each range due to lack of clear evidence in these populations.

CGM has been an advancing technology with tremendous improvements in accuracy, comfort, longer duration, convenience, and insurance coverage over the past decade. Some newer CGM devices are factory calibrated and do not require fingerstick glucose calibrations. There are also flash CGM systems on the market which require scanning of the sensor with a receiver to display the sensor glucose. The Freestyle Libre and Dexcom G7 are now approved for use in pregnancy, while several others continue to be used during pregnancy off-label. Pregnant individuals with diabetes may use CGM either in conjunction with an insulin pump or with MDI therapy to help achieve glycemic control.

Sensor glucose values from CGM may not be as accurate at extremes of hypo- or hyperglycemia or with rapid changes in glucose, so individuals should always check fingerstick glucose if she feels the glucose value is different than the displayed sensor glucose value. CGM values may have a lag time behind actual plasma glucose values.

## Glycosylated Hemoglobin (A1c)

A1c may be used as a secondary measure in pregnancy with a goal of <6% considered optimal if able to be achieved without increased risk of hypoglycemia (7,11). Improved pregnancy outcomes have been demonstrated with A1c <6-6.5% including lower risk of congenital anomalies, HDP, preterm delivery, shoulder dystocia, and NICU admission (8-10,149). However, A1c is a summative measure that may not capture fluctuations in hypoand hyperglycemia. Due to physiological changes in red blood cell turnover during pregnancy, A1c levels fall during normal pregnancy and levels may require more frequent monitoring than in non-pregnant populations (150, 151).

#### DIABETES MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

Individuals should be up-to-date on screening for complications of diabetes prior to conceiving. Diabetes care providers should discuss risk of adverse outcomes pregnancy and progression of complications during pregnancy especially in individuals with retinopathy and nephropathy (152,153).

## Retinopathy

Diabetic retinopathy may progress during pregnancy and throughout the first year postpartum. However, pregnancy does not cause permanent worsening in mild retinopathy (154,155). The cause for progression in moderate and especially severe proliferative retinopathy is likely due to a combined effect of the rapid and tight glycemic control, increased plasma volume, anemia, placental angiogenic growth factors, and the hypercoagulable state of pregnancy (156,157). In 179 pregnancies in individuals with T1DM who were followed prospectively, progression of retinopathy occurred in 5% of individuals. Risk factors for progression were duration of diabetes >10 years and moderate to severe background retinopathy (156). The risk of progression of retinopathy is most pronounced in individuals with more severe pregestational proliferative retinopathy. chronic hypertension, HDP, development of hypertension during pregnancy, and poor glycemic control prior to pregnancy (158). For these individuals, proliferative retinopathy may also progress during pregnancy, especially in individuals with hypertension or poor glycemic control early in pregnancy (159). Pregnancy can also contribute to macular edema, which is often reversible following delivery (160).

Therefore, individuals with T1DM and T2DM should ophthalmological assessment before have an conception. All guidelines recommend that individuals have a comprehensive eye exam or fundus photography before pregnancy and in the first trimester. Laser photocoagulation for severe nonproliferative or proliferative retinopathy prior to pregnancy reduces the risk of vision loss in pregnancy and should be done prior to pregnancy (31). Individuals with low-risk eye disease should be followed by an ophthalmologist during pregnancy, but vision-threatening progression significant of retinopathy is rare in these individuals. For visionthreatening retinopathy, laser photocoagulation can be used during pregnancy (160). Safety of

bevacizumab injections during pregnancy is not clear with some case reports of normal pregnancy after bevacizumab injections for macular edema in pregnancy, and other early pregnancy loss following bevacizumab injection. In individuals with severe untreated proliferative retinopathy, vaginal delivery with the Valsalva maneuver has been associated with retinal and vitreous hemorrhage. Little data exist to guide mode of delivery in individuals with advanced retinal disease and some experts have suggested avoiding significant Valsalva maneuvers—instead offering assisted second-stage delivery or cesarean delivery (26).

## Diabetic Nephropathy/Chronic Kidney Disease

Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications including HDP, preterm birth, cesarean section, congenital abnormalities, SGA, NICU admission, and perinatal mortality (152,161–164). Although proteinuria increases during pregnancy in individuals with preexisting nephropathy, those with a normal glomerular filtration rate (GFR) rarely have a permanent deterioration in renal function provided blood pressure and blood glucose are well-controlled (165–167). Those with more severe renal insufficiency (creatinine >1.5 mg/dl) have a 30-50% risk of a permanent pregnancy-related decline in GFR (168). Among pregnant individuals with diabetes. nephropathy significantly increases the risk of HDP. Factors which may contribute to worsening nephropathy in pregnancy include the hyperfiltration of pregnancy, increase in protein intake, hypertension, and withdrawal of ACE Inhibitors or ARBs. More stringent control of blood pressure in pregnancy may reduce the likelihood of increasing protein excretion and reduced GFR. In a series of 36 pregnant individuals with T1DM and nephropathy, maternal and obstetric outcomes were strongly dependent on the degree of maternal renal function (169). In normal pregnancy, urinary albumin excretion increases up to 30 mg/day and total protein excretion increases up to

300 mg/day (170). Individuals with preexisting proteinuria often have a significant progressive increase in protein excretion, frequently into the nephrotic range, in part due to the 30-50% increase in GFR that occurs during pregnancy. Prior to conception, individuals should be screened for chronic kidney disease. Dipstick methods are unreliable and random urine protein/creatinine ratios are convenient but not as accurate as other methods in pregnancy to carefully quantify proteinuria using 24-hour urine excretion. There have not been studies looking at spot urine albumin to creatinine ratio versus 24-hour urine protein assessment in pregnant individuals with diabetes. In hypertensive pregnant individuals, one study found that the spot urine albumin to creatinine ratio had higher diagnostic accuracy than 24-hour urine protein assessment (171). It is reasonable to collect a spot urine albumin to creatinine ratio in individuals who have not followed through with collection of 24-hour urine specimens.

There is conflicting information on whether firsttrimester exposure to ACE inhibitors and ARBs is associated with an increased risk of congenital malformations. A meta-analysis, limited by small study size (786 exposed infants), demonstrated a significant risk ratio (relative risk [RR] 1.78, 95% confidence interval [CI] 1.07-2.94) for increased anomalies in infants exposed to first-trimester ACE inhibitors and ARBs (172). However, the increased risk of congenital anomalies appears to be more related to hypertension itself, rather than drug exposure. There was no statistically significant difference when ACE inhibitor and ARB exposed pregnancies were compared with other hypertensive pregnancies. A large cohort study of individuals with chronic hypertension including over 4100 pregnant individuals exposed to ACE inhibitors during the first trimester of pregnancy found no significant increase in major congenital anomalies (173). Exposure in the second and third trimesters is clearly associated with a fetal renin-angiotensin system blockade syndrome, which includes anuria in the 2nd and 3rd trimester, which may be irreversible. However, one recent case report of a pregnant individuals with anhydramnios who had ARB exposure

at 30 weeks' gestation had normalization of amniotic fluid volume after cessation of the medication. Furthermore. there were no apparent renal abnormalities at birth or 2-year follow-up (174). Individuals who are taking ACE inhibitors or ARBs should be counseled that these agents are contraindicated in the 2nd and 3rd trimesters of pregnancy. Individuals who are actively trying to get pregnant should be switched to calcium channel blockers (such as nifedipine or diltiazem), methyldopa, hydralazine, or selected B-adrenergic blockers (such as labetalol).

Individuals who are considering pregnancy but are not likely to become pregnant in a short time and who are receiving renal protection from ACE inhibitors or ARBs due to significant underlying renal disease can be counseled to continue these agents. However, they should closely monitor their menstrual cycles and stop these agents as soon as pregnancy is confirmed.

Individuals with severe renal insufficiency should be counseled that their chances for a favorable obstetric outcome may be higher with a successful renal transplant. Individuals with good function of their renal allografts who have only mild hypertension, do not require high doses of immunosuppressive agents, and are 1-2 years post-transplant have a better prognosis than individuals with severe renal insufficiency and who are likely to require dialysis during pregnancy. Successful pregnancy outcomes have been reported in 89% of these individuals who underwent renal transplant (175). Timing of conception in relation to transplant is controversial and should be individualized. Pre-pregnancy graft function can help predict risk of adverse pregnancy outcomes, including HDP and graft function (176).

#### **Cardiovascular Disease**

Although infrequent, cardiovascular disease (CVD) can occur in individuals of reproductive age with diabetes. The increasing prevalence of T2DM with

associated hyperlipidemia, hypertension, obesity, and advanced maternal age (>35) is further increasing the prevalence of CVD. CVD most often occurs in individuals with long-standing diabetes, hypertension, and nephropathy (177). Because of the high morbidity and mortality of coronary artery disease in pregnancy, individuals with pregestational diabetes and cardiac risk factors such as hyperlipidemia, hypertension, smoking, advanced maternal age, or a strong family history should have their cardiac status assessed with functional testing prior to conception (11,178). There are limited case reports of coronary artery disease events during pregnancy, but with the increased oxygen demand from increased cardiac output, events do occur and need to be treated similarly to outside of pregnancy, trying to minimize radiation exposure to the fetus (177,179,180). In a recent study of 79 individuals with history of coronary artery disease prior to pregnancy, there were low rates of cardiac events during pregnancy in all individuals with and without diabetes but more frequent poor obstetric and neonatal outcomes including SGA, HDP, and preterm delivery.

Due to the increased cardiac output of pregnancy, decrease in systemic vascular resistance, and increase in oxygen consumption, the risk of myocardial ischemia is higher in pregnancy. Myocardial oxygen demands are even higher at labor and delivery, and activation of catecholamines and stress hormones can cause myocardial ischemia. Coronary artery dissection is also more common in pregnancy and typical chest pain should be appropriately evaluated. An electrocardiogram (EKG) should be considered preconception for any individual with diabetes older than 35 years (26). Individuals with longstanding diabetes and especially those with other risk factors for coronary artery disease (hyperlipidemia should or hypertension) be evaluated for asymptomatic coronary artery disease before becoming pregnant. Individuals with atypical chest pain, significant dyspnea, or an abnormal resting EKG should also have a cardiology consultation for consideration of a functional cardiac stress test before

pregnancy. As discussed above, statins are often discontinued before conception since there is limited data about their safety during pregnancy. However, a thorough discussion of risks and benefits of continuation versus discontinuation should occur for high-risk individuals such as those with familial hypercholesterolemia and prior atherosclerotic cardiovascular disease (7,40). If an individual has severe hypertriglyceridemia with random triglycerides (TG) >1000 or fasting >400 mg/dl, placing her at high risk for pancreatitis, it may be necessary to continue fibrate therapy if a low-fat diet, fish oil, or niacin therapy is not effective or tolerated. Triglycerides typically double to quadruple in pregnancy placing individuals at high risk for this condition. There is inadequate data on the use of ezetimibe in pregnancy.

## Neuropathy

There are limited data on diabetic neuropathy during pregnancy. Neuropathy may manifest as peripheral neuropathy, gastroparesis, and cardiac autonomic neuropathy. Gastroparesis may present as intractable nausea and vomiting, and it can be particularly difficult to control both the symptoms and glucose values in individuals with gastroparesis during pregnancy. For individuals with gastroparesis, timing of insulin delivery in relation to the meal needs to carefully be weighed against the risk of hypoglycemia as discussed previously.

# Associated Autoimmune Thyroid Disease

Up to 30-40% of young individuals with T1DM have accompanying thyroid disease, and individuals with T1DM have a 5-10% risk of developing autoimmune thyroid disease first diagnosed in pregnancy (most commonly Hashimoto's thyroiditis) (181). Thyroid stimulating hormone (TSH) should be checked prior to pregnancy since the fetus is completely dependent on maternal thyroid hormone in the first trimester (182,183). Pregnant individuals with positive thyroid peroxidase (TPO) antibodies should have their TSH checked in each trimester (Table 2) since the demands of pregnancy can unmask decreased thyroid reserve from Hashimoto's thyroiditis. Thyroid hormone requirements increase by 30-50% in most pregnant individuals, often early in pregnancy due to increase in thyroid binding globulin stimulated by estrogen. For most individuals on thyroid hormone replacement prior to pregnancy, the American Thyroid Association (ATA) and ACOG recommend TSH be within the trimesterspecific reference range for pregnancy at a particular lab, or if not provided, preconception and first trimester TSH <2.5 mU/L and second and third trimester TSH goals <3 mU/L, and thyroid hormone replacement should be adjusted to achieve these goals (184,185). For diagnosis of hypothyroidism during pregnancy, recent recommendations from the ATA recommend new reference ranges for TSH during pregnancy and screening in individuals with history of T1DM each trimester with reference range being 0.4 from the lower limit of the nonpregnant TSH reference range and 0.5 from the upper non-pregnant range which results in a new TSH range of ~0.1-4mUl/L (184,186). This recommendation is based on the TSH range in pregnant individuals in the Maternal Fetal Medicine Units Network in which there was no benefit in treating individuals with levothyroxine with TSH <4 (184,186).

# **Other Autoimmune Conditions**

Other autoimmune conditions are also more common among individuals with T1DM compared with individuals without T1DM. Celiac disease has been estimated to have a prevalence of 3-9% in individuals with T1DM and is more common among females than males (187,188). This can often lead to vitamin D deficiency and iron deficiency, and it is reasonable to screen individuals with T1DM for vitamin D deficiency in pregnancy if they have not been previously screened. Autoimmune gastritis and pernicious anemia are also more common among individuals with T1DM with a prevalence approximating 5-10% and 13%, respectively (189). Addison's disease is also seen in 0.5-1% of individuals with T1DM (189).

## **Diabetic Ketoacidosis in Pregnancy**

Pregnancy predisposes to accelerated starvation with enhanced lipolysis, which can result in ketonuria after an overnight fast. DKA may therefore occur at lower glucose levels (~200 mg/dl), often referred to as "euglycemic DKA" of pregnancy, and may develop rapidly than it does in non-pregnant more individuals(190,191). Up to 30% of episodes of DKA in pregnant individuals with diabetes occur with glucose values <250 mg/dl. Pregnant individuals also have a lower buffering capacity due to the progesteroneinduced respiratory alkalosis resulting in compensatory metabolic acidosis. Furthermore, euglycemic DKA is not uncommon in pregnancy due to the increased propensity to ketosis in pregnant individuals and glomerular hyperfiltration in pregnancy which causes glycosuria at lower serum glucoses. Any pregnant individual with T1DM with a glucose >200 mg/dL, with unexplained weight loss or who is unable to keep down food or fluids should check urine ketones at home. If positive, arterial pH, serum bicarbonate level, anion gap and serum ketones should be obtained to assess for DKA (11).

Maternal DKA is associated with significant risk to the fetus and poor neonatal outcomes including morbidity and mortality. Cardiotography of the fetus during maternal DKA may suggest fetal distress (as evidenced by late decelerations). In a study of 20 consecutive cases of DKA, only 65% of fetuses were alive on admission to the hospital (191). Risk factors for fetal loss included DKA presenting later in pregnancy (mean gestational age 31 weeks versus 24 weeks); glucose > 800 mg/dl; BUN > 20 mg/dl; osmolality > 300 mmol/L; high insulin requirements; and longer duration until resolution of DKA. The fetal heart rate must be monitored continuously until the acidosis has resolved. In another case series of DKA in pregnancy, almost all individuals presented with

nausea and vomiting (97%) and the majority had improvement of hyperglycemia to <200 mg/dL within 6 hours of admission and resolution of acidosis within 12 hours (192). Causes of DKA in pregnancy vary widely with infection less common as a precipitant compared with cases outside of pregnancy (193). Of the infectious causes, pyelonephritis is the most common. However, there is often no precipitant other than emesis in the pregnant individual who can develop starvation ketosis very quickly. In a 2024 case series of 129 admissions for DKA, the most common precipitating factors were vomiting or gastrointestinal infection illness (38%), (26%), and insulin nonadherence (21%) (194). Those with T1DM had higher serum glucoses and serum ketones on admission but those with T2DM required intravenous insulin therapy for a longer duration. Overall, those pregnant individuals with at least one admission for DKA during pregnancy delivered preterm with a median gestational age of approximately 35 weeks.

Prolonged fasting is a common precipitant for DKA, and it has been shown that even individuals with GDM can become severely ketotic if they are given Bmimetic tocolytic medications or betamethasone (to accelerate fetal lung maturity) in the face of prolonged fasting (195). Pregnant individuals unable to take carbohydrates orally require an additional 100-150 grams of intravenous glucose to meet the metabolic demands of the pregnancy in the 2nd and 3rd trimester. Without adequate carbohydrate (often a D10 glucose solution is needed), fat will be burned for fuel and the individual in DKA will remain ketotic. Diabetic ketoacidosis carries the highest risk of fetal mortality in the third trimester thought in part due to the extreme insulin resistance and insulin requirements to treat DKA that are nearly twice as high as in the second trimester (191).

## Hypertensive Disorders in Pregnancy

Pregnant individuals with pregestational diabetes are at increased risk of complications of pregnancy

secondary to hypertensive disease (11,196). Serum creatinine, AST, ALT, and platelets as well as proteinuria (24-hour collection or random protein to creatinine ratio) should be collected as early as possible in pregnancy to establish a baseline and provide counseling on risks associated with significant proteinuria or renal failure. The updated ACC/AHA categorization of normal and abnormal blood pressure ranges outside of pregnancy have not been adopted in the obstetric population (197). Normal blood pressure values in pregnancy are defined as <140/90 mmHg; blood pressures ≥160/110 mmHg are considered severely elevated and warrant prompt treatment for maternal stroke prevention (198).

Although outside of pregnancy achieving a BP < 120/80 mmHg is renal-protective, there are no prospective trials that have demonstrated that achieving this goal improves pregnancy outcomes.

Historically, establishing blood pressure thresholds at which treatment should be initiated in those with chronic hypertension has been challenging due to the competing interests of the mother and fetus (198,199). Concerns include the potential for relative hypotension to increase the risk for poor uteroplacental perfusion and fetal growth restriction, balanced against the increased risk of stroke, placental abruption, and preterm delivery with poorly controlled blood pressure (200-202). The 2015 international Control of Hypertension in Pregnancy Study (CHIPS) trial compared less-tight blood pressure control (target diastolic 100 mm Hg) to tight control (target diastolic 85 mm Hg) and found that tighter control was associated with lower frequency of severe hypertension (203). There was no difference in the frequency of pregnancy loss, higher level neonatal care, or severe maternal complications. The US Chronic Hypertension and Pregnancy (CHAP) trial found that titration of antihypertensive therapy to achieve a systolic pressure <140 mm Hg and diastolic pressure <90

mm Hg, compared with treatment only for systolic pressure,  $\geq$ 160 mm Hg or diastolic pressure,  $\geq$ 105 mm Hg, led to lower rates of adverse pregnancy outcomes without an increased risk of fetal growth restriction (204). A secondary analysis of the CHAP trial showed that those who achieved a blood pressure below 130/80 mm Hg, compared to blood pressures of 130-139/80-89 mm Hg, were at lower risk of adverse pregnancy outcomes (205).

Thus, among individuals with pregestational diabetes and chronic hypertension, blood pressure treatment should be continued or initiated and titrated with a goal value of  $\sim$ 135/85 mmHg(7,167). A lower goal of 120/80 mmHg should be achieved in the setting of diabetic nephropathy (167). Individuals with diabetic nephropathy are at extremely high risk of developing HDP which often leads to intrauterine growth restriction and prematurity. Even individuals with microalbuminuria are at a higher risk of HDP than individuals without microalbuminuria. Blood pressure control is imperative to try to minimize the deterioration of renal function. Preferred anti-hypertensive agents in pregnancy include calcium channel blockers (nifedipine, amlodipine), select beta-blockers (labetalol), and alpha-2 agonists (methyldopa) (198). ACE inhibitors and ARBs are contraindicated in all trimesters of pregnancy and diuretics are reserved for the treatment of pulmonary edema due concerns that further decreasing to the intravascular volume with diuretics could further compromise tissue and placental perfusion. All classes of hypertensive agents are safe in lactating mothers in the postpartum period (206).

After 20-24 weeks gestation, elevated blood pressure should prompt evaluation for HDP. The etiology and pathophysiology of HDP continues to be incompletely characterized, though evidence strongly suggests the microvascular disease may begin early in pregnancy at the time of implantation and manifest in the second or third trimesters (198,207). As a result, treatment of elevated blood pressure has not been shown to prevent HDP. Since 2014, the US Preventative Task Force (USPSTF) recommends low dose aspirin of 81 mg daily after 12 weeks' gestation for those at high risk of HDP who do not have a contraindication to aspirin use (198,208,209). High risk factors, including pregestational diabetes, chronic hypertension, history of HDP, and renal disease, should prompt low-dose aspirin initiation in the second trimester; ≥2 moderate risk factors such as nulliparity, obesity, age  $\geq$ 35, family history of HDP, or personal socioeconomic or poor obstetric history should also prompt use of low-dose aspirin (208,209). Recent data suggests that doses of aspirin above 100 mg may be required for HDP reduction (210,211). However, recommendations for low dose 81 mg aspirin from USPSTF and ACOG remain unchanged.

# FETAL SURVEILLANCE

Maternal hyperglycemia has temporal effects on the developing pregnancy based on gestational age at exposure (6,11,212). Hyperglycemia around the time of conception and early pregnancy is associated with increased risk of miscarriage, congenital anomalies, with cardiac malformations being most common, as well as placental dysfunction related to "end-organ damage" which could lead to growth-restricted fetuses (6). An early dating ultrasound in the first trimester is recommended to confirm gestational age of the fetus and to coordinate detailed anatomic survey at 18-20 weeks gestation. A fetal echocardiogram should be offered at 20-22 weeks if the A1c was elevated (>6.5-7.0%) during the first trimester (212).

Later in pregnancy, hyperglycemia is associated with excessive weight gain in the fetus, with abdominal circumference and shoulder girth primarily measuring larger than expected for gestational age (213–215). Consideration can be made for serial ultrasound evaluation of fetal growth if there is suspicion of abnormal growth, though at minimum, a growth ultrasound in the third trimester should be performed (11). Serial ultrasounds are used to monitor growth and if the estimated fetal weight is less than the 10th percentile (SGA), umbilical artery Doppler velocimetry as an adjunct antenatal test is recommended to estimate the degree of uteroplacental insufficiency, predict poor obstetric outcome and assist in determining the optimal timing of delivery (216).

The association of pregestational diabetes and increased risk for stillbirth was documented as early as the 1950s, leading to a historical practice of intense monitoring with weekly contraction stress test and fetal lung maturity testing prior to delivery emerged identifying congenital (217). Data anomalies as a key factor in stillbirth; with increased focus on improved glycemic control in early pregnancy, stillbirth rates were reduced significantly (218,219). Contemporary practice typically consists of non-stress testing 1-2 times per week, with or without biophysical profile testing, with initiation around 32 weeks gestation (220). However, due to the increased risk of uteroplacental insufficiency and intrauterine fetal demise in pregnant individuals with longstanding T1DM, especially in those with microvascular disease, diabetic nephropathy, hypertension, or evidence of poor intrauterine growth, fetal surveillance may be recommended earlier. While comorbidities such as poor glycemic control, vascular complications, hypertension, or nephropathy have a summative effect on risk for perinatal complications, antenatal testing is recommended for all individuals with pregestational diabetes (220). A positive correlation between HbA1c and stillbirth is observed- the higher the HbA1c >6.5%, the higher the risk (221,222). Fetal hypoxia and cardiac dysfunction secondary to poor glycemic control are probably the most important pathogenic factors in stillbirths among pregnant individuals with diabetes (223).

#### LABOR AND DELIVERY

Delivery management and the timing of delivery is made according to maternal well-being, the degree of glycemic control, the presence of diabetic complications, growth of the fetus, evidence of uteroplacental insufficiency, and the results of fetal surveillance (224). A third trimester anesthesia consultation should be considered in the setting of concerns about cardiac dysfunction or ischemic heart disease, pulmonary hypertension from sleep apnea, hypertension, thromboembolic risks. potential desaturation while laying supine in individuals with severe obesity, or the possibility of difficult epidural placement or intubations.

Optimal delivery timing in the setting of pregestational diabetes requires a balance of perinatal risks, typically stillbirth versus risks of prematurity. In general, individuals with reassuring fetal status and adequate glycemic control can continue a pregnancy until 39 weeks gestation, though expectant management beyond the estimated due date is not advised (225). Concurrent medical complications of mother or fetus may take precedent and require consideration for delivery prior to 39 weeks (225). When late preterm delivery is necessary, it should not be delayed for administration of corticosteroids for fetal lung maturity, as this practice has not been evaluated in pregnancies complicated by pregestational diabetes, and neonatal hypoglycemia may result (226).

With regards to route of delivery, vaginal delivery is preferred for pregnant individuals with diabetes due to the increased maternal morbidity of cesarean delivery such as infection, thromboembolic disease, and longer recovery time. Nevertheless, when the estimated fetal weight is >4500g in the setting of diabetes, an elective cesarean delivery may be offered (227). The target range for glycemic control during labor and at the time of delivery is 70-125 mg/dL; maintenance in this physiological range aims to reduce to risk of neonatal hypoglycemia (228). To achieve this goal, most pregnant individuals with pregestational diabetes require management with an insulin drip and a dextrose infusion, though laboring individuals can eat and continue their home insulin regimen prior to admission. Ideally scheduled cesarean deliveries will occur in the morning, so that individuals can simply reduce their morning long-acting insulin dosing by half on the day of surgery, though consideration can be made to skip it in an individual with well controlled T2DM who hadn't required medication prior to pregnancy. A pregnant individual being admitted for scheduled induction of labor can be instructed to reduce longacting insulin dosing for both the night before and morning of the induction (229). Once the individual is eating, the insulin drip can be discontinued and subcutaneous insulin resumed. Alternative management options include ongoing use of insulin pump or subcutaneous insulin, though both often pose logistic challenges due to the unpredictable length of labor. One 2023 trial compared intravenous insulin infusion to CSII intrapartum and found no difference in neonatal hypoglycemia (230). Prevention of neonatal hypoglycemia must be weighed against risk of maternal hypoglycemia during labor.

With delivery of the placenta, the insulin requirements drop in an acute and dramatic fashion, with most individuals needing roughly 10-30% less than their pre-pregnancy insulin doses or 1/2 to 1/3 of their third trimester insulin dosages; some individuals require no insulin for the first 24-48 hours (228). A glucose goal of 100-180 mg/dl postpartum seems prudent to avoid hypoglycemia given the high demands in caring for an infant and especially in nursing individuals as the increased caloric demands of lactation are known to reduce insulin requirements and can contribute to hypoglycemia.

#### Immediate Risks to Newborn

The immediate neonatal period is characterized by the transition from in-utero to independent physiology, with unique risks in neonates born to individuals with diabetes. Glycemic control throughout the entire gestation as well as in the hours before birth both influence this transition. As previously described, hyperglycemia early in pregnancy may result in congenital anomalies, such as cardiac anomalies, which complicate the transition to post-natal circulation. Glycemic control in the second and third trimester may result in a macrosomic infant with increased adiposity in the shoulders and abdomen. And finally, hyperglycemia during labor exacerbates the adjustment of the neonatal pancreas when glucose delivery via the placenta abruptly ceases increasing the risk of neonatal hypoglycemia.

Even with aggressive management of diabetes, the incidence of neonatal complications ranges from 12-75% (231). In a large analysis of nearly 200,000 neonates, severe neonatal morbidity was increased in neonates born to individuals with pregestational diabetes compared to those with gestational diabetes or no diabetes at an odds ratio of 2.27 and 1.96 respectively (232). Driving this relationship was the increased risks of respiratory distress syndrome, mechanical ventilation, and neonatal death (232). Additionally, neonates were more likely to be LGA and require neonatal intensive care unit admission (232). In the setting of poor glycemic control, respiratory distress syndrome may occur in up to 31% of infants due to known insulin antagonism of cortisol on fetal pneumocytes and surfactant production (233). The estimated odds ratio between pregestational diabetes and neonatal respiratory distress syndrome is 2.66 (234). With extremely poor glucose control, there is also an increased risk of fetal mortality due to fetal acidemia and hypoxia. One study found higher rates of neonatal hypoglycemia in individuals managed with continuous insulin infusion pump during pregnancy compared to multiple daily injection therapy, although confounders including early maternal BMI and duration of an insulin infusion play a role (235).

Macrosomia places the mother at increased risk of requiring a cesarean section and the infant at increased risk for shoulder dystocia. Shoulder dystocia can result in Erb's palsy, Klumpke palsy, clavicular and humeral fractures, and hypoxic ischemic encephalopathy, with overall neonatal injury rate of 5.2% (236,237). Shoulder dystocia occurs nearly 20% of the time when a 4500-gram infant is delivered vaginally. Nevertheless, shoulder dystocia remains challenging to predict, with 60% of shoulder dystocias occurring in neonates weighing <4000g (238). There are a number of conflicting studies regarding induction versus cesarean section for suspected macrosomia (239-241). A large RCT performed in France, Switzerland, and Belgium compared induction of labor at 39 weeks gestation to expectant management among individuals with LGA fetuses, though insulindependent diabetes was an exclusion factor (241). Induction of labor was associated with a significant reduction in the composite primary outcome (significant shoulder dystocia, fracture of the clavicle or long bone, brachial plexus injury, intracranial hemorrhage, or neonatal death), with a RR of 0.32 (95% CI 0.15-0.71) (241). While a small but significant difference in spontaneous vaginal delivery was noted between groups, rates of operative vaginal delivery and cesarean deliveries were not significantly different (241). Current guidelines from ACOG do not recommend delivery prior to 39 weeks for suspected macrosomia (242).

# POSTPARTUM CARE AND CONCERNS FOR PREGESTATIONAL DIABETES

The postpartum care for mothers with diabetes should include counseling on a number of critical

issues including maintenance of glycemic control, diet. exercise, weight loss, blood pressure management, breastfeeding, contraception/future pregnancy planning, and postpartum thyroiditis screening (for T1DM). It has been demonstrated that most individuals with pregestational diabetes, even those who have been extremely adherent and who have had optimal glycemic control during pregnancy, have a dramatic worsening of their glucose control after the birth of their infant (243,244). While previously many individuals utilizing public insurance lost access as early as 6 weeks postpartum in recent years, the majority of states in the US have implemented a 12-month extension of Medicaid postpartum coverage (245). Historically, the postpartum period has been relatively neglected, as both the new mother and her physician relax their vigilance. However, this period offers a unique opportunity to institute health habits that could have highly beneficial effects on the quality of life of both the mother and her infant and potentially achieve optimal glycemic control prior to a subsequent pregnancy.

Home glucose monitoring should be continued vigilantly in the postpartum period because insulin requirements drop almost immediately and often dramatically at this time, increasing the risk of hypoglycemia. Individuals with T1DM often need to decrease their third trimester insulin dosages by at least 50%, often to less than pre-pregnancy doses, immediately after delivery; they may have a "honeymoon" period for several days in which their insulin requirements are minimal. Some estimates of insulin requirements postpartum suggest that individuals may require as little as 60% of their prepregnancy doses, and requirements continue to be less than pre-pregnancy doses while breastfeeding (246). For individuals on an insulin pump, the postpartum basal rates can be discussed and preprogrammed prior to delivery to allow a seamless transition to the lower doses following delivery (247). If well controlled prior to pregnancy, pre-pregnancy insulin delivery settings can serve as

an excellent starting point for the postpartum period, with an expected decrease in basal rates of 14% and increase in carb ratios by 10% (247).

Individuals with T1DM have been reported to have a between 3-25% incidence of postpartum thyroiditis (248). Hyperthyroidism can occur in the 2–4-month postpartum period and hypothyroidism may present in the 4-8 month period. Given the significance of this disorder, a TSH measurement should be offered at 3 and 6 months postpartum and before this time if an individual has symptoms (184).

## Breastfeeding

Both the benefits of breastfeeding- and conversely, the risks of failing to do so- are profound and well documented for both mother and child (249). Pregestational diabetes and obesity have been identified as independent risk factors for low milk supply, raising the question whether the metabolic milieu during lactogenesis I in mid-pregnancy or during the transition to lactogenesis II and III after delivery may be contributing (250). Additional challenges emerge at the time of delivery, with considerable separation of mothers and infants due to NICU admission and treatment for prematurity, respiratory distress syndrome, and hyperglycemia (232). Dyads can be set up for success with policies and procedures that encourage antenatal colostrum collection, early initiation of pumping if unable to directly breastfeed, and ample lactation consultant support. Individuals with both T1DM and T2DM have lower rates of breastfeeding despite good When individuals have intentions (251,252). stopped breastfeeding, most stop due to low milk supply rather than diabetes specific reasons (253).

When individuals with diabetes are successful in breastfeeding their infants, benefits include reduction in postpartum weight retention, reduced risk for obesity and insulin resistance in offspring (254). Conflicting data exists on the relationship between breastfeeding and the incidence of T1DM in offspring of individuals with pregestational diabetes, though breastmilk induction at the time of complementary food introduction is linked to reduced risk of islet autoimmunity and T1DM (255,256).

Additional considerations must be made for individuals with T2DM as consider they pharmacotherapy in the postpartum period. Insulin dosing may require adjustment in the setting of breastfeeding due to increased risk of overnight hypoglycemia (7). With respect to oral agents, acceptable levels of metformin have been identified in breastmilk, rendering it a safe medication for lactating individuals (257,258). A small study suggested that glyburide and glipizide do not appreciably cross into breast milk and may be safe (259). There are no adequate data on the use of thiazolidinediones, meglitinides, incretin therapy, GLP-1 agonists, and SGLT2 inhibitors in nursing mothers.

Statins should not be started if the individual is nursing due to inadequate studies in breastfeeding mothers. Individuals who are candidates for an ACE inhibitor can be started on one of these agents at this time as they have not been shown to appear significantly in breast milk (206).

## Contraception

Starting at puberty, it is recommended to provide individuals with diabetes preconception counseling including discussion of options for contraceptive use based on the Medical Eligibility Criteria (MEC) according to WHO and CDC (260,261). Counseling on contraceptive choices should be patientcentered and focused on the short- and long-term reproductive goals of the individual, taking into consideration the alternative-no contraception- and associated individualized risks of carrying a pregnancy to term. A meta-analysis found that lowincome individuals with diabetes had low rates of postpartum birth control and more often were offered permanent contraception rather than reversible options (262).

Taken in isolation, a diagnosis of diabetes without vascular complications is compatible with all hormonal and non-hormonal contraception options: copper intrauterine device (IUD), levonorgestrelprogestin implant, releasing IUD, depo medroxyprogesterone acetate, progestin only pills, and combined estrogen-progestin methods (261). Evidence of vascular disease is a contraindication to combined hormonal contraception and depo medroxyprogesterone acetate (261). A large study recently found an overall low risk of venous thromboembolism among individuals with T1DM and T2DM (263). Concurrent conditions and habits such as poorly controlled hypertension, hypertriglyceridemia, or smoking increase the risk of venous thromboembolic events (264). Systematic reviews failed to find sufficient evidence to assess whether progestogen-only and combined contraceptives differ from non-hormonal contraceptives in diabetes control, lipid metabolism, and complications in individuals with pregestational diabetes (265,266).

(LARC) Long-acting reversible contraception methods lasting 3-10 years include copper and hormonal IUDs as well as progestin implants. There is no increase in pelvic inflammatory disease with the use of IUDs in individuals with well controlled T1DM or T2DM after the post-insertion period. Immediate postpartum implants and IUDs are becoming increasingly available to individuals who desire LARCs and are effective in spacing pregnancies in high-risk populations (267). For individuals who have completed childbearing and desire permanent sterilization, laparoscopic methods are safe and effective (268).

#### **OBESITY IN PREGNANCY**

Obesity alone or accompanied by T1DM, T2DM, or GDM carries significant risks to both the mother and the infant, and obesity is the leading health concern in pregnant individuals (269-271). By the most recent NHANES statistics in individuals over age 20, 57% of black individuals, 44% of Hispanic or Mexican American individuals, and 40% of white individuals are obese (272). Independent of pregestational diabetes or GDM, obesity increases the maternal risks of hypertensive disorders, MASLD, proteinuria, gall bladder disease. aspiration pneumonia, thromboembolism, sleep apnea, cardiomyopathy, and pulmonary edema (270,273). In addition, it increases the risk of induction of labor, failed induction of labor, cesarean delivery, multiple anesthesia complications, postoperative infections including endometritis, wound dehiscence, postpartum hemorrhage, venous thromboembolism, postpartum depression and lactation failure. Maternal obesity independently increases the risk of first trimester loss, stillbirth, recurrent pregnancy losses, and congenital malformations including CNS, cardiac, and gastrointestinal defects and cleft palate, shoulder dystocia, meconium aspiration, and impaired fetal growth including macrosomia. Most significantly, obesity increases the risk of perinatal mortality (269). Because so many individuals with T2DM are also obese, all of these complications increase the risk of poor pregnancy outcomes in this population. The majority (50-60%) of individuals who are overweight or obese prior to pregnancy gain more than the recommended amount of gestational weight by the Institute of Medicine (IOM) guidelines (274,275). This results in higher weight retention postpartum and higher prepregnancy weight for subsequent pregnancies.

Obesity is an independent risk factor for congenital anomaly including spina bifida, neural tube defects, cardiac defects, cleft lip and palate, and limb reduction anomalies (276). Several reports have demonstrated an association of maternal BMI with neural tube defects and possibly other congenital anomalies (277). One study concluded that for every unit increase in BMI the relative risk of a neural tube defect increased 7% (277). In addition to an increased anomaly risk with maternal obesity, it is well known that detection of fetal anomalies in the first and second trimester is reduced by 20% due to difficulty in adequate visualization in the setting of maternal obesity (278,279). There is conflicting evidence on the role of folic acid in these obesity-associated congenital anomalies (280– 283).

Obese individuals with normal glucose tolerance on a controlled diet have higher glycemic patterns throughout the day and night by CGM compared to normal weight individuals both early and late in pregnancy (284). The glucose area under the curve (AUC) was higher in the obese individuals both early and late in pregnancy on a controlled diet as were all glycemic values throughout the day and night. The mean 1 hour postprandial glucose during late pregnancy by CGM was 115 versus 102 mg/dl in the obese and normal weight individuals respectively and the mean 2-hour postprandial values were 107 mg/dl versus 96 mg/dl, respectively, both still much lower than current therapeutic targets (<140 mg/dl at 1 hour; < 120 mg/dl at 2 hours).

Individuals with Class III obesity (BMI>40) have improved pregnancy outcomes if they undergo bariatric surgery before becoming pregnant given such surgery decreases insulin resistance resulting in less diabetes, hypertension, and macrosomia compared to those who have not had the surgery (285,286). In any individual who has had prior bariatric surgery, it has been shown in systematic review to reduce the rate of gestational diabetes and HDP in future pregnancies, however many studies are confounded given 80% of individuals post bariatric surgery remain obese (287). Following bariatric surgery, pregnancy should not be considered for 12-18 months post-operatively and after the rapid weight loss phase has been completed. Close attention nutritional to deficiencies must be maintained, especially with fat soluble vitamins D and K as well as folate, iron, thiamine, and B12. In a study of a cohort of infants born to obese individuals who had bariatric surgery, the offspring had improved fasting insulin levels and reduced measures of insulin resistance compared to siblings born prior to bariatric surgery (288).

# MEDICAL NUTRITION THERAPY, EXERCISE AND WEIGHT GAIN RECOMMENDATIONS FOR INDIVIDUALS WITH DIABETES OR OBESITY

Medical nutrition therapy in collaboration with a registered dietician nutritionist remains a crucial component of achieving glycemic control and optimizing outcomes in individuals with pregestational diabetes (7,11). Currently, there is no consensus on the ideal macronutrient prescription for pregnant individuals or individuals with diabetes, and there is concern that significant restriction of carbohydrate (33- 40% of total calories) leads to increased fat intake given protein intake is usually fairly constant at 15-20% (31,289,290). Severe restrictions or elimination of any macronutrient class is advised against (291). It is also important to assess intake along with energy requirements which is known to increase in pregnancy by approximately 200, 300, and 400 kcal/d in the first, second, and third trimesters, respectively, but these values vary depending on

BMI, total energy expenditure, and physical activity (292). Individuals with pregestational diabetes and GDM should receive individualized medical nutrition therapy (MNT) as needed to achieve treatment goals.

Pregravid BMI should be assessed and GWG recommendations should be consistent with the current IOM weight gain guidelines (See Table 3) due to adverse maternal, fetal and neonatal outcomes (293). However, there are many trials which support no weight gain for individuals with a BMI of  $\geq$ 30 kg/m<sup>2</sup> with improved pregnancy outcomes and the lack of weight gain or even modest weight loss, did not increase the risk for SGA infants in the obese cohort. Further, targeting GWG to the lower range of the IOM guidelines (~11 kg or 25 lbs. for normal weight individuals; ~7 kg or 15 lbs. for overweight individuals; and 5 kg (11 lbs.) for individuals with Class 1 obesity (BMI 30-34 kg/m<sup>2</sup>) has been shown in many trials to decrease the risk of HDP, cesarean delivery, GDM, and postpartum weight retention (294). This is an increasing public health concern given risks of weight gain (greater than excessive IOM recommendations) including cesarean deliveries, postpartum weight retention for the mother and LGA infants, macrosomia, and childhood overweight or obesity for the offspring (292). Obese individuals are at increased risk of venous thromboembolism postpartum, and this risk is augmented in those who have had a cesarean section, resulting in ACOG's recommendation for pneumatic sequential compression devices for those who have had cesarean section (295-297).

Table 3. Institute of Medicine Weight Gain Recommendations in Singleton Pregnancy					
BMI	Total weight gain	2 <sup>nd</sup> /3 <sup>rd</sup> trimester rate of weight gain			
	(lbs.)	(kg/week)			
Low (<19.8 kg/m <sup>2</sup> )	28-40	1.0 (1-1.3 lb./week)			
Normal (19.8-26 kg/m <sup>2</sup> )	25-35	1.0 (0.8-1 lb./week)			
High (>26-29 kg/m²)	15-25	0.66 (0.5-0.7 lb./week)			
Obese (>29 kg/m²)	11-20	0.5 (0.4-0.6 lb./week)			

There is also increasing evidence that overweight or obese individuals with GDM may have improved pregnancy outcomes with less need for insulin if they gain weight less than the IOM recommendations without appreciably increasing the risk of SGA (298–300). For obese individuals, ~25 kcal/kg rather than 30 kcal/kg is currently recommended (301). However, other investigators would argue for a lower caloric intake (1600-1800 calories/day), which does not appear to increase ketone production (302).

The recommended diet should be culturally appropriate, and individuals should consume 150-175 grams of carbohydrate (40-50% of total calories), primarily as complex carbohydrate and limit simple carbohydrates, especially those with high glycemic indices (290,303). Protein intake should be at least 71 g per day (15-30% of total calories), unless individuals have severe renal disease. Individuals should be taught to control fat intake and to limit saturated fat to <10-15% of energy intake, trans fats to the minimal amount possible, and encourage consumption of the n-3 unsaturated fatty acids that supply a DHA intake of at least 200 mg/day (25). Diets high in saturated fat have been shown to worsen insulin resistance, provide excess TGs and FFAs for fetal fat accretion. increase inflammation, and have been implicated in adverse fetal programming effects on the offspring (see risk to offspring above). A fiber intake of at least 28 g/day is advised and the use of artificial sweeteners, other than saccharin, are deemed safe in pregnancy when used in moderation (26). Overall, a diet composed of whole grains, legumes, fruits, vegetables, lean protein and healthy fats is recommended with avoidance of processed foods and sweetened foods and beverages when possible (7,303).

For normal weight individuals with T1DM with appropriate gestational weight gain, carbohydrate and calorie restriction is not necessary, but carbohydrates need to be appropriately covered by insulin. Emphasizing consistent timing of meals with at least a bedtime snack to minimize hypoglycemia in proper relation to insulin doses is important. Many individuals who dose prandial insulin based on an insulin to carbohydrate ratio are skilled at carbohydrate counting.

Exercise is an important component of healthy lifestyle and is recommended in pregnancy by ACOG, the ADA, and Society of Obstetricians and Gynaecologists of Canada (30,304). The U.S. Department of Health and Human Services issued physical activity guidelines for Americans and recommend healthy pregnant and postpartum individuals receive at least 150 minutes per week of moderate-intensity aerobic activity (i.e., equivalent to brisk walking) (305). A large meta-analysis of all RCTs on diet and physical activity, which evaluated RCTs (using diet only n=13, physical activity n=18 or both n=13) concluded that dietary therapy was more effective in decreasing excess GWG and adverse pregnancy outcomes compared to physical activity (306). However, there was data suggesting

that physical activity may decrease the risk of LGA infants (LGA, >90<sup>th</sup> percentile). There was no increase in SGA infants (<10<sup>th</sup> percentile) with physical activity. Submaximal exertion (≤70% maximal aerobic activity) does not appear to affect the fetal heart rate and although high intensity at maximal exertion has not been linked to adverse pregnancy outcomes, transient fetal bradycardia and shunting of blood flow away from the placenta and to exercising muscles has been observed with maximal exertion. Observational studies of individuals who exercise during pregnancy have shown benefits such as decreased GDM, cesarean and operative vaginal delivery, and postpartum recovery time, although evidence from RCTs is limited (307,308).

Some data suggest that individuals who continued endurance exercise until term gained less weight and delivered slightly earlier than individuals who stopped at 28 weeks but had a lower incidence of cesarean deliveries, shorter active labors, and fewer fetuses with intolerance of labor (309). Babies weighing less were born to individuals who continued endurance exercise during pregnancy compared with a group of individuals who reduced their exercise after the 20th week (3.39 kg versus 3.81 kg). Contraindications for a controlled exercise program include individuals at risk for preterm labor or delivery or any obstetric or medical conditions predisposing to growth restriction.

#### RISK TO OFFSPRING FROM AN INTRAUTERINE ENVIRONMENT CHARACTERIZED BY DIABETES OR OBESITY

Given the strong associations between maternal diabetes and obesity and the risk of childhood obesity and glucose intolerance, the metabolic milieu of the intrauterine environment is a critical risk factor for the genesis of adult diabetes and cardiovascular disease (270,310–313). The evidence of this fetal programming and its

contribution to the developmental origins of human disease (DoHAD) is one of the most compelling reasons why optimizing maternal glycemic control, identifying other nutrients contributing to excess fetal fat accretion, emphasizing weight loss efforts before pregnancy, ingesting a healthy low fat diet, and avoiding excessive weight gain are so critical and carry long term health implications to both the mother and her offspring. The emerging field of epigenetics has clearly shown in animal models and non-human primates that the intrauterine environment, as a result of maternal metabolism and nutrient exposure, can modify fetal gene expression (314,315).

Maternal hyperglycemia in early pregnancy has been associated with childhood leptin levels at 5 years of age, even when adjusted for maternal BMI and other confounders ( $\beta$ =0.09 ± 0.04, p=0.03) (316). In this study, higher maternal glucose levels post-75-gram glucose tolerance test in the second trimester were associated with greater total body fat percentage as measured by DXA in the children at 5 years of age.

There are data, especially in animal and non-human primate models, to support that a maternal high fat diet and obesity can influence mesenchymal stems cells to differentiate along adipocyte rather than osteocyte pathways, invoke changes in the serotonergic system resulting in increased anxiety in non-human primate offspring, affect neural pathways involved with appetite regulation, promote lipotoxicity, regulate gluconeogenic enzymes in the fetal liver generating histology consistent with MASLD, alter mitochondrial function in skeletal muscle and program beta cell mass in the pancreas (312,317-324). These epigenetic changes are being substantiated in human studies with evidence of differential adipokine methylation and gene expression in adult offspring of individuals with diabetes in pregnancy and through alterations in fetal placental DNA methylation of the lipoprotein lipase gene which are associated with the anthropometric profile in children at 5 years of age (325). These findings further support the concept of fetal metabolic programming through epigenetic changes (326). As a result, the intrauterine metabolic environment may have a transgenerational influence on obesity and diabetes risk in the offspring, influencing appetite regulation, beta cell mass, liver dysfunction, adipocyte metabolism, and mitochondrial function.

Offspring of mothers with T2DM and GDM have higher risk of childhood obesity, young adult or adolescent insulin resistance and diabetes. MASLD, hypertension, and cardiovascular disease (327-332). The risk of youth onset diabetes is higher in offspring of mothers born with pregestational T2DM than with GDM (14-fold compared to 4-fold risk) (333). These epigenetic changes are not isolated to maternal BMI alone, but it has also been demonstrated that paternal factors impact offspring risk of obesity and diabetes (334,335). Offspring of individuals with T1DM have a risk of developing T1DM of about 1-3%. The risk is higher for the offspring if the father has T1DM rather than the mother (~3-6%) and if both parents have T1DM, the risk is ~20% (336,337).

#### CONCLUSION

The obstetric outlook for pregnancy in individuals with pregestational diabetes has improved over the last century and has the potential to continue to improve as rapid advances in diabetes technology and management, fetal surveillance, and neonatal care emerge. However, the greatest challenge health care providers face is the growing number of individuals developing GDM and T2DM as the obesity epidemic increases affecting individuals prior to pregnancy. In addition, the prevalence of T1DM is increasing globally. Furthermore, obesityrelated complications exert a further deleterious effect on pregnancy outcomes. The development of T2DM in individuals with a history of GDM as well as obesity and glucose intolerance in the offspring of individuals with pregestational DM or GDM set the stage for a perpetuating cycle that must be aggressively addressed with effective primary prevention strategies that begin in-utero. Pregnancy is clearly a unique opportunity to implement strategies to improve the mother's lifetime risk for CVD in addition to that of her offspring and offers the potential to decrease the intergenerational risk of obesity, diabetes, and other metabolic derangements.

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