# DIABETES IN PREGNANCY
**diabetes-in-pregnancy**

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# ABSTRACT

In this chapter, we will review the metabolic changes that occur during normal pregnancies and those affected by diabetes as well as review the risks of maternal obesity and hyperglycemia on maternal, fetal, and neonatal outcomes. Management of both preexisting and gestational diabetes in pregnancy will be reviewed in detail including up to date medications and diabetes technologies. Postpartum issues including changes in insulin sensitivity, breastfeeding and contraception for women with preexisting diabetes will be discussed, the importance of postpartum glucose screening and lifestyle modifications for women with a history of gestational diabetes will be highlighted. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

# 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, TNFα, and oxidative stress biomarkers. In addition decreases in adiponectin worsen maternal insulin resistance in the second trimester, in order to facilitate fuel utilization by the conceptus [1]. There is even data that the maternal human intestinal microbiome dramatically changes to an "obesigenic" microbiome from the first to third trimester. Remarkably, transfer of the human third trimester microbiome to a sterile mouse results in obesity, likely due to changes in the proportion of energy-harvesting bacteria and production of LPS (lipoprotein saccharide), an

endotoxin that can leak out of the maternal gut and result in inflammation and further insulin resistance [2].

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? Women are at increased risk for hypoglycemia, especially if accompanied by nausea and vomiting in pregnancy. Although most women show an increase in insulin sensitivity between 6-20 weeks' gestation of pregnancy 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) [3] usually followed by increased insulin sensitivity up until 14-20 weeks.

In the fasting state, pregnant women deplete their glycogen stores quickly due to the fetoplacental glucose demands, and switch from carbohydrate to fat metabolism within 12 hours, resulting in increased lipolysis and ketone production [4-6]. The second and third trimesters are characterized by insulin resistance with a nearly 50% decrease in insulin mediated glucose disposal (assessed by the hyperinsulinemic-euglycemic clamp technique) and a 200-300% increase in the insulin response to glucose [7]. 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 [5]. In addition, the maternal metabolic rate increases by ~150-300 kcal/day in the third trimester, depending on the amount of gestational weight gain in pregnancy. These increased nutritional needs place the mother at risk for ketosis, which occurs much earlier than usual without adequate oral or intravenous nutrients, frequently referred to as "accelerated starvation of pregnancy" [4]. Glucose transport to the fetus occurs in direct proportion to maternal glucose levels, and is augmented by a five-fold increase in a placental glucose transporter, (GLUT-1) which increases facilitated transplacental glucose flux even in the absence of maternal hyperglycemia [8]. The placenta is responsible for the production of hormones, which reprogram maternal physiology to become insulin resistant in the 2nd and 3rd trimesters of pregnancy to ensure an adequate supply of nutrients to the growing fetus [9]. This appears to be due to an increase in placental growth hormone [1, 10] in combination with human chorionic somatomammotropin (HCS), progesterone, and TNFα, the latter correlating with maternal insulin resistance measured by hyperinsulinemic-clamps [11]. Human placental growth hormone (hPGH) has been characterized as a metabolically active hormone capable of causing severe insulin resistance in transgenic animals, which express this hormone at levels comparable to those measured in the third trimester of pregnancy [12]. This key hormone may mediate insulin resistance as does excess pituitary growth hormone (pit GH) when it is administered or expressed chronically. Human placental growth hormone differs from pit GH by 13 amino acids. It almost completely replaces pit GH in the maternal circulation by 20 weeks, and it is unregulated by growth hormone releasing hormone [10]. HCS (HPL) may play a key role in stimulating insulin production in human islets [13] in order for the mother to increase her insulin secretion 2-3 fold. While it has long been thought that the expansion of β-cell mass to maintain normal glucose tolerance in the setting of insulin resistance in pregnancy was primarily driven

by placenta derived hormones, HCS and prolactin, there is evolving evidence that the failure of this compensatory response may be mediated by adiponectin [14]. In recent animal models, pregnant adiponectin -/- mice developed glucose intolerance and hyperlipidemia in late pregnancy demonstrating that adiponectin plays an important role in controlling maternal metabolic adaptation to pregnancy [15].

At the same time it has been demonstrated that in the third trimester of normal pregnancy there is decreased expression of the GLUT-4 glucose transporter protein in maternal adipose tissue [16] and decreased translocation of GLUT-4 to the plasma membrane in skeletal muscle, both of which contribute to the insulin resistance of pregnancy. At the insulin signaling level in skeletal muscle, the insulin resistance of pregnancy involves reduced tyrosine phosphorylation of the insulin receptor, decreased expression of IRS-1, and increased levels of the p85α subunit of phosphatidylinositol kinase (PI 3-kinase), all serving to attenuate glucose uptake [1, 17]. Glucose is not the only fuel altered in normal pregnancy. Triglycerides (TGs), cholesterol, and free fatty acids (FFA) are increased; the latter may serve to further increase the insulin resistance of pregnancy [5, 18] and provide an important fuel supply for fetal fat accretion in the third trimester. There is a 2-3 fold increase in TGs and a 25-50% increase in total cholesterol and low density lipoprotein (LDL) during pregnancy. During the first trimester of pregnancy when insulin sensitivity is increased, lipogenesis is favored and centrally distributed subcutaneous fat mass is increased so that there is a significant increase in adipose tissue stores. However, later in pregnancy, coincident with the insulin resistance, lipolysis is enhanced and the subcutaneous fat stores are a source of calories for the fetus during pregnancy and for lactation postpartum. The ability of insulin to suppress whole body lipolysis is reduced resulting in an increase in FFAs, which can also be used as a fuel by the fetoplacental unit [5]. The placenta has lipoprotein lipase as well as TG-hydrolase enzymes so that maternal TGs can be used in addition to FFAs for fetoplacental fuels and to increase fat deposition. A number of studies support the influence of elevated maternal triglycerides and FFAs as an important substrate contributing to excess fetal fat accretion [18-20].

# NORMAL GLUCOSE LEVELS IN PREGNANCY

Understanding normal glucose levels in pregnancy is important for setting glycemic targets in women with diabetes. The first change that happens is a fall in fasting glucose levels which occurs early in the first trimester. In second and third trimester glucose levels rise slightly due to insulin resistance. A careful 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 women (body mass index (BMI) 22-28 kg/m2) during the 3rd 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, much lower than the current targets for glycemic control for women with diabetes during pregnancy [21]. (See figure 1). Increasing gestational age and maternal BMI affect "normal" glucose levels. A longitudinal study of 32 healthy, normal weight women between 16 weeks' gestation to 6 weeks postpartum demonstrated a rise in mean glucose levels from 16 weeks (4.57 mmol/l (82.3 mg/dl) to 36

weeks (5.22 mmol/l (94.0 mg/dl) which was maintained at 6 weeks postpartum (5.20 mmol/l (93.7 mg/dl)) using CGM [22]. 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 levels are lower in pregnancy, postprandial glucose levels are slightly elevated which is likely related to the many impaired insulin actions; altered β cell secretion, hepatic gluconeogenesis and placenta derived circulating hormones [23].

**Figure 1: Glucose Levels During Pregnancy**
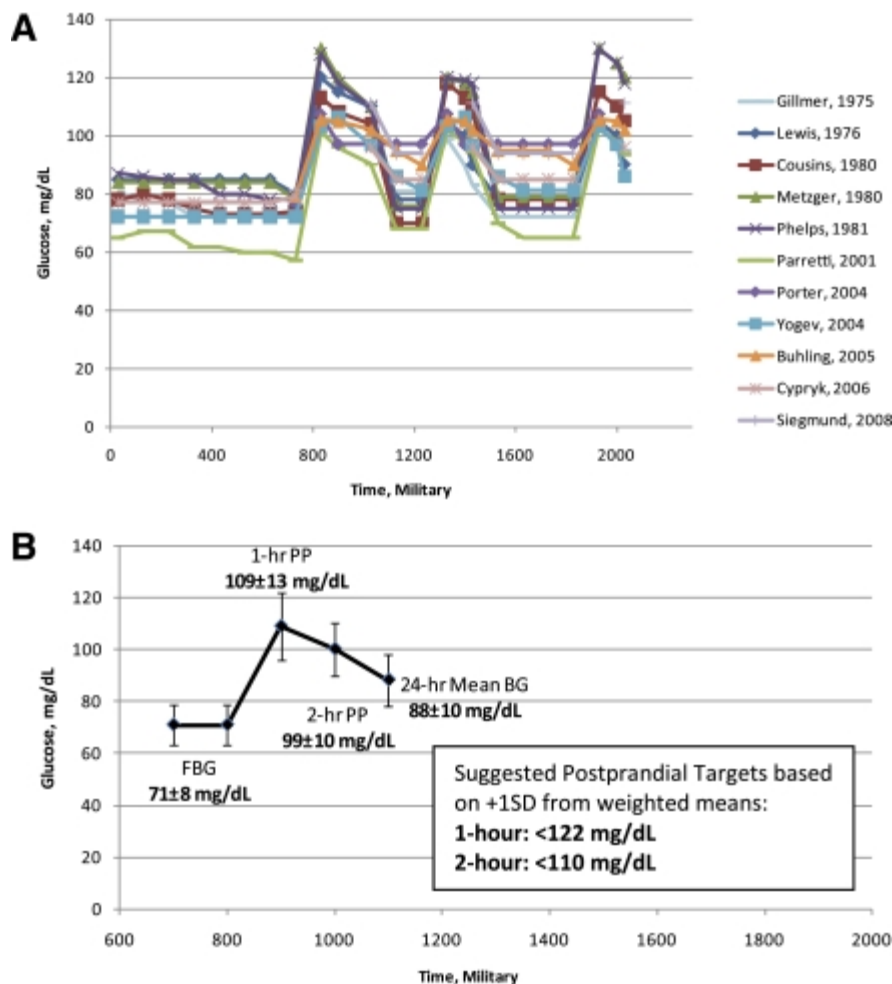


# OBESITY IN PREGNANCY

Obesity alone or accompanied by Type 1 diabetes (T1DM), Type 2 diabetes (T2DM) or gestational diabetes (GDM) carries significant risks to both the mother and the infant, and obesity is the leading health concern in pregnant women [24-26].  By the most recent NHANES statistics in women ages 20-39, 57% of black women , 43% of Hispanic or Mexican American women, and 33% of white women are obese [27].  Independent of preexisting diabetes or GDM,

obesity increases the maternal risks of hypertensive disorders, non-alcoholic fatty liver disease (NAFLD), proteinuria, gall bladder disease, aspiration pneumonia, thromboembolism, sleep apnea, cardiomyopathy, and pulmonary edema [26, 28]. 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 central nervous system (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 [24].  Because so many women with T2DM are also obese, all of these complications increase the risk of poor pregnancy outcomes in this population.

Glycemic control may not be the only factor leading to increased congenital anomalies. Women with T2DM have increased congenital anomalies even when under good glycemic control [29, 30] suggesting that obesity itself is a risk factor. Women with obesity or with T2DM complicated by obesity may be older and often have underlying hypertension, hyperlipidemia, and inflammation all of which may explain some of the increased risk despite similar glycemic control compared to their T1DM counterparts. Several recent reports have demonstrated an association of maternal BMI with neural tube defects and possibly other congenital anomalies [31].  One study concluded that for every unit increase in BMI the relative risk of a neural tube defect increased 7% [31]. In addition to an increased anomaly risk with maternal obesity, it is well known that detection of fetal anomalies in first and second trimester is reduced by 20% due to difficulty in adequate visualization in the setting of maternal obesity [32, 33]. There is conflicting evidence about the role of folic acid deficiency in these obesity-associated congenital anomalies. Obese women have a lower folic acid intake and have lower serum folate levels even with the same intake [34, 35].  This has resulted in some international organizations recommending higher dosages of preconception folic acid (5 mg) for women with diabetes and/or BMI>35 [36].  However, there is not clear evidence that this intervention alone will substantially decrease the risk. One trial which was not a randomized controlled trial (RCT), evaluated the risk of spina bifida in pregnant women with diabetes and obese pregnant woman who had adequate or inadequate folic acid supplementation found that in women with diabetes, adequate folic acid supplementation decreased the risk of spina bifida. In adequately supplemented obese pregnant women, they had the same rates of spina bifida as those that had poor folic acid supplementation, demonstrating another possible etiology to CNS anomalies in obese women [37].

Obese women with normal glucose tolerance on a controlled diet have higher glycemic patterns throughout the day and night by CGM compared to normal weight women both early and late in pregnancy [18].  The glucose area under the curve (AUC) was higher in the obese women both early and late in pregnancy on a controlled diet as were all glycemic values throughout the day and night.  The mean 1 hour PP glucose during late pregnancy by CGM was 115 versus 102 mg/dl in the obese and normal weight women respectively and the mean 2-hour PP 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).

Women with Class III obesity (BMI>40) actually 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 [38, 39]. In any woman who has had prior bariatric surgery, it has been shown in systematic review to reduce the rate of gestational diabetes and preeclampsia in future pregnancies [40], however many studies are confounded given 80% of patients post bariatric surgery remain obese.  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 to nutritional deficiencies must be maintained, especially with fat soluble vitamins D and K as well as folate, iron, thiamine, and B12.  Women who have undergone malabsorption procedures such as the Roux-en-Y may be at increased risk for internal hernia formation and any abdominal pain and vomiting must be investigated promptly. Malabsorptive procedures also increase the risk of dumping syndrome and if patients experience this, an alternative form of testing for GDM should be considered over the oral 50-gram glucose challenge, such as once weekly blood glucose monitoring.

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

## Early Life Origins of Metabolic Diseases

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 now considered to be a critical risk factor for the genesis of adult diabetes and cardiovascular disease [26, 41-44].  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 [45, 46].  Histone posttranslational modifications, such as acetylation and methylation, occur at specific residues and depending on their combination, regulate transcriptional activation and silencing, DNA repair, and recombination.  The factors that elicit these modifications are enzymes that use metabolites (e.g. NAD+, acetyl Co-A, ATP, β-hydroxybutyrate) as sources for these acetyl or

methyl groups whose availability is partly dependent on energy excess, energy depletion, dietary factors, and redox state [26, 47].

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, [48, 49] invoke changes in the serotonergic system resulting in increased anxiety in non-human primate offspring [50], affect neural pathways involved with appetite regulation, promote lipotoxicity, regulate gluconeogenic enzymes in the fetal liver generating histology consistent with NAFLD [51, 52], alter mitochondrial function in skeletal muscle and program beta cell mass in the pancreas [44, 53-55]. These epigenetic changes are being substantiated in human studies with evidence of differential adipokine methylation and gene expression in adult offspring of women with diabetes in pregnancy [56] 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. These findings further support the concept of fetal metabolic programming through epigenetic changes [57]. 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. Increasing evidence in humans and non-human primates suggest that maternal nutrition affects the placenta and fetal tissues. Given that the mother transmits her microbiome to her offspring, a maternal microbiome characterized by obesity or a high fat diet may lead to persistent changes in the offspring microbiome, hepatic metabolism, mitochondrial function, liver macrophage activation and susceptibility to NAFLD postnatally [58, 59].

The long-term sequelae of preexisting diabetes, GDM, or obesity for offspring are being increasingly recognized [60]. Reports of an increased risk of adolescent obesity and of T2DM are compelling, and it appears that fetal islet hyperplasia occurs in-utero with maternal hyperglycemia resulting in an increased risk of developing T2DM in teenage years or as a young adult [61]. Elevated amniotic fluid insulin levels (due to fetal hyperinsulinemia as a result of maternal hyperglycemia) predicted teenage obesity in one study, independent of fetal weight, and one-third of these offspring had impaired glucose tolerance by 17 years of age [62]. Further, maternal obesity itself is a significant risk factor, and the prevalence of childhood obesity is ~2.5 times higher in offspring of obese women compared to women with normal BMIs [63]. Maternal BMI is also the strongest predictor of excess neonatal adiposity which has been associated with childhood obesity and adiposity at birth and appears to be better predictor of the risk of childhood obesity than birth weight alone [42, 64]. Maternal BMI is not only associated with childhood obesity but also is also positively associated with offspring BMI at 60 years of age, in addition to less favorable body composition in offspring at age 62 [65] demonstrating lifelong implications to offspring. Recently, it has also been shown that infants born to GDM women who are obese already have evidence of increased intrahepatic fat at birth using NMR spectroscopy [66]. These findings raise the question about whether excess FFA flux across the placenta could be deposited in the fetal liver and might result in changes in hepatic metabolism that predispose to the development of NAFLD later in childhood, estimated to affect 40% of all obese children and the leading cause of liver transplant. While observational studies have long

shown an increased risk in offspring of obese mothers of obesity, coronary artery disease, stroke, T2DM and asthma, there is emerging data to suggest that maternal obesity could be associated with poorer cognition and risk for neurodevelopmental disorders [67]. Although the offspring of obese women who lose weight before pregnancy have a reduced risk of obesity, few controlled intervention studies have been done in which maternal obesity is reversed and the consequences for offspring have been examined. The importance of this new epigenetic knowledge creates enormous potential on a public health level for the incidence of T2DM and obesity to escalate as these children with impaired glucose tolerance become mothers themselves, perpetuating the cycle, as well as becoming adults with multiple co-morbidities associated with obesity and diabetes. These epigenetic changes are not isolated to maternal BMI alone but it has also been demonstrated that newborns from obese fathers showed altered methylation overall and significant hypomethylation at the Insulin-like Growth Factor 2 (IGF2) gene, suggesting the importance of healthy family behavior periconception [68].

## Immediate Risks to Newborn

Macrosomia is the major risk to the fetus in women with obesity, T2DM, GDM, and also T1DM without placental insufficiency. Many theories have been generated over the years to explain the macrosomia associated with diabetes in pregnancy. Overall, the theory of excessive fetal insulin due to increased transport of maternal fuel to the conceptus holds the most credence and has the most supportive data (Freinkel hypothesis). Diabetes in pregnancy is associated with increased delivery of glucose and amino acids (AA) to the fetus via the maternal circulation. These fuels can stimulate increased production of fetal insulin which promotes somatic growth. Other maternal substrates (e.g., FFA, TG, AA) add to the burgeoning supply of fetal substrate and further support excessive growth. It is, therefore, the goal of management of pregnancies complicated by diabetes to normalize the above parameters with good metabolic control. However, even infants born average for gestational age (AGA) from offspring of women with diabetes have increased fat mass, as do offspring of obese women [41]. Maternal obesity appears to be an independent risk factor for LGA, macrosomia, and excess neonatal fat and in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial [69], 78% of all of the LGA infants were born to mothers without GDM. Overweight and obese women have a two-fold increased risk of delivering a macrosomic infant. Given that the prevalence of overweight and obese women is ~ 10 times that of gestational or preexisting diabetes, maternal body habitus is likely to have the strongest attributable risk on the prevalence of macrosomia [41]. Although obesity increases the risk for macrosomia, studies have shown that maternal obesity is a poor predictor of associated shoulder dystocia at delivery [70].

It is also clear that some mothers with diabetes who appear to have optimal metabolic control still give birth to macrosomic infants. It has recently been shown that women may have glucoses within target range yet there is excess shunting of glucose to the fetus as demonstrated by increased amniotic fluid insulin levels reflecting fetal hyperinsulinemia. Recently, the level of TGs has been strongly correlated with excess fetal growth and LGA [20], supporting that other maternal fuels such as TGs and FFAs play an important role in excess fetal fat accretion. In

fact, results from a trial in which obese and normal weight women were given fixed diets while wearing a CGM both early and late in pregnancy showed that maternal TGs and FFAs were much higher in the obese women and correlated more strongly with infant adiposity than the differences in glycemic patterns between the groups [18]. It has been shown that there is differential placental regulation of placental genes involved in lipid transport in GDM women [71]. The results suggest that fatty acids are lipogenic substrates for placental cells and for fetal fat accretion and suggest that genes for fetoplacental lipid metabolism are enhanced in women with diabetes. Furthermore, the placenta has a lipoprotein lipase, endothelial lipase, and a TG hydrolase capable of hydrolyzing maternal TGs to FFAs. These FFAs can be transported across the placenta by FA binding proteins and FA transport proteins. Adiponectin may serve as an important regulator of nutrient flux across the placenta and appears to have a role negatively downregulating the activity of key placental nutrient transporters [72]. Recent studies have shown that circulating adiponectin levels were lower in woman who gave birth to LGA offspring or had fetuses with a large abdominal circumference (AC) late in pregnancy [73]. This is consistent with the current evidence surrounding hypoadiponectinemia which leads to insulin resistance and thus glucose intolerance and the emerging question of whether it also leads to β cell dysfunction [15].

Even with the advent of screening and aggressive management of diabetes, the incidence of neonatal complications ranges from 12-75% [74]. 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% [75]. Shoulder dystocia occurs nearly 50% of the time when a 4500 gram infant is delivered vaginally [76], However studies demonstrate that even in the presence of maternal diabetes and fetal macrosomia, clinicians accurately predict shoulder dystocia in only 55% of cases [77]. This creates a clinical dilemma for delivery management, so the American College of Obstetrics and Gynecology (ACOG) states unless other delivery indication such as poor diabetes control, preeclampsia, chronic hypertension, or any fetal indications, recommendation is for delivery >39 weeks' gestation but that best delivery mode is unclear. Delivery can be considered between 37-39 weeks if poorly controlled diabetes. With advancing maternal age and BMI, the risk of perinatal death is higher after 38 weeks. The optimal mode of delivery is unclear, based on only ultrasound measures and other considerations that weigh in on whether the fetus appears to have body to head disproportion (AC 3 weeks ahead of the bi-parietal diameter suggesting abnormal fetal growth from inadequately controlled diabetes) and whether or not the woman has had a successful vaginal delivery, and presence of polyhydramnios. There are a number of conflicting studies regarding induction versus cesarean section for suspected macrosomia [77, 78]. Preterm labor leading to prematurity can result due to polyhydramnios from the fetus ultra-filtrating glucose through the kidneys. In mothers who have 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 [79] and cardiac septal hypertrophy may be seen in 35-40% (59,61). With extremely poor glucose control, there is also an increased risk of fetal mortality due to fetal acidemia and hypoxia. Common metabolic abnormalities in the infant of a mother with diabetes include neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia and

polycythemia. Neonatal hypoglycemia is common in women with diabetes, especially with hyperglycemia in the intrapartum period because the infant may continue to produce excessive insulin for up to 48 hours after birth before the normal feedback loop is operating. Among neonates born to mothers with diabetes, LGA neonates are found to have 2.5-fold increased odds of hypoglycemia. This is important for neonatal glycemic management post-delivery, and maternal late third trimester hemoglobin A1C (A1c) can be more predictive for adverse neonatal outcomes than mean blood glucose [80].

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

Currently, there is no consensus on the ideal macronutrient prescription for pregnant women or women with GDM [81-83] 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%. It is also important to asses 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, as determined by studies that evaluate basal metabolic rate by calorimetry, total energy expenditure by doubly labeled water, and individual physical activity [84]. Women with pre-existing diabetes and GDM should receive individualized medical nutrition therapy (MNT) as needed to achieve treatment goals. Pregravid BMI should be assessed and gestational weight gain (GWG) recommendations should be consistent with the current Institute of Medicine (IOM) weight gain guidelines (See Table 1) [85], due to adverse maternal, fetal and neonatal outcomes. However, there are many trials which support no weight gain for women with a BMI of ≥30 kg/m2 with improved pregnancy outcomes and the lack of weight gain or even modest weight loss, did not increase the risk for small for gestational age (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 women; ~7 kg or 15 lbs. for overweight women; and 5 kg (11 lbs.) for women with Class 1 obesity (BMI 30-34 kg/m2).9 kg/m2) has been shown in many trials to decrease the risk of preeclampsia, cesarean delivery, GDM, and postpartum weight retention [86]. This is an increasing public health concern given risks of excessive weight gain (greater than IOM recommendations) including cesarean deliveries and post-partum weight retention for the mother and large for gestational age infants, macrosomia, and childhood overweight or obesity for the offspring [84].

**TABLE 1: Institute of Medicine Weight Gain Recommendations in Singleton Pregnancy**

| BMI | Total weight gain (lbs.) | 2nd/3rd trimester rate of weight gain (kg/week) |
|---|---|---|
| Low (<19.8 kg/m$^2$) | 28-40 | 1.0 (1-1.3 lb./week) |
| Normal (19.8-26 kg/m$^2$) | 25-35 | 1.0 (0.8-1 lb./week) |
| High (>26-29 kg/m$^2$) | 15-25 | 0.66 (0.5-0.7 lb./week) |

| Obese (>29 kg/m$^2$) | 11-20 | 0.5 (0.4-0.6 lb./week) |
| --- | --- | --- |

There is also increasing evidence that overweight or obese women with GDM may have improved pregnancy outcomes with less need for insulin if they gain weight less than the IOM recommendations [87-89] without appreciably increasing the risk of SGA.  For obese women, ~25 kcal/kg rather than 30 kcal/kg is currently recommended [90].  However, other investigators would argue for a lower caloric intake (1600-1800 calories/day) [91], which does not appear to increase ketone production.

The diet should be culturally appropriate and women should consume at least 175 grams of carbohydrate, primarily as complex carbohydrate and limit simple carbohydrates, especially those with high glycemic indices [82].  Protein intake should be at least 1.1 g/kg/day (15-20% of total calories) unless patients have severe renal disease.  Patients 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 [92].  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 [93] and the use of artificial sweeteners, other than saccharin, is considered safe in pregnancy and may be useful in controlling total calories and glycemic excursions.

For normal weight women with T1DM, carbohydrate and calorie restriction may not be necessary as long as it is 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.  Patients receiving insulin based on an insulin to carbohydrate ratio should estimate grams of carbohydrate with each meal.  Preferably blood glucoses can be recorded on the same food and beverage record for comparison of carbohydrate intake with glucose excursions.

 Exercise is an important component of healthy lifestyle and is recommended in pregnancy by ACOG, the American Diabetes Association (ADA), and Society of Obstetricians and Gynaecologists of Canada [94-96]. The U.S. Department of Health and Human Services issued physical activity guidelines for Americans and recommend healthy pregnant and postpartum women receive at least 150 minutes per week of moderate-intensity aerobic activity (i.e., equivalent to brisk walking) [97].  A large recent meta-analysis of all RCTs on diet and physical activity [98], 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.  However, there was data suggesting that physical activity may decrease the risk of LGA infants (LGA, >90th percentile).  There was no increase in SGA infants (SGA; <10th 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 women 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 [99].

Some data suggests that women who continued endurance exercise until term gained less weight and delivered slightly earlier than women who stopped at 28 weeks but they had a lower incidence of cesarean deliveries, shorter active labors, and fewer fetuses with intolerance of labor [100]. Babies weighing less were born to women who continued endurance exercise during pregnancy compared with a group of women who reduced their exercise after the 20th week (3.39 kg versus 3.81 kg).  The primary recommendation is motivational interviewing with a patient centered approach to obesity and GWG which have been most effective in reaching IOM goals. These strategies have been less examined in women with T2DM but are likely to be equally beneficial due to the effects of exercise on improving insulin resistance. Contraindications for a controlled exercise program include women at risk for preterm labor or delivery or any obstetric or medical conditions predisposing to growth restriction.

# DIABETES COMPLICATIONS AND TREATMENT OPTIONS IN WOMEN WITH PRE-EXISTING DIABETES AND THE ROLE OF PRECONCEPTION COUNSELING

Although historically, T1DM has been more prevalent than T2DM in women of child-bearing age, this is changing with increased obesity rates worldwide. There has been an increase in both prediabetes and T2DM among US adults greater than age 20 over the last two decades, including reproductive aged women. There was higher prevalence of diabetes among non-Hispanic blacks and Mexican Americans [101]. In Canada, the number of women with pre-existing diabetes has increased 50% between 1996 and 2001 with T2DM representing a growing proportion [102]. There is limited data on the burden of diabetes during pregnancy in low and middle income countries around the world [103].

Both women with T1DM and T2DM are at increased risk of poor obstetrical outcomes, and both can have improved outcomes with optimized care [104, 105]. The White Classification (Table 2) was developed decades ago by Priscilla White at the Joslin Clinic to stratify risk of adverse pregnancy outcomes in women with T1DM according to the age of the patient, 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 (e.g. retinopathy, nephropathy, hypertension, coronary artery disease, etc.), it is still often used in the U.S. to indicate level of risk for adverse pregnancy outcomes [106].  Although it was developed to use in women with T1DM rather than T2DM, given the very low prevalence of T2DM in women of childbearing age decades ago when it was first established in 1949, many also apply it to this group of women.  ACOG further modified it in 1986 and GDM was added to the classification and designated as A1 (controlled by diet alone) and A2 (controlled by medication).  Women with

T2DM are at least as high of a risk of pregnancy complications as women with T1DM. The reasons for this may include older age, a higher incidence of obesity, a lower rate of preconception counseling, disadvantaged socioeconomic backgrounds, and the co-existence of the metabolic syndrome including hyperlipidemia, hypertension, and chronic inflammation [29]. Furthermore, the causes of pregnancy loss appear to differ in women with T1DM versus T2DM. In one series comparing outcomes, >75% of pregnancy losses in women with T1DM were due to major congenital anomalies or prematurity [107]. In women with T2DM, >75% were attributable to stillbirth or chorioamnionitis, suggesting that obesity may play a role.

| Table 2: Modified White Classification of Pregnant Diabetic Women | | | | |
|---|---|---|---|---|
| Class | Diabetes onset age (year) | Duration (year) | Type of Vascular Disease | Medication Need |
| Gestational Diabetes (GDM) | | | | |
| A1 | Any | Pregnancy | None | None |
| A2 | Any | Pregnancy | None | Yes |
| Pre-gestational Diabetes | | | | |
| B | 20 | <10 | None | Yes |
| C | 10-19 OR | 10-19 | None | Yes |
| D | <10 OR | 20 | Benign Retinopathy | Yes |
| F | Any | Any | Nephropathy | Yes |
| R | Any | Any | Proliferative Retinopathy | Yes |
| T | Any | Any | Renal Transplant | Yes |
| H | Any | Any | Coronary Artery Disease | Yes |

Preconception care for women with pre-existing diabetes is associated with improved outcomes [105, 108]. The importance of strict glycemic control, folic acid supplementation, discontinuation of potentially harmful medications (such as statins, angiotensin converting enzyme [ACE] inhibitors), encouraging weight loss in overweight/obese women and optimization of associated medical conditions, including complications of diabetes, are all important components of preconception care. The ADA recommends preconception counseling and care as a part of every visit for adolescents and women with diabetes starting at puberty [96]. In order to reduce congenital anomalies and spontaneous abortion, interventions need to be in place well before conception. Embryogenesis is complete by 6 weeks after conception, so hyperglycemia during the first 6-8 weeks of pregnancy carries dramatic risk for development of congenital anomalies as well as miscarriage. Unfortunately, about 50% of women with diabetes plan their pregnancies, similar to women without diabetes. Unfortunately, many women with diabetes do not seek preconception care and planning for diabetes. Certain maternal characteristics such as poor health literacy, smoking, being unmarried, lower family income and poor relationship with their provider that predict lower likelihood of receiving preconception care. Women who attend specialized pre-pregnancy clinics for preconception counseling have improved outcomes vs. non-attenders, but those that access the clinics tend to be the lowest risk women [109].

# Reducing Risk of Congenital Anomalies

Hyperglycemia is a known teratogen whether occurring from T1DM or T2DM and can result in complex cardiac defects, CNS anomalies such as anencephaly and spina bifida, skeletal malformations and genitourinary abnormalities [110, 111]. A systematic review of 13 observational studies of women with T1DM and T2DM 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 women with optimal glycemic control [112]. Women with a normal A1c at conception and during the first trimester have no increased risk while women with a A1c of 10-12% or a fasting blood glucose >260 mg/dl have up to a 25% risk of major malformations (92,93). The offspring of women with T1DM have higher prevalence of neonatal death (RR 4.56 [95% CI 3.42, 6.07], p < 0.0001) as well as infant death (RR 1.86 [95% CI 1.00, 3.46], p = 0.046) compared to offspring of women without diabetes[113]. Periconception A1c >6.6% (adjusted odds ratio [aOR] 1.02 [95% CI 1.00, 1.04], p = 0.01), preconception retinopathy (aOR 2.05 [95% CI 1.04, 4.05], p = 0.04), and lack of preconception folic acid supplementation (aOR 2.52 [95% CI 1.12, 5.65], p = 0.03) were all independently associated with risk of neonatal and infant death [113]. Most organizations recommend women achieve an A1c of less than 6.5% prior to conception [96, 114]. For women 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 6.0-6.5% is recommended.

The mechanism of glucose induced congenital anomalies has not been fully elucidated [115]. 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 are also associated with altered expression of genes which control development of the neural tube [116].

Offspring of women with T1DM DM have a risk of developing T1DM DM of about 1-3%. The risk is higher to the offspring if the father has T1DM rather than the mother (~3-6%) and if both parents have T1DM, the risk is ~20% [117, 118].

Women with Type 2DM are more likely to be treated for dyslipidemia and hypertension. Chronic hypertension occurs in 13-19% of women with T2DM and many of these will be prescribed an ACE-inhibitor or Angiotensin receptor blocker (ARB) [119]. 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 [120]. Currently there is an ongoing multicenter trial examining pravastatin in prevention of preeclampsia due to its favorable effect of vascular

endothelial growth factor in animal studies [121-123]. Ideally statins should be stopped prior to pregnancy, but definitely at diagnosis of pregnancy.

**Treatment Options in Achieving Glycemic Control**

*All women with T1DM and T2DM should target an A1c of <6.5-7% preconception when possible. For women with T2DM on oral or noninsulin injectable agents, it must be decided whether to switch to insulin prior to pregnancy, even in women who are achieving the target A1c < 6.5-7.0%.*

No oral hypoglycemics are approved for pre-existing diabetes in pregnancy although glyburide and metformin have been used in multiple RCTs for GDM. There is no evidence that exposure to glyburide or metformin in first trimester are teratogenic, but both do cross the placenta, metformin substantially more than glyburide [124-126]. There appear to be no metformin receptors in the embryo but there are metformin receptors in the fetus. There is minimal data on thiazolidinediones or metiglinides and no data on incretin-based therapies (dipeptiydyl peptidase [DPP]-4 inhibitors and glucagon-like peptide [GLP]-1 analogues). It is recommended that women 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. Furthermore, oral hypoglycemic agents alone are likely to fail to control glucoses during pregnancy given the insulin resistance of pregnancy. However, women who conceive on any oral agents should not have them stopped until they can be switched effectively to insulin because hyperglycemia is potentially much more dangerous than any of the current available therapies to treat diabetes [114]. There are potential concerns for sodium-glucose cotransporter-2 (SGLT2) inhibitors in pregnancy based on a case of profound polyuria in a pregnant patient with familial renal glycosuria (mutation in gene encoding SGLT2 transporter) [127]. Furthermore, pregnancy causes polyuria and glycosuria normally due to increased glomerular filtration rate so SGLT2-inhibitors would not be expected to be beneficial. Metformin is sometimes used pre-conception and throughout the first trimester in women with polycystic ovary syndrome (PCOS) not for glycemic control but to improve fertility and prevent early miscarriage. Recent guidelines do not recommend metformin as a first line agent for ovulation induction in women with PCOS and infertility [128], but rather letrazole. There has not been shown any teratogenic effect of metformin when used in women with PCOS [126, 129]. However, a large multicenter RCT did not support the use of metformin to decrease first trimester miscarriage or pregnancy complications in women with PCOS and thus there does not appear to be any clear value in continuing it during the first trimester [130].  However, abrupt cessation of this agent before 8 weeks' gestation could result in hyperglycemia for women with PCOS who are glucose intolerant which could increase the risk of major malformations.  For these women, there is no evidence that continuing it throughout organogenesis (first trimester) poses any risk to the fetus [114].  However, there is no available long-term safety data on metformin use in pregnancy [131].

Given lack of long-term safety data on metformin use in pregnancy, the ADA and ACOG recommends insulin as the first line agent for treatment of diabetes in pregnancy, including preexisting diabetes and GDM [83, 96]. Insulin therapy must be individualized. Increasingly, individuals with diabetes, especially those with T1DM, are being managed with a flexible intensive self-management program in which they learn to dose their short acting insulin according to a pre-meal correction factor and insulin to carbohydrate ratio [132]. Lispro and aspart have been used in multiple trials in pregnancy and are superior to regular insulin with improvement in postprandial glycemia and reduced hypoglycemia [133, 134], while fetal outcomes were similar. There are no data on short acting insulin glulisine nor the recent FDA approved ultra-fast-acting insulin aspart in pregnancy.

Although there are less safety data on the use of long acting insulin analogues in pregnancy they do appear to be safe. There were early concerns that glargine may have a pronounced mitogenic effect due to the higher affinity to the IGF-1 receptor. A recent meta-analysis did not demonstrate any difference in maternal or fetal outcomes in pregnancies exposed to glargine vs. NPH [135]. Early case reports raised concern over progression of retinopathy with glargine, however recent studies in the non-pregnant population have not shown this. The efficacy and safety of detemir has been confirmed in a multinational RCT involving 371 women, approximately half of whom were enrolled prior to pregnancy [136, 137]. There were no differences in any of the maternal or neonatal outcomes. Overall glycemic control was slightly better with detemir compared to NPH, with lower fasting glucose, less risk of maternal hypoglycemia and slightly reduced A1c levels. There have been no studies looking at safety of newer basal insulins such as degludec (Tresiba), glargine 300 (Toujeo), and the biosimilar glargine (Basaglar). Many women with T1DM use continuous insulin infusion pumps and CGM during pregnancy[138]. CGM will be reviewed in detail below. There have been several studies showing insulin pump use is safe in pregnancy. In a large multicenter trial of women with T1DM during pregnancy, there was improved A1c both in the first trimester as well as in the third trimester and no difference in rates of diabetic ketoacidosis (DKA) or severe hypoglycemia compared to women with T1DM treated with multiple daily injections during pregnancy [139]. Most studies have shown improvement in glycemic control [140], but not all [141, 142]. Most studies have shown similar maternal and perinatal outcomes [143]. Disadvantages of insulin pump therapy include cost and the risk for marked hyperglycemia or DKA as a consequence of insulin delivery failure from a kinked catheter or from infusion site problems [144], although rare. Patients 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 rates due to the changing insulin resistance in pregnancy. Several studies demonstrate the significant changes in bolus more than basal insulin requirements during pregnancy which should be understood to achieve optimal glycemic control [143, 145]. A recently published paper on the use of a closed loop pump in pregnancy was very favorable but a pregnancy–specific algorithm was required [146]. The current closed loop pump by Medtronic is not approved in pregnancy, partly due to the algorithm that fixes the target at 120 mg/dl throughout the 24-hour period and cannot be decreased overnight unless the patient switched off auto mode to manual mode. Well-designed randomized clinical trials with appropriate glycemic control outcomes (using CGM) and

adequate power to examine obstetric and neonatal outcomes are needed to make strong recommendations regarding the benefits of pump therapy. However, recruitment to such trials will become more difficult given an increasing number of women with T1DM who are candidates for pumps prior to conception. The next generation of closed loop pumps that allow lower targets for pregnancy and are responsive to the fairly rapid changes in insulin sensitivity from week to week are anticipated in the near future [147].

# Diabetes Microvascular and Macrovascular Complications

It is essential that both the care provider and woman recognize the impact of pregnancy on the risk of progression of certain preexisting complications and the impact of microvascular complications on poor pregnancy outcomes. Careful assessment of severity and stability of complications and review of medications is essential prior to pregnancy.

**Retinopathy:**

Diabetic retinopathy may progress during pregnancy, and up to one year postpartum. However, pregnancy does not cause permanent worsening in mild retinopathy[148, 149]. The cause for progression in moderate and especially severe proliferative retinopathy is likely due to a combined effect of the rapid institution of tight glycemic control, increased plasma volume, anemia, placental angiogenic growth factors, and the hypercoagulable state of pregnancy[150, 151]. In 179 pregnancies in women with T1DM DM who were followed prospectively, progression of retinopathy occurred in 5% of women. Risk factors for progression were duration of diabetes >10 years (10% versus 0% in the <10-year duration of diabetes group), moderate to severe background retinopathy (30% versus 3.7% in the no or background diabetic retinopathy group), and a trend for those women who had the greatest fall in A1c [150]. The risk of progression of retinopathy is most pronounced in women with more severe pre-existing proliferative retinopathy, chronic hypertension, preeclampsia, development of hypertension during pregnancy, and poor glycemic control prior to pregnancy and dilated retinal exams during pregnancy are indicated [152]. Proliferative retinopathy may also progress during pregnancy, especially in women with hypertension or poor glycemic control early in pregnancy [153]. Pregnancy can also contribute to macular edema, which is often reversible following delivery [154].

Women with T1DM and T2DM should have ophthalmological assessments before conception. Laser photocoagulation for severe non-proliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy [82] and should be done prior to pregnancy. Women with low-risk eye disease should be followed by an ophthalmologist during pregnancy, but significant vision-threatening progression of retinopathy is rare in these

individuals. For vision-threatening retinopathy, laser photocoagulation can be used during pregnancy [155]. In women 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 women with advanced retinal disease and some experts have suggested avoiding significant Valsalva maneuvers—instead offering assisted second-stage delivery or cesarean delivery [93].

**Diabetic Nephropathy/Chronic Kidney Disease:**

Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications [156-159]. Although proteinuria increases during pregnancy in women with preexisting nephropathy, those with a normal GFR rarely have a permanent deterioration in renal function provided blood pressure and blood glucose are well controlled [160-162]. Those with more severe renal insufficiency (creatinine >1.5 mg/dl) have a 30-50% risk of a permanent pregnancy-related decline in GFR [163]. 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 women with T1DM DM and nephropathy, maternal and obstetric outcomes were strongly dependent on the degree of maternal renal function [164].  In women with a creatinine clearance of >80 cc/min, the prematurity rate was 19% and the mean birth weight was 2670 grams in comparison to women with a creatinine clearance of 30-80 cc/min in whom 60% of the infants were premature and the mean birth weight was only 1640 grams. Overall, ~50% of the patients developed nephrotic range proteinuria, 97% of the patients required antihypertensive treatment, and 20% of the children had neurodevelopmental delays. In normal pregnancy, urinary albumin excretion increases up to 30 mg/day and total protein excretion increases up to 300 mg/day.   Women with pre-existing proteinuria often have a significant progressive increase in protein excretion, frequently into the nephrotic range, in part due to the 30-50% increase in glomerular filtration rate (GFR) that occurs during pregnancy. Prior to conception, women should be screened for chronic kidney disease. Dipstick methods are unreliable and random urine protein/creatinine ratios are convenient but not as accurate as methods to carefully quantify proteinuria using 24-hour urine excretions in pregnancy. There have not been studies looking at spot urine albumin to creatinine ratio versus 24-hour urine protein assessment in pregnant women with diabetes. In hypertensive pregnant women, one study found that the spot urine albumin to creatinine ratio had higher diagnostic accuracy than 24-hour urine protein assessment [165].

There is conflicting information on whether first-trimester 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 compared to the normal population [166]. 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 (RR 1.41, 95% confidence interval (CI) 0.66–3.04) when ACE inhibitor and ARB exposed pregnancies were compared to other hypertensive pregnancies. A recent large cohort study of women with chronic hypertension including over 4100 pregnant women exposed to ACE inhibitors during the first trimester of pregnancy found no significant increase in major congenital anomalies [167]. 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 women 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 [168]. Women who are taking ACE-inhibitors or ARBs should be counseled that these agents are contraindicated in the 2$^{nd}$ and 3$^{rd}$ trimester of pregnancy. Women 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. Women who are considering pregnancy but 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 cycles and obtain home pregnancy tests for any late menses and stop these agents immediately if they are at all late for their menses or as soon as pregnancy is confirmed. Women with severe renal insufficiency should be counseled that their chances for a favorable obstetric outcome may be higher with a successful renal transplant. Women 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 out from their renal transplant have a much better prognosis than women with severe renal insufficiency and who are likely to require dialysis during pregnancy. Successful pregnancy outcomes have been reported in 89% of these successful renal transplant patients [169]. 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, especially preeclampsia, and postpartum graft function [170].


**Cardiovascular Disease:**

Although infrequent, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. The increasing prevalence of T2DM with associated hyperlipidemia, hypertension, obesity, advanced maternal age, and inflammation is further increasing the prevalence of CVD. CVD most often occurs in women with long-standing diabetes, hypertension, and nephropathy [171]. Because of the high morbidity and mortality of coronary artery disease in pregnancy, women with pre-existing diabetes and cardiac risk factors such as hyperlipidemia, hypertension, smoking, advanced maternal age (>35) or a strong family history should have their cardiac status assessed with functional testing prior to conception[114, 172]. 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 [171, 173, 174].

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 EKG should be considered preconception for any woman with diabetes older than 35 [93]. Women with longstanding diabetes and especially those with other risk factors for coronary artery disease (hyperlipidemia or hypertension) should be evaluated for asymptomatic coronary artery disease before becoming pregnant. Women 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. Statins should be discontinued before conception since there is inadequate data about their safety during pregnancy. However, if a woman has severe hypertriglyceridemia with random TG >1000 or fasting >400, 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 women 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 glucoses in women with gastroparesis during pregnancy.

## Associated Autoimmune Thyroid Disease:

Up to 30-40% of young women with T1DM have accompanying thyroid disease [175], and women with T1DM have a 5-10% risk of developing autoimmune thyroid disease first diagnosed in pregnancy (usually Hashimoto's thyroiditis). TSH should be checked prior to pregnancy since the fetus is completely dependent on maternal thyroid hormone in the first trimester [176, 177]. Women with positive TPO antibodies should have their TSH checked each trimester (Table 3) since the demands of pregnancy can unmask decreased thyroid reserve from Hashimoto's thyroiditis. Thyroid hormone requirements increase by 30-50% in most pregnant women, often early in pregnancy due to increase in thyroid binding globulin stimulated by estrogen. For most women on thyroid hormone replacement prior to pregnancy, the American Thyroid Association (ATA) and ACOG recommend TSH be within the trimester-specific 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 [178, 179]. For diagnosis of hypothyroidism during pregnancy, recent recommendations from the ATA recommend new reference ranges for TSH during pregnancy and screening in women 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 ~0.1-4mUI/L[178, 180]. This recommendation is based on the TSH range in pregnant women in the Maternal Fetal Medicine Units Network, and there was no benefit in treating women with levothyroxine with TSH <4.

**Table 3**

| Evaluation of Pregnant Women with Preexisting Diabetes in Addition to Prenatal Labs | |
|---|---|
| A1c | Initially and every 1 – 3 months |
| TSH | TSH every trimester if + TPO antibodies |
| TG | Repeat if borderline due to doubling in pregnancy |
| ALT; AST | For evaluation for non-alcoholic fatty liver disease and as baseline preeclampsia labs |
| Cr; Urine albumin or protein | If abnormal, obtain 24-hour urine for protein and estimated CrCl Repeat Prot/Cr ratio or 24-hour urine every 1 – 3 months if significant proteinuria or hypertension |
| Ferritin, B12 | Obtain for anemia or abnormal MCV, especially B12 if T1DM DM |
| Baseline preeclampsia labs | Consider Uric Acid; Obtain CBC with platelet count in addition to AST, ALT, BUN, Cr, 24-hour urine for protein, Cr |
| EKG | For women ≥35 years or CV risk factors; Consider further evaluation if indicated |
| Dilated Retinal Exam | Within 3 months of pregnancy or first trimester and repeat evaluation according to risk of progression |

## Other Autoimmune Conditions:

Other autoimmune conditions are also more common among women with T1DM compared to women 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 [181, 182]. This can often lead to vitamin D deficiency and iron deficiency and it is reasonable to screen women 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 than patients without diabetes with prevalence approximating 5-10% and 1-3%, respectively [183]. Addison's disease is also seen in 0.5-1% of patients with T1DM [183].

# MANAGEMENT OF PRE-EXISTING DIABETES DURING PREGNANCY

## Glucose Management

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 patient. Current guidelines are that fasting and premeal blood glucose should be <95 mg/dl, the 1 hour postprandial glucose <130-140mg/dl and the 2-hour postprandial glucose <120mg/dl [82]. Although a review of the literature suggests that the mean FPG, 1 hour PP, and 2-hour PP +/- 1 SD glucoses are significantly lower in normal weight women in the 3$^{rd}$ trimester (FPG ~71 +/- 8 mg/dl; 1 hour PP ~109 +/- 13 mg/dl; 2-hour PP 99 +/- 10 mg) than current therapeutic targets, (19), no RCTs have been completed to determine whether lowering the therapeutic targets results in more favorable pregnancy outcomes or decreases LGA. A prospective study in pregnant women with T1DM showed less preeclampsia with glucose targets of fasting <5.1 mmol/L (92 mg/dl), pre-prandial <6.0 mmol/L (108 mg/dl) and 1 hour postprandial <7.8 mmol/L (140 mg/dl) [184].   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) [96, 114]. Additional labs and exams recommended for women with preexisting diabetes during pregnancy are summarized in Table 3.

Increasingly, individuals with T1DM manage glucoses with a flexible intensive insulin program with multiple daily injections. Basal insulin is given 1-2 times daily or via a continuous insulin infusion pump and bolus insulin dosing is provided with short acting insulin with doses calculated based on pre-meal glucose and carbohydrate intake using a correction factor and insulin to carbohydrate ratio [132]. For women that do not know how to carbohydrate count, fixed insulin dosing can be prescribed. T1DM patients usually require multiple daily injections (5 injections per day) or an insulin pump to achieve optimal glycemic control during pregnancy. Women with T2DM usually require a similar basal/bolus insulin regimen.  Lispro and aspart have been used in multiple trials in pregnancy and their safety and efficacy have been well established (see Section IV).  Their use over regular insulin has been shown in both gestational and pre-gestational diabetes to result in improved glycemic control, fewer hypoglycemic episodes, and improved patient satisfaction.  Lispro or aspart insulin may be especially helpful in women with hyperemesis or gastroparesis because they can be dosed after a successful meal and still be effective.  There is inadequate data on the use of glulisine in pregnancy but it is unlikely to cross the placenta.  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 [185]. Thus, for some women it may be necessary to take meal time insulin 15-30 minutes prior to the meal (pre-bolusing).

Basal insulin may be provided as two doses of NPH or with one of the long acting analogues - detemir preferred over glargine. The absence of a peak with glargine and detemir may result in inadequate control of fasting glucoses, which can often be ameliorated by the use of NPH before bedtime to take advantage of its 8-hour peak.  The evening dose of NPH usually needs to be moved to bedtime to avoid nocturnal hypoglycemia and prevent fasting hyperglycemia.  Although women with T2DM may sometimes achieve adequate glycemic control with twice daily injections, perinatal outcomes were better with four times daily compared to twice daily regimens in both women with T2DM and GDM in a randomized study [186].

The risk of maternal hypoglycemia needs to be weighed with the risk of maternal hyperglycemia. Maternal hypoglycemia is common and often severe in pregnancy in women 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. Women must be counseled that their insulin requirements in the first trimester are likely to decrease by 10-20% [187]. This is especially true at night when prolonged fasting and continuous fetal-placental glucose utilization places the woman at even a higher risk for hypoglycemia. One of the highest risk periods for severe hypoglycemia is between midnight and 8:00 a.m. Pregnant women with diabetes complicated by gastroparesis or hyperemesis gravidarum are at the greatest risk for daytime hypoglycemia. In a series of 84 pregnant women with T1DM, hypoglycemia requiring assistance from another person occurred in 71% of patients with a peak incidence at 10-15 weeks' gestation [188]. One third of subjects had a least one severe episode resulting in seizures, loss of consciousness, or injury. There are also data to suggest that the counter-regulatory hormonal responses to hypoglycemia, particularly growth hormone and epinephrine, are diminished in pregnancy [189, 190]. This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control preconception and by the use of analogue insulins [191, 192] . In addition, insulin pumps with or without CGM may help achieve glycemic targets without increasing hypoglycemia [139, 146, 193]. The risk of hypoglycemia is also present in pregnant women with T2DM [194], but tends to be less so than in women with T1DM. The risk of hypoglycemia to the fetus is difficult to study but animal studies indicate that hypoglycemia is potentially teratogenic during organogenesis which would translate into a gestational age between 3-10 weeks in the human [195]. Exposure to hypoglycemia in utero may have long-term effects on the offspring including neuropsychological defects [195] so intensive efforts must be made to avoid it. Women with T1DM must have a bedtime snack and usually need to have their overnight long acting insulin lowered. The patient should have a glucagon kit and carry easily absorbed carbohydrate with her at all times. Education of patients and care providers to avoid hypoglycemia can reduce the incidence of hypoglycemia unawareness.  The incidence of severe hypoglycemia in pregnant women with T1DM can be reduced often 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 [196].

By 20 weeks of gestation, peripheral insulin resistance increases resulting in increasing insulin requirements so that it is not unusual for a pregnant woman to require 2-3 times as much insulin as she did prior to pregnancy. In a study of 27 women with T!DM 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% [143].

There are no definitive studies favoring continuous subcutaneous insulin infusion (insulin pump) over multiple daily injections [142, 197, 198]. RCTs of multiple daily injections versus the insulin pump generally showed equivalent glycemic control and perinatal outcomes. The insulin pump can be especially useful for patients with nocturnal hypoglycemia or a prominent dawn phenomenon [197]. However, insulin pump technology now integrated with CGM, sensor augmented pump therapy with threshold suspension of insulin delivery at or nearing

hypoglycemia targets and hybrid closed loop systems have not been extensively studied during pregnancy in comparison with multiple daily injection regimens. With the changing technologies to manage diabetes, these devices need to be studied in pregnant women with diabetes who are a high-risk population. As noted earlier, insulin delivery failure from a kinked catheter can result in DKA rapidly so it is optimal to start pump therapy prior to conception due to the steep learning curve using the pump effectively and the rapidly changing insulin sensitivity in pregnancy resulting in frequent changes to basal and bolus rates.

Also, as noted earlier, neither glyburide nor metformin are recommended for use in pregnancy for pre-existing diabetes and are likely to have high failure rates for these women given the high functional insulin demands and rising insulin resistance during pregnancy. However, for women with preexisting diabetes who decline insulin therapy, either agent or both are preferable to no therapy. Their use is unlikely to result in adverse outcomes from the agents themselves unless hyperglycemia is inadequately controlled. There are few studies looking at metformin use among pregnant women with T2DM [199, 200]. One study of 106 women with T2DM receiving metformin during pregnancy compared to insulin alone treatment found a large failure rate of metformin monotherapy (84.9% of metformin only group required addition of insulin), less neonatal hypoglycemia (p=<0.01), less NICU stay >24 hours (p=o.o1), less maternal weight gain (p<0.01), less gestational hypertension (p=0.029); however, SGA infants were more common in the metformin group compared to the insulin only group (p<-0.01) [199]. In a small randomized pilot study of 19 pregnant women with T2DM (8 receiving metformin and 11 receiving insulin), there was no significant difference in glycemic control, NICU stay, cesarean section, need for neonatal dextrose between the two groups [200]. The Metformin in Women with Type 2 Diabetes in Pregnancy Trial (MiTy) is currently enrolling pregnant women with T2DM who are on insulin, randomizing them to metformin or placebo, and should be a very helpful in evaluation of maternal and neonatal outcomes [201].

## Monitoring

Pregnant women with diabetes must do frequent self-glucose monitoring in order to achieve the level of glycemic control associated with better obstetrical outcomes. Since fetal macrosomia (overgrowth) is related to both the fasting and postprandial glucose excursions, pregnant women with diabetes need to monitor their post-meal and fasting glucoses regularly [202] and women with T1DM or T2DM using a flexible intensive insulin regimen also need to monitor their pre-meal glucoses. Pre-prandial determinations guide the meal-time insulin dose adjustment so that an appropriate insulin correction can be given if the pre-meal glucose is elevated. Postprandial glucose measurements determine if the insulin to carbohydrate ratios are effective in meeting glycemic targets as optimal control is associated with less macrosomia, metabolic complications in the fetus, and possibly preeclampsia. [184, 203]. Due to the increased risk of nocturnal hypoglycemia with any 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.

CGM may help identify periods of hyper- or hypoglycemia [204] and certainly confirm glycemic patterns and variability [205]. CGM has been an advancing technology with tremendous improvements in accuracy, comfort, ease of use and insurance coverage over the past decade. Although CGM is currently not approved for use during pregnancy, many women with T1DM and some with T2DM who are using the technology preconception will continue to use this helpful technology during pregnancy, or are started on CGM during pregnancy.  Pregnant women with diabetes may use CGM either in conjunction with an insulin pump or with MDI therapy to help achieve glycemic control. Sensor-augmented pump therapy (SAPT) and hybrid closed loop pump therapy have growing data in pregnancy. A recent large multicenter trial examined CGM use in women planning pregnancy as well as pregnant women with T1DM using either MDI or insulin pump therapy [206]. This study found statistically significantly lower incidence of LGA infants, less neonatal intensive care unit stays more than 24 hours, and less neonatal hypoglycemia. This study found a small difference in A1c among the pregnant women 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 outcomes for CGM use in pregnancy [206]. A recent randomized study evaluating hybrid closed loop therapy in women with T1DM during pregnancy vs SAPT showed that hybrid closed loop insulin pump therapy achieved a higher percentage of glucose time in range compared to patients using SAPT alone [146]. This study included a subset of women who continued closed loop therapy through labor and delivery, and these women achieved a high percentage of glucose in range during hospitalization and delivery. In this study, there were no significant differences in time in hypoglycemic range or adverse outcomes between the hybrid closed loop group and SAPT group. In one study using intermittent blinded CGM in which the information was used by the health care team to adjust insulin treatment, there was improved glycemic control in the third trimester and a reduction in macrosomia rates [204]. In another study of intermittent use of real time CGM (where glucose results are simultaneously displayed) there was no improvement of glycemic control or macrosomia [207].  It must be stressed to the patient that the values displayed by CGM may not be as accurate at extremes of hypo- or hyperglycemia or with rapid changes in glucose, so that checking fingerstick glucose is required when the patient feels the glucose is different than the displayed sensor glucose. CGMS values are interstitial glucose values and depend on the sensor glucose preceding it and is not an independent measure, the physiological diffusion of blood into capillaries and separation to interstitial fluid creates a time measurement delay, and calibration errors are not infrequent.  However, CGM is most helpful in identifying otherwise unrecognized glycemic patterns, and especially assessing for unrecognized nocturnal hypoglycemia.  There are no standardized approaches to define and analyze the enormous amount of data offered by CGM to facilitate comparisons among research studies, but most provide a proportion of time spent in target glucose range, time spent below range, time spent above range in addition to average sensor glucose and standard deviation. One study offers an approach for the study of fetal growth and infant outcomes [208]. Whether closed loop systems will become approved for clinical use in pregnancy remains to be seen given the need to change the target range for pregnancy (more stringent than in nonpregnant patients) and developing effective and safe algorithms.  With the burgeoning technology options for management of diabetes during pregnancy, research on these technologies during pregnancy is needed.  A newly approved flash glucose monitoring system

(a CGM that does not require fingerstick glucose calibration) has not been studied in pregnancy, but a single case report of its use in a pregnant woman with gestational diabetes mellitus showed achievement of excellent glucose control [209].

## Diabetic Ketoacidosis in Pregnancy

Pregnancy predisposes the mother 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 or ~11 mmol/l), often referred to as "euglycemic DKA" of pregnancy, and may develop more rapidly than it does in non-pregnant individuals [210, 211]. Women also have a lower buffering capacity due to the progesterone-induced respiratory alkalosis resulting in a compensatory metabolic acidosis. Furthermore, euglycemic DKA is not uncommon in pregnancy due to earlier ketosis in pregnant women and glomerular hyperfiltration in pregnancy which causes glycosuria at lower serum glucoses. Any pregnant woman with T1DM unable to keep down food or fluids should check urine ketones at home and if positive, a chemistry panel should be ordered to rule out an anion gap even if the maternal glucose is < 200 mg/dl. It should also be recommended to check urine ketones with any glucose >200 mg/dL.

In a study of 20 consecutive cases of DKA, only 65% of fetuses were alive on admission to the hospital [211]. Once the patient was hospitalized and treated, the risk of fetal loss declined dramatically. 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. There was no maternal mortality in this small series. In another case series of DKA in pregnancy, almost all women 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 [212]. Causes of DKA in pregnancy vary widely with infection less common as a precipitant [213]. Of the infectious causes, pyelonephritis was the most common. However, there is often no precipitant other than emesis in the pregnant woman who can develop starvation ketosis very quickly. In a series of 37 pregnant women with DKA, emesis alone accounted for 42% of the cases (60% of these women had gastroparesis), and 17% were non-compliant with prescribed insulin dosing. Beta agonist therapy, insulin pump failure, infection, undiagnosed pregnancy, and new onset diabetes each accounted for 8% of the cases. Prolonged fasting is a common precipitant for DKA and it has been shown that even women with GDM can become severely ketotic if they are given B-mimetic tocolytic medications or betamethasone (to accelerate fetal lung maturity) in the face of prolonged fasting [214]. It is imperative to remember that the pregnant woman unable to take glucose orally require an additional 100-150 grams of intravenous glucose to meet the metabolic demands of the pregnancy in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester. Without adequate carbohydrate (often a D10 glucose solution is needed), fat will be burned for fuel and the patient 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 in these patients and insulin requirements to treat DKA that are nearly twice as high as in the second trimester [211].

## Hypertensive Disorders in Pregnancy

Women with diabetic nephropathy are at extremely high risk of developing preeclampsia which often leads to intrauterine growth restriction and prematurity. Even women with microalbuminuria are at a higher risk of preeclampsia than women without microalbuminuria. Blood pressure control is imperative to try to minimize the deterioration of renal function. The goal for blood pressure control in women with chronic hypertension is not as low in pregnancy (120-160 /80-105) [96, 215] as outside of pregnancy due to the concerns about decreasing uteroplacental blood flow in the face of high vascular resistance in women at high risk of preeclampsia [161], however suboptimal hypertensive control has been associated with preterm delivery [216]. Hypertension should be treated in the pregnant woman with pre-existing diabetes at a BP level of ~140/90 and if the patient has underlying diabetic nephropathy, a goal closer to 120/80 should be achieved.   Although women with a blood pressure of >130/80 do not appear to do worse than women with a pressure < 130/80 in regards to preterm delivery, women with a higher BP tended to have worse renal function and greater proteinuria [216].  Although outside of pregnancy achieving a BP < 120/80 is renal protective, there are no prospective trials that have demonstrated that achieving this goal improves pregnancy outcome and there is a potential risk that lowering maternal blood pressure too aggressively could decrease placental perfusion, especially if the placental blood flow is already compromised.  After 24 weeks, any further elevation of BP requires an evaluation for superimposed preeclampsia given the high risk to women with preexisting diabetes. Treating mother's blood pressure has not been shown to prevent preeclampsia given it is characterized by an abnormality in placentation early in pregnancy. Agents such as methyldopa, hydralazine, calcium channel blockers, or labetalol can all be used [215]. ACE-inhibitors and ARBs are contraindicated in all trimesters of pregnancy and diuretics are reserved for the treatment of pulmonary edema due to concerns that further decreasing the intravascular volume with diuretics could further compromise tissue and placental perfusion. Since 2014, the US Preventative Task Force recommends low dose aspirin (81 mg) daily after 12 weeks' gestation for those at high risk of preeclampsia who do not have a risk or contraindication to aspirin use [217]. This includes pregnant women with T1DM or T2DM, as noted in the ADA Standard of care guidelines [96], a history of preeclampsia, chronic nephropathy, or chronic hypertension.

## Fetal Surveillance

Still birth rates are increased in women with T1DM and T2DM, especially those with poor glycemic control, vascular complications, hypertension, or nephropathy, who are at the highest risk for abnormal placentation and fetal overgrowth. Fetal hypoxia and cardiac dysfunction secondary to poor glycemic control are probably the most important pathogenic factors in stillbirths among pregnant women with diabetes [218].

An early dating ultrasound is necessary to accurately determine the gestational age of the fetus and a formal anatomy scan at 18-20 weeks should be done to evaluate for fetal anomalies. A fetal echocardiogram should be offered at 20-22 weeks if the A1c was elevated (>6.5-7.0) during the first trimester. Women with T1DM can be at risk for macrosomic infants (due to excess delivery of nutrients to the fetus from poor glycemic control) or intrauterine growth restriction due to the common finding of poor placental perfusion in women with longstanding diabetes and microvascular disease. Most recently, it is being recognized that although the mother may have glucoses in the target range, the fetus may still demonstrate abnormal growth (LGA) due to excessive nutrients being shunted to the fetus. This appears to be due to increased glucose transport across the placenta and also the effect of high lipids on fetal fat accretion, most importantly TGs or FFAs [20]. This abnormal growth is usually in a characteristic pattern of head to body disproportion. The fetus exhibits advanced growth in the AC measurement due to excessive subcutaneous fat, compared to the head measurement and this can be an early sign of excessive fetal growth due to diabetes. Increasingly, fetal criteria and growth patterns by ultrasound at this time are dictating the aggressiveness of maternal glycemic treatment rather than simply using maternal glycemic control as the goal for therapy [219, 220]. In addition to fetal ultrasound, antepartum fetal monitoring including fetal movement records, the non-stress test, and the biophysical profile are usually recommended for women with pre-gestational diabetes with initiation of testing typically at 32-34 weeks' gestation. However, due to the increased risk of uteroplacental insufficiency and intrauterine fetal demise in patients with longstanding T1 DM, especially in those women with microvascular disease, diabetic nephropathy, hypertension, or evidence of poor intrauterine growth, fetal surveillance may be recommended earlier. 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 [215].

## 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 [221]. The anesthesiologist should be made aware of any concerns about cardiac dysfunction or ischemic heart disease, pulmonary hypertension from sleep apnea, hypertension, thromboembolic risks, potential desaturation while laying supine in women with severe obesity, or the possibility of difficult epidural placement or intubations. Stillbirth can occur near term, especially in women with poorly controlled diabetes and complications, so the optimal timing of delivery requires a balance of the risk of intrauterine fetal death with the risks of preterm birth. A vaginal delivery is preferred for women with diabetes due to the increased maternal morbidity of cesarean delivery such as infection, thromboembolic disease, and longer recovery time. A cesarean delivery may be offered for obstetric indications such as an estimated fetal weight >4500 grams.

The significance of dropping insulin requirements later in pregnancy as a sign of poor placental health and risk to fetal well-being is not clearly established [222]. In one retrospective study of 54 women 10% of women had a >15% fall in insulin requirements after 30 weeks' gestation but this was not associated with adverse obstetrical outcomes [223]. In a recent study of 158 women with T1DM and T2DM, falling insulin requirements by ≥15% after 20 weeks' gestation was associated with preeclampsia and altered antiangiogenic factors [224].

At labor and delivery, most women with preexisting diabetes should be managed with an insulin drip and a dextrose infusion to maintain the glucose in the desired range (70-110 mg/dl), which decreases the incidence of neonatal hypoglycemia. Once the woman is eating, the drip can be discontinued and subcutaneous insulin started.  One study found higher rates of neonatal hypoglycemia in women 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 [225]. However, insulin requirements postpartum drop dramatically and most women need only ~1/3 to 1/2 of their pre-pregnancy insulin dosages and some women require no insulin for the first 24-48 hours.  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 women as lactation is known to reduce insulin requirements. There are few studies looking at CGM use during labor and delivery [146] and the postpartum period, but potential benefits include recognizing trends toward hypoglycemia prior to severe hypoglycemic episodes especially with the dramatic changes in insulin sensitivity postpartum. The CONCEPPT trial did not find significant changes in maternal hypoglycemia with use of CGMS during pregnancy, but did find reductions in neonatal hypoglycemia with maternal CGM use [206].

## POSTPARTUM CARE AND CONCERNS FOR PRE-EXISTING 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 (for T1 DM). It has been demonstrated that the majority of women with pre-existing 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 [226]. Furthermore, many quit seeking medical care for their diabetes or lose health insurance. The postpartum period is relatively neglected, therefore, 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. Women 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 and may have a "honeymoon" period for several days in which their insulin requirements are minimal. Some estimates of insulin requirements postpartum suggest that women may require as little as 60% of their pre-pregnancy doses, and requirements continue to be less than pre-pregnancy doses while breastfeeding [227].   For women 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. If well controlled prior to pregnancy, pre-pregnancy insulin delivery settings can serve as an excellent starting point for the postpartum period.

Women with T1DM have been reported to have a 25% incidence of postpartum thyroiditis [228]. 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 a patient has symptoms [178].

## Breastfeeding

Breastfeeding should be encouraged for all women. However, it may have even more benefits for women with pre-gestational diabetes and their children [229]. Although the association is weak, some studies suggest that breastfeeding reduces the likelihood of T1DM in offspring [230, 231], although other studies have not found an association [232]. For women with T2DM, especially those with a high pre-pregnancy BMI or excessive GWG, breastfeeding may reduce postpartum weight retention, and reduce the risk of offspring obesity and insulin resistance although this group of women and their breast milk composition has been inadequately studied [233]. Women with both T1 DM and T2DM have lower rates of breastfeeding despite good intentions [234-236]. Among women with both T1DM and T2DM, low milk supply is more common than among women without diabetes [237]. For women with T2DM, there has been a reluctance to reintroduce oral agents during the breastfeeding period due to early reports of high breast milk concentrations of first-generation sulfonylureas and lack of safety data.   However, a small study suggested that glyburide and glipizide do not appreciably cross into breast mild and may be safe [238].  Very low metformin levels were detected in breast milk in 3 studies with very low or undetectable serum levels in the infant [239]. If these agents are used, the lowest possible dose should be prescribed, the pediatrician should be aware of this decision, and the medications should be taken immediately after nursing to avoid a peak effect.  There are no adequate data on the use of thiazolidinediones, meglitinides, or incretin therapy in nursing mothers. Mothers with T1DM DM who are breastfeeding will need significantly lower basal insulin doses than women who are not breastfeeding [240, 241]. Breastfeeding may require an additional 200-300 calories to maintain weight but may be helpful in facilitating weight loss in women who struggle with postpartum weight retention.  Breastfeeding initiation may be difficult

in women with diabetes as more often neonates are in the NICU than mothers without diabetes. When women have stopped breastfeeding, most stop due to low milk supply rather than diabetes specific reasons [242].

Statins should not be started if the woman is nursing due to inadequate studies in breastfeeding mothers. Women 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, but there is limited data on this.

## Contraception

Starting at puberty, it is recommended to provide women with diabetes preconception counseling including discussion of options for contraceptive use [96] based on the Medical Eligibility Criteria (MEC) according to WHO and CDC [243]. The vast majority of contraceptive methods are relatively safe in women with diabetes who do not have poorly controlled hypertension or hypertriglyceridemia and who are not at increased risk for thromboembolic disease [244]. A recent systematic review 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 women with pre-existing diabetes [245]. However, estrogen-containing contraceptives are contraindicated in women with a history of thromboembolic disease or who have high triglycerides and at risk for triglyceride-induced pancreatitis.  A large study recently found an overall low risk of venous thromboembolism among women with T1DM and T2DM [246]. A recent meta-analysis found that low-income women with diabetes had low rates of postpartum birth control and more often were offered permanent contraception rather than reversible options [247]. Low dose combined oral contraceptives and the NuvaRing have been shown to be effective and to have minimal metabolic effects in women with GDM, however their use in women with known micro- or macrovascular disease is more controversial [248]. Implantable progestin agents are also excellent alternatives for women desiring longer acting reversible contraception (LARC) as are intrauterine devices. There is no increase in pelvic inflammatory disease with the use of intrauterine devices in women with well controlled T1DM or T2DM after the post-insertion period. Therefore, this may be an attractive choice in older women who do not desire future pregnancies.  Immediate postpartum implants and IUDs are becoming increasingly available to prevent undesired pregnancies in high risk populations.  Nearly any contraceptive method is superior to an unwanted pregnancy given the risks to the mother with preexisting diabetes which is often coupled with other medical complications. For women who desire permanent sterilization, both laparoscopic and hysteroscopic tubal occlusion methods are safe and effective [249].

# GESTATIONAL DIABETES

## Prevalence and Pathophysiology

The prevalence of GDM is rapidly rising and ranges from 6-9% of pregnancies throughout the world and is highest in ethnic groups that have a higher incidence of T2DM (Hispanic Americans, Native Americans, and Pacific Islanders) [83, 250]. Asian women have a higher risk of developing GDM at a lower BMI, possibly secondary to having more of a central fat distribution and diminished insulin secretion.  Interestingly, women of African ancestry have a high prevalence of obesity but lower GDM rates for their level of obesity.  Postpartum they have a higher rate of developing diabetes after GDM.  The prevalence of GDM doubled in the past 10-15 years due to the obesity epidemic.

GDM is caused by carbohydrate intolerance due to abnormalities in at least 3 aspects of fuel metabolism: insulin resistance, impaired insulin secretion, and increased hepatic glucose production [7, 251]. The beta cell defects reflect the spectrum of B-cell defects that leads to diabetes in nonpregnant individuals [252].  Although women with GDM increase their insulin secretion during pregnancy as glucose tolerant women do, their B-cell compensation is inadequate for the level of insulin resistance in order to maintain euglycemia. In GDM women, serum adiponectin levels have been shown to be decreased and leptin, IL-6, and TNFα were increased [253].   Insulin resistance during pregnancy is usually compensated for by a considerable increase in insulin secretion. However, in women who develop GDM, insulin resistance is more profound and this challenge, combined with decreased pancreatic beta-cell reserve, triggers GDM [252, 253].  Investigators have also shown more pronounced insulin resistance during pregnancy in GDM patients compared to women with normal glucose tolerance may contribute to hyperglycemia in addition to defects in insulin secretion [1, 254]. Although diabetes usually remits after pregnancy, up to 70% of women diagnosed with GDM go on to develop T2DM later in life, particularly if obesity is present. GDM shares many of the characteristics of T2DM. Both are aggravated by increasing obesity and age, supporting that the components of insulin resistance and decreased insulin secretion of GDM, may be common to T2DM. Thus, pregnancy is a "stress test" for the development of glucose intolerance and GDM may represent an unmasking of the genetic predisposition of T2DM induced by the hormonal changes of pregnancy.

Although insulin resistance is a universal finding in pregnancy in GDM, the cellular mechanisms for this type of insulin resistance are multi-factorial and just beginning to be understood. Insulin binding to its receptor is unchanged in pregnant and GDM subjects, and in skeletal muscle, GLUT4 is unchanged as well. Pregnancy reduces the capacity for insulin-stimulated glucose transport independent of obesity, due in part to a tissue-specific decrease in insulin receptor phosphorylation and decreased expression of Insulin Receptor Substrate-1 (IRS-1), a major docking protein in skeletal muscle. In addition to these mechanisms, in muscles from GDM subjects, IRS-1 is further decreased and there are reciprocal and inverse changes in the degree

of serine and tyrosine phosphorylation of the insulin receptor (IR) and IRS-1, further inhibiting insulin signaling [1]. GDM subjects also tend to have higher circulating FFA and reduced PPAR expression in adipose tissue, a target for thiazolidinediones [5]. There is evidence for a decrease in the number of glucose transporters (GLUT-4) in adipocytes in GDM subjects and an abnormal translocation of these transporters that results in reduced ability of insulin to recruit them to the cell surface, which contributes to the overall insulin resistance of GDM [255].

## Risks to the Mother and Infant with Gestational Diabetes

The pregnancy associated risks to the mother with GDM are an increased incidence of cesarean delivery (~25%), preeclampsia (~20%), and polyhydramnios (~20%) [74]. The long-term risks to the mother are related to recurrent GDM pregnancies and the substantial risk of developing T2DM. Women with GDM represent a group of patients with an extremely high risk (~50-70%) of developing T2DM in the subsequent 5-20 years. Women with fasting hyperglycemia, GDM diagnosed prior to 24 weeks (preexisting glucose intolerance), obesity, those belonging to an ethnic group with a high prevalence of T2DM (especially Latin-American women), or who demonstrate impaired glucose tolerance or fasting glucose at 6 weeks postpartum, have the highest risk of developing T2DM [254]. Latino women with impaired glucose tolerance postpartum have up to an 60% risk of developing T2DM DM within five years and should be targeted for primary prevention [256]. Counseling with regard to diet, weight loss, and exercise is essential and is likely to improve insulin sensitivity. Such dietary modifications should be adopted by the family since the infant is also at increased risk of developing impaired glucose tolerance as discussed above. Thiazolididiones, metformin, and lifestyle modifications have all been demonstrated to decrease the risk of developing T2DM in GDM women who have impaired fasting glucose or glucose intolerance postpartum [257, 258].

The risks to the infant from GDM are similar to women with T1DM or T2DM if poorly controlled including stillbirth, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia, with the exception of congenital malformations since GDM should not occur until after organogenesis.  If GDM is well controlled, the risk of stillbirth is much less so that women requiring only diet alone are not usually managed with non-stress testing [259].  However, women with GDM requiring medical therapy, who have medical complications, or who have suboptimal glycemic control are usually offered serial ultrasounds for growth and non-stress testing due to the potential risk of similar complications from poorly controlled diabetes. In addition to immediate postnatal risks, infants of GDM mothers are at increased risk for childhood and adult-onset obesity and diabetes. Specifically, in Pima Indians, the incidence of childhood T2DM at 10-14 years in the offspring of GDM mothers was 20 times higher compared to the offspring of non-diabetic mothers and 5-fold higher than that of pre-diabetic mothers who develop T2DM after pregnancy [260], underscoring the importance of the intrauterine environment.

## Data to Support the Screening, Diagnosis, and Treatment of Gestational Diabetes

Although there used to be significant controversy in the utility of screening and treatment of GDM, due to the absence of high-quality randomized controlled trials, two major randomized controlled trials have been published demonstrating the benefit in identifying and treating GDM [261, 262]. The first was a landmark trial conducted in Austria and New Zealand referred to as the ACHOIS trial (Australian Carbohydrate Intolerance Study in Pregnant Women).  This RCT enrolled 1000 women to receive dietary advice, SMBG, and insulin therapy as needed versus routine care and the results of the 2-hour 75-gram oral glucose tolerance test (OGTT) were blinded to practitioners and subjects.  Entry criteria included women whose FBG was < 140 mg/dl (7.8 mmol/L) with a mean FBG of 86 mg/dl (4.8 mmol/L) and a 2-hour value between 140-199 mg/dl (7.8-11.0 mmol/L) corresponding to a mean of 155 mg/dl (8.6 mmol/L).  Primary outcomes included serious perinatal complications including death, shoulder dystocia, bone fracture, and nerve palsy.  The rate of serious perinatal complications was significantly lower among infants whose mothers were identified and treated compared to those mothers who were not treated (1% versus 4%), although 10% more infants in the treated group were admitted to the neonatal nursery.  Although the induction of labor rate was higher in the intervention group, the cesarean delivery rate was not different [261].

A second landmark RCT, the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network study (NICHD MFMU Network), examined whether the treatment of mild GDM improves pregnancy outcome [262].  A total of 958 women who met criteria for mild GDM between 24-31 weeks were randomly assigned to usual prenatal care (control) or dietary interventions, SMBG, and insulin therapy if necessary (treatment group).  Women with fasting hyperglycemia (FBG ≥95 mg/dl) were excluded so that only women who had two elevated values on the 1 hour, 2 hour, or 3 hour 100 gm OGTT were included.  Furthermore, an additional 931 women with normal results in the 3 hour OGTT were included in the usual prenatal care group in order to mask the status of the control group.  The primary outcome was a composite of stillbirth or perinatal death and neonatal complications including hyperbilirubinemia, hypoglycemia, hyperinsulinemia, and birth trauma.  Although there was no significant difference in groups in the frequency of the composite outcome and no perinatal deaths in this population with very mild GDM, there were significant reductions with treatment in several pre-specified secondary outcomes including birth weight (3302 vs 3408 gm), neonatal fat mass by anthropometric measurements, the frequency of large-for-gestational-age (LGA) infants (7.1% vs 14.5%), macrosomia (5.9% versus 14.3%), shoulder dystocia (1.5% versus 4.0%), and cesarean delivery (26.9% vs 33.8%).  Furthermore, treatment of mild GDM was also associated with reduced rates for preeclampsia and gestational hypertension (8.6 versus 13.6% for combined rates). It is important to note in both landmark articles, that insulin was used when nutritional intervention failed and no oral hypoglycemics were used.

There is also new compelling data that the risk of adverse maternal-fetal outcomes from maternal carbohydrate intolerance is along a graded continuum [69, 263].  For the first time,

there are evidence-based outcomes regarding the level of maternal hyperglycemia at which adverse pregnancy outcomes clearly increase and the glucose thresholds at which they occur was found to be lower than the diagnostic criteria utilized for GDM in the United States (Carpenter and Coustan criteria for the 100 gram OGTT). The HAPO trial enrolled 25,505 pregnant women at 15 centers in nine countries [263].  Everyone underwent a 2 hour 75 gm OGTT at 24-32 weeks' gestation and the data remained blinded if the FBG was ≤105 mg/dl (5.8 mmol/l) and the 2-hour plasma glucose was ≤ 200 mg/dl (11.1 mmol/l).  Primary outcomes were LGA infants, primary cesarean delivery, clinically diagnosed neonatal hypoglycemia, and cord-blood serum C-peptide >90th percentile (a biomarker of fetal hyperinsulinemia).  Secondary outcomes were delivery < 37 weeks, shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia.  This trial demonstrated that a FBG ≥92 mg/dl, a 1-hour value ≥180 mg/dl, or a 2-hour value of ≥ 153 mg/dl increased the risk by 1.75-fold for LGA and an elevated cord-blood C-peptide consistent with fetal hyperinsulinemia.  Furthermore, the FBG was more strongly predictive of these outcomes than the 1 hour or 2-hour value.  The results also indicated a strong and continuous association with these outcomes and maternal glucose levels below those diagnostic of GDM and stressing the importance of fasting glucose levels in predicting poor perinatal outcomes.

## Diagnosis of Gestational Diabetes—Lack of Consensus

The previous definition of GDM as a glucose-intolerant state with onset or first recognition during pregnancy [254] was recently challenged by the International Association of Diabetes in Pregnancy Study Group (IADPSG). They recognized that many women with undiagnosed pre-existing (overt) diabetes were being referred to as GDM when the degree of their hyperglycemia or its early manifestation (before 24 weeks) clearly indicated that these women had diabetes that was simply not identified until GDM screening was performed in pregnancy.  Given that these women have a much higher risk of maternal and fetal complications, including major malformations if their A1c is ≥ 6.5, the IADPSG recommended that GDM be only diagnosed if the glucose intolerance was identified in pregnancy AND women did not qualify for pre-existing (overt) diabetes.  Given this concern for undiagnosed pre-gestational diabetes, the 2017 ADA guidelines recommend screening women at first prenatal visit if BMI >25 (or >23 in Asian Americans) and one or more risk factors (Table 3). The IADPSG/ADA recommends that women diagnosed for the first time in pregnancy should be considered as having overt diabetes (and not GDM) if any of the following criteria are fulfilled:  A1c of ≥ 6.5%; FBG ≥126 mg/dL, or random glucose ≥200 mg/dL, which are the same criteria for diabetes outside of pregnancy. The IADPSG recommends diagnosing GDM at lower glucose thresholds than what has been used by ACOG based on findings from the HAPO trial.  Further, given the HAPO trial showed an increased risk in LGA using a single abnormal threshold value on a 75 gm 2-hour OGTT, they advised this test be used to diagnose GDM rather than 2 abnormal values on a 100 gm 2-hour OGTT traditionally used by ACOG.  However, adopting the new IADPSG criteria would result in a tripling of the prevalence of GDM (estimated to be 18% of the pregnant population) compared to the current 5-6%.  This prevalence could be even higher in some ethnic groups

(Hispanic Americans, Native Americans, Pacific Islanders, and Asian Americans). In 2018, an ADA statement recognizes that there is no clear evidence which supports IADPSG versus traditional ACOG two-step screening approach.

The Carpenter and Coustan diagnostic criteria continue to be used by the 95% of U.S. obstetricians but ACOG recently recommended that either the Carpenter and Coustan criteria or the National Diabetes Data group could be used, both of which require 2 abnormal values out of 4 values on a 100 gm 3-hour OGTT [254] (Table 4). For diagnosis by the Carpenter and Coustan Criteria 100 gm 3-hour OGTT, 2 abnormal values are required (FBG≥95 mg/dl; 1 hr≥180; 2 hour ≥155; 3 hour ≥140).  For the diagnosis by the National Diabetes Data Group, 2 abnormal values are also required but are higher (FBG≥105 mg/dl; 1 hr≥190 mg/dL; 2 hour ≥165 mg/dL; 3 hour ≥145 mg/dL), which results in ~50% decrease in the diagnosis of GDM compared to the Carpenter and Coustan criteria. Both the 75 gm and 100 gm diagnostic tests should be performed after 3 days of unrestricted carbohydrate to prime the pancreas and avoid false positive tests.

The controversy with diagnosis of GDM relies heavily on the outcomes studied. The IADPSG recommendations based on the HAPO trial, which showed that a single value on a 75 gm 2 h-OGTT resulted in a 1.75 increased risk of LGA and thus should be the basis for the diagnosis; however, critics disagree.  Critics complained that a 2.0-fold increase in LGA risk instead of 1.75 could have been chosen which would not have appreciably increased the prevalence of GDM over the ACOG criteria [264, 265].  Nearly 90% of all of the women who met criteria for GDM using the 75 gm 2-hour OGTT were diagnosed based on the FBG and 1 hour values [266], raising the question of whether the 2-hour value is worth the extra time and cost. Some countries are considering making the diagnostic criteria for GDM be based only on a FBG and 1 hour value which would decrease subject burden and possibly cost.

According to ACOG, high-risk status requires glucose testing as soon as pregnancy is diagnosed and again at 24 to 28 weeks if the early testing is normal in accordance with recent ADA screening recommendations (Table 3). ACOG recommends that high risk women be screened on their first prenatal visit with a 50-gram glucose load and if the value at 1 hour exceeds 130-140 mg/dl, a diagnostic 3-hour 100 gm OGTT be performed.  The sensitivity and specificity of the screening test depend on what threshold value is chosen, and the cutoff may be selected according to the prevalence of GDM in the population being screened [96, 254]. The test does not have to be performed during a fasting state but a serum sample must be drawn exactly 1 hour after administering the oral glucose.

The options given by the ADA to diagnose overt diabetes in early pregnancy has resulted in some opponents underscoring that some high-risk women with only impaired glucose tolerance (by an OGTT) will be missed early using the IADPSG criteria since a practitioner can choose whether to obtain an A1c, fasting glucose, or 75 gm 2-hour OGTT *early* in pregnancy.  Some practitioners are recommending that an A1c of ≥ 5.7% be used to diagnose GDM early since this level diagnoses prediabetes outside of pregnancy.  However, an A1c of 5.7% or greater was not given as optional criteria by either IADPSG or the ADA to diagnose GDM but a

recommendation to screen. Further, studies outside of pregnancy have demonstrated that the A1c is the least sensitive test to diagnose either prediabetes or diabetes, especially given that anemia is common in pregnancy and the A1c will be falsely low in conditions of high red blood cell turnover states.  Further, it has been demonstrated that the FBG is less sensitive than the post glucose load value on a 75 gram 2- hour OGTT for diagnosing prediabetes or diabetes, especially for Asian women who have been shown to typically have normal FBGs.  A recent article underscored that there is a profound difference amongst different ethnic populations studied in the HAPO trial in regards to the sensitivity of a FBG versus a 1 or 2 hour 75 gm glucose value in diagnosing GDM [266].  In Hong Kong, of all of the women in the HAPO trial who were diagnosed as having GDM using the new criteria, only 26% had an abnormal FBG and the remainder were diagnosed by either a 1 hour post glucose value (45%) or abnormal 2-hour value (29%). Thus, guidelines recommended lower BMI criteria/stricter criteria for screening in the Asian American population. Both ACOG and the ADA agree that if initial testing is normal, repeat testing should be performed at 24 to 28 weeks' gestation.

ACOG recently noted that prior use of historic factors to identify GDM failed to identify 50% of patients with GDM and currently agree with USPSTF recommendations for universal screening of all women 24-28 weeks pregnant for GDM [254].

Currently there is no consensus about the adoption of the IADPSG criteria over the ACOG criteria.  The NIH held a Consensus Conference in March of 2013 [267].  They acknowledged that the HAPO study was the first to demonstrate that glycemic thresholds currently lower than the ACOG diagnostic criteria thresholds were correlated with LGA and adopting the 75 gm OGTT globally would be beneficial in standardizing diagnostic criteria internationally. However, they concluded that there were insufficient data from RCTs demonstrating that adopting the lower glucose thresholds would significantly benefit the much larger population of women who make diagnostic criteria for GDM based on the IADPSG criteria and such adoption could markedly increase cost of treatment.  Further, there was a concern that adopting the IADPSG criteria could triple the prevalence of GDM, potentially outstripping the resources to treat it. They also argued that it is not clear how much the increased risk of LGA at lower glucose thresholds observed in the HAPO trial on which it was based was due to maternal obesity or mild hyperglycemia.  A recent retrospective review of nearly 10,000 women who were diagnosed with GDM using the IADPSG criteria showed an overall GDM prevalence of 24%. After excluding women who required treatment for GDM, 75% of GDM women were overweight or obese.  Although GDM nearly doubled the risk of LGA over obesity alone (22.3% versus 12.7% respectively), in women without GDM, 21.6% of LGA was attributable to being overweight and obese.  The combination of GDM in addition to being overweight or obese did not add much to the attributable risk for LGA and accounted for 23.3% of LGA infants [254]. The NIH also underscored the concerns that there is considerable variability in the 2-hour OGTT and that results may differ in ~25% of women if performed at different times resulting in 1 step testing likely resulting in more false positives.  They provided data from a pooled meta-analysis of 5 RCTs showing treatment of GDM resulted in an absolute difference in birth weight of less than 150 gm and only a 6% absolute risk reduction of LGA.  They also cautioned that the prevalence of cesarean delivery and neonatal intensive care admission rate may increase with a

higher GDM prevalence.   As noted earlier, in the HAPO study, 78% of women who delivered LGA infants did not have GDM, further underscoring the independent contribution of obesity to LGA. Without available RCTs, treating milder forms of GDM as proposed by IADPSG (ADA) may not be beneficial.  Disappointingly, the 4-5 year old follow-up of infants in the ACHOIS study showed that there was no difference in childhood obesity in Rx vs non-Rx groups.  The NIH recommended that further randomized trials be done to put the diagnostic criteria against each other to determine whether implementation and treatment based on the new IADPSG criteria will result in less LGA or other adverse pregnancy outcomes compared to the ACOG criteria. There are plans by the Maternal Fetal Medicine Network (MFMU Network) to undertake this tremendous challenge. Obviously, the lack of consensus in which criteria to use can be confusing for patient management as well as for clinical research trials for which a number of diagnostic criteria could be used.  Again, the ADA in 2017 changed recommendations to state that either screening modality is appropriate (ACOG or IADPSG).

**Table 4.**

| SCREENING FOR GESTATIONAL DIABETES<br>**American College of Obstetrics and Gynecology (ACOG)/American Diabetes Association (ADA)** |
|---|
| High Risk Status: High risk status requires glucose testing as soon as pregnancy is diagnosed and again at 24-28 weeks if the early testing is normal.<br>Women with BMI >25 (>23 if Asian American) **AND** one or more risk factor:<br><br>• Obesity >40 or acanthosis nigricans<br>• Personal history of GDM<br>• Family history of diabetes in a first-degree relative<br>• Polycystic ovarian disease (PCOS)<br>• Physical inactivity<br>• High risk ethnicity (African American, Latino, Native American, Asian American, Pacific Islander)<br>• Prior neonate >4000g<br>• Hypertension<br>• HDL <35<br>• TG >250<br>• A1C >5.7%<br>• History of cardiovascular disease. |
| **CRITERIA FOR A POSITIVE 50 gm GLUCOLA CHALLENGE per ACOG**<br>-Screening for all pregnant women 24-28 weeks |
| Glucose > 140 mg/dl (7.8 mmol/l): Identifies ~80% of women with GDM at the cost of performing a 3 hour OGTT in ~15% of patients. |
| Glucose > 130 mg/dl (7.2 mmol/l): Identifies ~90% of women with GDM at the cost of performing a 3 hour OGTT in ~25% of patients. |
| **ACOG Criteria for a Positive 100 gm OGTT per Carpenter and Coustan** |

- Fasting glucose: 95 mg/dl
- 1 hour glucose: 180 mg/dl
- 2-hour glucose: 155 mg/dl
- 3-hour glucose: 140 mg/dl

**ACOG Criteria for a Positive 100 gm OGTT per National Diabetes Data Group**

- Fasting glucose: 105 mg/dl
- 1 hour glucose: 190 mg/dl
- 2-hour glucose: 165 mg/dl
- 3-hour glucose: 145 mg/dl

*2 abnormal values required

**Screening and Diagnosis of GDM Outside the U.S.**
**International Association of Diabetes and Pregnancy Study Groups (IADPSG)**
**Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy: 2010**
**Threshold Values for Diagnosis of GDM or Overt Diabetes in Pregnancy**

**First Prenatal Visit**

Measure FPG, A1C, or random plasma glucose on all or only high-risk women†
If results indicate overt diabetes

**Overt Diabetes**
Fasting glucose        ≥125 mg/dl;
A1c                    ≥6.5%
Random glucose         ≥200 mg/dl
**\*Any of above**

Treatment and follow-up as for pre-existing diabetes

If results not diagnostic of overt diabetes and fasting plasma glucose ≥5.1 mmol/l (92 mg/dl) but <7.0 mmol/l (126 mg/dl).
diagnose as GDM
If fasting plasma glucose < 5.1 mmol/l (92 mg/dl) and no criteria for overt DM, test for GDM from 24 to 28 weeks' gestation with a 75-g OGTT‡

**24-28 Weeks gestation: Diagnosis of GDM**

2-h 75-g OGTT: perform after overnight fast on all women not previously found to have overt
    diabetes or GDM during testing earlier in this pregnancy
    Overt diabetes if fasting plasma glucose ≥7.0 mmol/l (126 mg/dl)
    GDM if one or more values equals or exceeds thresholds

IADPSG and ADA Criteria for a Positive 75-g Oral Glucose Tolerance Test
Fasting glucose                ≥92 mg/dl

| | |
|---|---|
| 1-hour glucose | ≥180 mg/dl |
| 2-hour glucose | ≥153 mg/dl |
| **\*1 abnormal value needed** | |
| Normal if all values on OGTT less than thresholds | |

## Medical Nutrition Management and Exercise

Women with GDM should be taught home glucose monitoring to ensure that their glycemic goals are being met throughout the duration of pregnancy. The best therapy for GDM depends entirely on the severity of the glucose intolerance and on the mother's response in addition to the effect on fetal growth. In at least half of the cases, diet alone will maintain the fasting and postprandial blood glucose values within the target range. Since postprandial glucose levels have been strongly associated with the risk of macrosomia [202] it has been suggested that carbohydrate restriction to ~33-40% of total calories may be helpful to blunt the postprandial glucose excursions, in addition to controlling excessing weight gain. However, the actual dietary composition that optimized perinatal outcomes is unknown. There is also growing concern that women are substituting fat for carbohydrates which has recently been associated with adverse fetal programming including oxidative stress as well as an insulin resistant phenotype [43, 90].  Although a low carbohydrate higher fat diet has been conventionally recommended to minimize postprandial hyperglycemia, a recent review of the few randomized controlled trials examining nutritional management in 250 GDM women suggested that a diet higher in complex carbohydrate and fiber, low in simple sugar and lower in saturated fat may be effective in blunting postprandial hyperglycemia, preventing worsened insulin resistance, and excess fetal growth [81]. A more recent trial challenged the traditional low-carb/higher-fat diet and demonstrated that a diet with higher complex carbohydrates and lower-fat reduced fasting blood glucose and infant adiposity [268]. Given these trials, a diet of complex carbohydrates is recommended over simple carbohydrates primarily due to slower digestion time which prevents rapid rises in blood glucose.   A recent randomized study liberalizing complex carbohydrates to 60% of total calories and limiting fat to 25% was shown to achieve similar glycemic goals as a conventional low carbohydrate, higher fat diet and result in lower FFAs [268]. A higher fat diet when given to non-human primates is capable of causing TG deposition in the liver of the offspring, histologically identical to NAFLD [51]. Further, the authors subsequently showed that a maternal high fat diet results in decreased uterine blood flow, placental dysfunction, and an increased risk of stillbirth [269] in non-human primates. Therefore, recommendations are to consume at least 175 gm of carbohydrate but substitute complex for simple carbohydrates, increase the amount of fiber and protein, and avoid saturated fats [270], consistent with the recommendations discussed earlier for women pre-existing diabetes or obesity. There is little evidence to support one dietary approach over another but common practice is three meals and 2-3 snacks to distribute carbohydrate intake and reduce postprandial hyperglycemia. The caloric intake and weight gain recommendations are also consistent with what is recommended in women with obesity or T2DM.  However, there are two studies suggesting that weight gain less than IOM recommendations for overweight GDM women may decrease insulin requirements,

cesarean delivery, and improve pregnancy outcomes without appreciably increasing SGA [88, 89]. Further, a third study suggesting that slight weight loss (mean of 1.4 kg) in overweight GDM women decreased birth weight without increasing SGA [87].

The role of exercise in GDM may be even more important than in women with preexisting diabetes given exercise in some women may lessen the need for medical therapy. This idea is similar to the evidence in non-pregnant patients with diabetes which supports weight training due to increases in lean muscle and increased tissue sensitivity to insulin. A recent review showed that in women with GDM, five of seven (~70%) activity-based interventions showed improvement in glycemic control or limiting insulin use [271]. In most successful studies (3 times/week), insulin needs decrease by 2-3 fold, and overweight or obese women benefited the most with a longer delay from diagnosis to initiation of insulin therapy. Moderate exercise is well tolerated and has been shown in several trials in GDM women to lower maternal glucose levels [99, 272, 273]. Using exercise after a meal in the form of a brisk walk may blunt the postprandial glucose excursions sufficiently in some women that medical therapy might be avoided. Establishing a regular routine of modest exercise during pregnancy, per ACOG of 30 minutes of moderate-intensity aerobic activity at least 5 days/week, may also have long lasting benefits for the GDM patient who clearly has an appreciable risk of developing T2DM in the future.

## Medical Treatment Options

### Metformin:

The largest experience with metformin has been in GDM women later in pregnancy [274]. In this randomized, controlled Metformin in Gestation (MIG) trial, 751 women with GDM were randomized to metformin versus insulin. Women that did not get adequate glycemic control on metformin received insulin. There was no difference in both groups concerning the primary composite outcome (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5 minute APGAR <7), or premature birth). As such, metformin did not appear to increase any adverse outcomes, although it was associated with a slight increase in preterm birth; however, this did not appear to be clinically relevant. Importantly, 46% of the women in the metformin group required supplemental insulin to achieve adequate glycemic control. This study demonstrated interesting metformin benefits including: reduced maternal weight gain, improved patient satisfaction, and reduced incidence of gestational hypertension. In a smaller RCT, Ijas et al demonstrated metformin had a 32% failure rate. They also noted metformin failures were more likely to be obese, have higher fasting blood glucose levels, and initiated pharmacotherapy earlier [275]. Spaulonci et al randomized 47 women to metformin or insulin and also demonstrated significant metformin benefits including: less gestational weight gain, lower mean glucose levels, and lower rates of neonatal hypoglycemia. [276]. Overall, meta-analyses have demonstrated largely reassuring outcomes for metformin compared to insulin and glyburide [277-281]. Given these studies, both ACOG and ADA report insulin as first line

but metformin is a reasonable second line treatment option for women who are unable or unwilling to inject insulin.

Metformin should be avoided in patients with renal insufficiency. It is typically prescribed in divided doses starting with 500 mg daily for 1 week and then increasing to a maximum dose of 2500-3000 mg daily in divided doses with meals. Common side effects include gastrointestinal complaints (occurring in 2.5-45.7% of pregnant patients in studies) [277].  These randomized trials have shown short term efficacy and safety of metformin use in pregnancy for GDM treatment. However, long-term safety data is lacking. A follow-up report of the infants in the MiG trial [278] demonstrated that children exposed to metformin had larger measures of subcutaneous fat.  The authors suggested that this could potentially be due to a decrease in visceral fat due to overall body fat being similar by DEXA (dual-energy X-ray absorptiometry). However, DEXA does not measure visceral fat, only 43% of the cohort received anthropometric measures at 2 years and only ~15% of the cohort received DEXA scans. Interestingly, a greater increase in triglycerides were also seen in the mothers who were randomized to metformin compared to insulin in the MiG trial.  Maternal triglycerides, C-peptide at 36 weeks, and maternal BMI were correlated with LGA and anthropometric measures of infant adiposity [279]. A recent study of 211 women with GDM randomized to insulin versus metformin during pregnancy found similar developmental outcomes by 2 years of age [280]. Another study in PCOS women comparing metformin to placebo showed that although women randomized to metformin gained less weight during pregnancy, at 1 year postpartum the women who used metformin in pregnancy lost less weight and their infants were heavier than those in the placebo group [281].   These fetal and neonatal results are likely because metformin is concentrated in the fetal compartment with umbilical artery and vein levels being up to twice those seen in the maternal serum [124, 282]. Hypothetically if metformin increases insulin sensitivity in the fetus, it might be possible for excess nutrient flux across the placenta to result in increased fetal adipogenesis.

In review, the ADA and ACOG note that insulin is the first line agent for treatment of GDM if lifestyle changes have not achieved glycemic targets [96, 254]. The ADA notes that although individual RCTs have shown short term benefits and safety of metformin and glyburide, long-term safety data are lacking [131]. Both organizations acknowledge that 20-45% of women fail metformin monotherapy necessitating that insulin be added [254].  Counseling is necessary to explain to women that although current data do not demonstrate any adverse short term outcomes, there are concerns about placental transfer of metformin, potential increased preterm birth, and lack of data on long term outcomes of fetuses exposed to metformin in utero, metformin's effect on fetal insulin sensitivity, hepatic gluconeogenesis, and the long term fetal programming implications are unknown.


## Glyburide and Other Agents:

Glyburide is the only sulfonylurea that has been studied in a large randomized trial in GDM women.  It was approved by the 5th International Workshop and IADPSG as a possible

alternative to insulin in GDM women [82] due to a number of randomized controlled trials [283, 284]. However more recent data have been concerning in terms of increased risk of neonatal hypoglycemia and macrosomia [277]. In some trials, maternal glycemic control, macrosomia, neonatal hypoglycemia, and neonatal outcomes were not different between groups [283] although in others, there was a significantly greater rate of macrosomic infants in the glyburide group [285-287]. In a recent meta-analysis examining metformin versus insulin versus glibenclamide (glyburide) treatment for women with GDM, there were significant increases in macrosomia (risk ratio 2.62) and neonatal hypoglycemia (risk ratio 2.04) among women treated with glibeclamide compared to insulin [277]. This is the same publication reviewed above that showed the increased risk of preterm birth in the group of women treated with metformin compared to insulin. This meta-analysis in addition to a second meta-analysis show statistically significantly worse neonatal outcomes among offspring of women with GDM treated with glyburide compared to insulin during pregnancy [277, 285]. There were higher rates of neonatal hypoglycemia, respiratory distress syndrome, macrosomia, and birth injury [285] without significant differences in glycemic control.

Although it was initially thought not to appreciably cross the placenta or significantly affect fetal insulin levels, more recent examination using HPLC mass spectrometry suggested a modest amount does cross[124]. The dose ranges from 2.5-20 mg daily in divided doses. A RCT compared the efficacy of metformin with glyburide for glycemic control in gestational diabetes [284]. In the patients who achieved adequate glycemic control, the mean glucose levels were not statistically different between the two groups. However, 26 patients in the metformin group (34.7%) and 12 patients in the glyburide group (16.2%) did not achieve adequate glycemic control and required insulin therapy (p=.01). Thus, in this study, the failure rate of metformin was twice as high as the failure rate of glyburide when used in the management of gestational diabetes [284]. These findings are consistent with the general finding that approximately, 15% of patients will fail maximum dose glyburide therapy and need to be switched to insulin, especially if dietary restriction is not carefully followed.

Glyburide exposure in most RCTs is limited to after 24 weeks gestation so the effect on embryogenesis was not studied, but there are no convincing reports that it is a teratogen. Its use in women with T2DM has not been adequately studied. Given it has been shown to have a high failure rate in women diagnosed with GDM < 24 weeks [288] and in women with fasting hyperglycemia, it is expected to have a high failure rate in women with preexisting diabetes as would be the case with metformin, which has an even higher failure rate. Furthermore, due to its peak at 3-4 hours, many women have inadequate control of their 1 or 2 hour postprandial glucoses and then become hypoglycemic 3-4 hours later and data suggest that serum concentrations with usual doses are lower in pregnant women. If used, it should be given 30 mins-1 hour before breakfast and dinner and should not be given before bedtime due to the risk of nocturnal or early morning hypoglycemia in light of its 3-4 hour peak (similar to Regular insulin). For women unwilling to administer multiple daily insulin injections who have postprandial glucoses well controlled by glyburide but have fasting hyperglycemia, adding NPH before bedtime to the glyburide can sometimes be useful. If both postprandial and fasting glucoses remain elevated, the patient should be switched to insulin. There is not sufficient

information available on thiazolidinediones, meglinitides, DPP-4 inhibitors, GLP-1 agonists and such agents should only be used in the setting of approved clinical trials as their teratogenic potential is unknown. Acarbose was studied in two very small studies in GDM women and given its minimal GI absorption is likely to be safe but GI side effects are often prohibitive [289].

## Institution of Medical Therapy, Fetal-Based Treatment Strategies, Insulin Options

Although there are few data from randomized controlled trials to determine the optimal therapeutic glycemic targets, the standard of care is that women who have fasting blood glucose levels > 95 mg/dl, 1 hour postprandial glucose levels >140 mg/dl or 2-hour postprandial glucose levels > 120 mg/dl be started on medical therapy. In 5 randomized trials it was demonstrated that if insulin therapy is started in women with GDM whose maternal glucoses are at target levels on diet alone but whose fetuses demonstrate excessive growth by an increased AC relative to the biparietal diameter (BPD) i.e. body to head disproportion, the rate of fetal macrosomia can be decreased [290]. This fetal based strategy [219, 220] using ultrasound at 29-33 weeks to measure the AC in order dictate the aggressiveness of maternal glycemic control has been recommended by the Fifth International Workshop-Conference on Gestational Diabetes and the IADPSG [291]. GDM can often be treated with twice daily injections of NPH and mealtime injections of Lispro or aspart as necessary for postprandial hyperglycemia. Short acting insulin (Lispro or aspart) is preferred over Regular insulin due to time of onset and duration to better control postprandial glycemic excursions.

## Fetal Surveillance and Delivery Options in Gestational Diabetes

Women with GDM who require insulin, glyburide, or metformin, who have other chronic medical conditions, or those with suboptimal glycemic control (either treated with medication or not) should have fetal surveillance at ~32 weeks' gestation [83, 286]. However, there is no consensus regarding antepartum testing in women with well-controlled GDM [83]. An ultrasound for growth to look for head to body disproportion (large AC compared to the BPD) and evidence of LGA should be considered at ~29-32 weeks [217, 218].

Delivery is usually recommended by 41 weeks for uncomplicated diet controlled GDM and between 39-40 weeks for well controlled GDM on medication. Earlier delivery should be considered with suboptimal glucose control or other complicating factors such as hypertension. In a trial in which women with insulin-treated GDM were randomized to induction of labor between 38-39 weeks if they had an appropriately grown fetus, favorable cervix and no contraindications for induction versus a strategy of expectant management, there were no differences in cesarean delivery rates but less LGA infants and shoulder dystocia in the induction of labor group [292].

In another cohort of women with insulin-treated GDM in which a policy of induction of labor at 38-39 weeks was compared to historic controls who were expectantly managed, there were no significant differences in cesarean delivery rates or macrosomia, but shoulder dystocia was experienced by 10% of the expectant management group beyond 40 weeks of gestation versus 1.4% in the induction group [293]. An estimated fetal weight of > 4500 grams on ultrasound carries a significantly increased risk for shoulder dystocia. It is recommended that women with GDM be counseled regarding the option of a scheduled cesarean delivery if estimated fetal weight of >4500 grams is anticipated at delivery [294].

## Postpartum Issues in Women with GDM

### Re-evaluating Glucose Tolerance Postpartum and Future Risk of Diabetes:

Women with a history of GDM should have their glycemic status reassessed at 4-12 weeks postpartum [96, 254]. A weight loss program consisting of diet and exercise should be instituted for women with GDM in order to improve their insulin sensitivity and hopefully to prevent the development of T2DM [295]. Hyperglycemia generally resolves in the majority of patients during this interval but up to 10% of patients will fulfill criteria for T2DM. At the minimum, a fasting blood glucose should be done to determine if the woman has persistent diabetes (glucose >125 mg/dl) or impaired fasting glucose tolerance (glucose ≥ 100 mg/dl). A 75 gm 2h OGTT is recommended by the ADA, Canadian Diabetes Association (CDA), Fifth International Workshop, and ACOG since most women with impaired glucose intolerance will be missed if only a FBG is checked [296]. Unfortunately, this is seldom accomplished and a large series of ~23,000 women who received lab testing through Quest diagnostics suggested that only 19% of women receive postpartum diabetes testing within a 6 month period [297]. A 2-hour value of at least 200 mg/dl establishes a diagnosis of diabetes and a 2-hour value of at least 140 mg/dl but less than 200 mg/dl makes the diagnosis of impaired glucose tolerance. Of note, breastfeeding has been shown to improve insulin resistance and glucose values in postpartum women with recent GDM [298, 299].

Utility of using the A1c postpartum to predict the subsequent occurrence of T2DM in women with a history of GDM has not been studied extensively, and may be affected by glycemic control during pregnancy if done before 3 months postpartum [300]. A study looking at utility of using A1c vs 2h OGTT vs FPG for screening of women with recent GDM showed that A1c and A1c plus FPG did not have the sensitivity and specificity to diagnosis impaired carbohydrate metabolism postpartum [301, 302]. The importance of diagnosing impaired glucose intolerance lies in its value in predicting the future development of T2DM. In one series which mainly studied Latino women, a diagnosis of impaired glucose tolerance was the most potent predictor of the development of T2DM in women with a history of GDM; 80% of such women developed diabetes in the subsequent 5-7 years [256], Intensified efforts promoting diet, exercise and weight loss should be instituted in these patients. Other studies have shown other risk factors for development of prediabetes and/or T2DM after GDM including earlier diagnosis of GDM in

pregnancy [303], insulin therapy during pregnancy [304, 305] and BMI. A study in Italy showed pre-pregnancy BMI and PCOS as strong predictors of postpartum impaired glucose tolerance[306]. A1c within 12 months postpartum may be useful in addition to OGTT to diagnose some women with history of GDM and normal glucose tolerance. A study of 141 women in Spain with recent GDM found that 10% had normal glucose tolerance, normal FPG, and isolated A1c 5.7-6.4% [307] suggesting that A1c is a useful tool to diagnose prediabetes in women with a history of GDM with normal glucose tolerance postpartum. Interestingly, in this study the group of women with isolated A1c 5.7-6.4% with normal glucose tolerance and normal FPG were more likely to be Caucasian and more likely had higher LDL values. A1c is a sensitive test in detecting prediabetes and overt diabetes in postpartum women with history of GDM [308]. The TRIPOD study demonstrated that the use of a thiazolidinedione postpartum in women with a history of GDM and persistent impaired glucose intolerance decreased the development of T2DM. The rate of T2DM in the 133 women randomized to troglitazone was 5.4% versus 12.1% in the 133 women randomized to placebo at a median follow-up of 30 months [309]. The protection from diabetes was closely related to the degree of reduction of insulin secretion three months after randomization and persisted 8 months after the medication was stopped. In the PIPOD study, use of Pioglitazone to the same high-risk patient group stabilized previously falling B-cell function and revealed a close association between reduced insulin requirements and low risk of diabetes [252, 257]. However, using thiazolidinediones for the purpose of preventing the development of T2DM in women with a history of GDM has not been recommended. Recently, the Diabetes Prevention Trial analyzed their data in women with a history of GDM [258]. A total of 349 subjects had a history of GDM, and such a history conferred a 74% hazard rate to the development of T2DM compared to women without a history of GDM. In the placebo arm, women developed T2DM at an alarming rate of 17% per year but this rate was cut in half by either use of metformin or diet and exercise. The DPP, TRIPOD, and PIPOD studies support clinical management that focuses on identifying women who meet criteria for metabolic syndrome, achieving postpartum weight loss, and instituting aggressive interventions beginning with lifestyle changes to decrease insulin resistance for primary prevention of T2DM DM. Women with a history of GDM who display normal testing postpartum should undergo lifestyle interventions for postpartum weight reduction and receive repeat testing at least every 3 years [96]. For women who may have subsequent pregnancies, screening more frequently has the advantage of detecting abnormal glucose metabolism before the next pregnancy to ensure preconception glucose control [254].

## Breastfeeding:

Women who breastfeed appear to have a lower incidence of developing impaired glucose tolerance and T2DM [310] and it also appears to decrease the risk of developing infant obesity and impaired glucose tolerance [298]. Higher intensity of lactation (exclusive or mostly breastfeeding) was associated with a lower FPG, fasting insulin, and a lower prevalence of prediabetes or diabetes at 6-9 weeks postpartum in women with a history of GDM [311]. Recent studies that included GDM women have also shown it to decrease the risk of childhood obesity [312, 313]. In the large EPOCH study (Exploring Perinatal Outcomes Among Children

Study), offspring of women with diabetes (primarily GDM) who were breast fed for at least 6 months had a slower BMI growth trajectory during childhood and a lower childhood BMI than those who were not breastfed for this time period [314].  There is a growing literature suggesting that some of the protective benefits on childhood obesity and programming the infant immune system from breast milk may be influenced by appetite regulatory hormones, biomarkers of oxidative stress and inflammation, and the milk microbiome [315].  Calcium intake should be at least ~1500 mg per day since exclusive breast-feeding for an extended period of time can cause a modest and usually reversible decrease in bone density. Breastfeeding should be encouraged in all women with a history of preexisting and gestational diabetes for maternal and offspring health outcomes.

## Contraception:

The same contraception choices recommended for preexisting diabetes apply for women with GDM with the possible exception of Depo-Provera injections.  Although combined oral contraceptives do not appear to influence the development of T2DM, Depo-Provera was shown in one trial to increase the subsequent risk of developing T2 DM in women with GDM, but this was largely due to the weight gain associated with its use [248, 316, 317]. Benefits must be weighed against risks of contraception [243] given effective contraception is critical given there is data that recurrent pregnancies in women with GDM appear to increase the risk of later development to T2DM, possibly secondary to increasing weight gain, worsening insulin resistance, and beta cell failure. Further, unrecognized hyperglycemia from the development of diabetes between pregnancies places the fetus at risk for major malformations in a subsequent pregnancy.

# CONCLUSION

The obstetric outlook for pregnancy in women with pre-existing diabetes has improved over the last century and has the potential to continue to improve as rapid advances in diabetes management, fetal surveillance, and neonatal care emerge. However, the greatest challenge health care providers face is the growing number of women developing GDM and T2 DM as the obesity epidemic increases affecting women prior to pregnancy. In addition, the prevalence of T1DM is increasing globally. Furthermore, obesity-related complications exert a further deleterious effect on pregnancy outcomes.  The development of T2DM in women with a history of GDM as well as obesity and glucose intolerance in the offspring of women with preexisting 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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