

Chapter 20 DIABETES IN PREGNANCY

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I. 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 adipokines and inflammatory cytokines. There are high levels of estrogen, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone, human placental lactogen, leptin, TNF α , 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. 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 are a few studies of women reporting 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 (4,5,6). 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 when 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 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 trimester 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

(10,1) in combination with human placental lactogen, progesterone, and TNF α , the latter correlating with maternal insulin resistance measured by hyperinsulinemic-clamps (11). Human placental growth hormone (hPGH) has been recently 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) Human placental lactogen 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.

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 (14, 1) 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 p85 α subunit of phosphatidylinositol kinase (PI 3-kinase), all serving to attenuate glucose uptake (15,1)

Glucose is not the only fuel altered in normal pregnancy. Triglycerides, cholesterol, and free fatty acids are increased; the latter may serve to further increase the insulin resistance of pregnancy [5,16] 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 LDL during pregnancy (5). 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 placental has lipoprotein lipase as well as TG-hydrolase enzymes so that maternal TGs can be used in addition to FFAs for fetoplacental fuels and especially 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 (16,17,18).

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 (CGMS), plasma glucose samples, and SMBG (self-monitored blood glucose) demonstrated that normal pregnant women (BMI 22-28) during the 3rd trimester (~34 wks) have on average a FBG of 71 mg/dl; a 1 hr 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 (19). (See figure 1). 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 continuous glucose monitoring. (20). 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.

II. OBESITY IN PREGNANCY

Obesity alone or accompanied by Type 1 DM, Type 2 DM or gestational diabetes (GDM) carries significant risks to both the mother and the infant, and obesity is the leading health concern in pregnant women (21,22). By the most recent NHANES statistics, 56% of black women ages 20-39 are obese, 34-

38% of Hispanic or Mexican American women, and 27% of white women (23). Independent of preexisting diabetes or GDM, obesity increases the maternal risks of hypertensive disorders, non-alcoholic fatty liver disease (NAFLD), gall bladder disease, aspiration pneumonia, thromboembolism, sleep apnea, cardiomyopathy, and pulmonary edema (24,21). In addition it increases the risk of induction of labor, failed induction of labor, Cesarean delivery, multiple anesthesia complications, postoperative wound infections, postpartum hemorrhage, and lactation failure. Maternal obesity independently increases the risk of first trimester and recurrent pregnancy losses and congenital malformations including CNS, cardiac, GI defects and cleft palate. Furthermore it is associated with higher rates of shoulder dystocia and meconium aspiration and it quadruples the risk of perinatal mortality. Because so many women with Type 2 DM 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 Type 2 DM have increased congenital anomalies even when under good glycemic control (25,26) suggesting the obesity itself is a risk factor. Women with obesity or with Type 2 DM complicated by obesity may be older and often have underlying hypertension, hyperlipidemia, and inflammation all of which lead to increased oxidative stress and may explain some of the increased risk despite similar glycemic control compared to their Type 1 DM counterparts. Several recent reports have demonstrated an association of maternal BMI with neural tube defects and possibly other congenital anomalies (27). One study concluded that for every unit increase in BMI the relative risk of a neural tube defect increased 7% (27).

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. (28, 29). This has resulted in some international organizations recommending higher dosages of preconception folic acid (5 mg) for women with diabetes and/or BMI>35. (30,31), but there is not clear evidence that intervention alone will substantially decrease the risk.

Obese women with normal glucose tolerance on a controlled diet have higher glycemic patterns throughout the day and night by CGMS compared to normal weight women both early and late in pregnancy (16). 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 (16). The mean 1 hour PP glucose during late pregnancy by CGMS 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, and still much lower than current therapeutic targets (<140 mg/dl at 1 hr; < 120 mg/dl at 2 hrs).

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 (32,33). However, pregnancy should not be considered until 12-18 months after surgery and after the rapid weight gain 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.

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

a. 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 (34, 24, 35, 36). 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 (37,38,39). 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 (40). There is data, especially in animal and non-human primate models, to support that a maternal high fat diet and obesity can influence mesenchymal stem cells to differentiate along adipocyte rather than osteocyte pathways, (41,42) invoke changes in the serotonergic system resulting in increased anxiety in non-human primate offspring (43), affect neural pathways involved with appetite regulation, promote lipotoxicity, regulate gluconeogenic enzymes in the fetal liver generating histology consistent with NAFLD (44,45), alter mitochondrial function in skeletal muscle and program beta cell mass in the pancreas (46,40,47,48). 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.

The long-term sequelae of preexisting diabetes, GDM, or obesity for offspring are being increasingly recognized (49). Reports of an increased risk of adolescent obesity and of Type 2 DM are compelling and it appears that fetal islet hyperplasia occurs in-utero with maternal hyperglycemia resulting in an increased risk of developing Type 2 DM in teenage years or as a young adult (50). 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 (51). This scenario creates enormous potential on a public health level for the incidence of Type 2 DM to escalate as these children with impaired glucose tolerance become mothers themselves, perpetuating the cycle. 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 (52). Maternal BMI is also the strongest predictor of excess neonatal adiposity which has been associated with childhood obesity and adiposity at birth is probably a better predictor of the risk of childhood obesity than birth weight alone (34,53). 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 (54). 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.

b. Immediate Risks to Newborn

Macrosomia is the major risk to the fetus in women with obesity, Type 2 DM, GDM, and also Type 1 DM in women without placental insufficiency (see Section III). 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 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., free fatty acids, triglycerides, amino acids) 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 (35). Maternal obesity appears to be an independent risk factor for LGA, macrosomia, and excess neonatal fat and in the HAPO trial (55), 78% of all of the LGA infants were born to mothers without gestational diabetes (56). Overweight and obese women are at increased risk of delivering a macrosomic infant by ~2 fold and given the prevalence of overweight and obese women are ~ 10 times that of gestational or preexisting diabetes, maternal body habitus is likely to have the strongest attributable risk on the prevalence of macrosomia (35).

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 maternal triglycerides (TGs) have been strongly correlated with excess fetal growth and LGA (18), 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 CGMS 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 (16). It has been shown that there is differential placental regulation of placental genes involved in lipid transport in GDM women (57). 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 diabetic women. 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 (58).

Even with the advent of screening and aggressive management of diabetes, the incidence of neonatal complications ranges from 12-75% (59). Macrosomia places the mother at increased risk of requiring a cesarean section and the infant at risk for shoulder dystocia. Shoulder dystocia can result in Erb's palsy, clavicular fractures, fetal distress, low APGAR scores, and even birth asphyxia when unrecognized. Shoulder dystocia occurs nearly 50% of the time when a 4500 gram diabetic infant is delivered vaginally (60). Preterm labor can result due to polyhydramnios from the fetus ultrafiltrating glucose through the kidneys. In mothers who have poor glycemic control, respiratory distress syndrome may occur in up to 31% of infants while 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 diabetic mother include neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia and polycythemia. Neonatal hypoglycemia is common in women in suboptimal glycemic control because the infant may continue to produce excessive insulin for up to 48 hours after birth before the normal feedback loop is operating

IV. 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 gestational diabetes (62,63,64) 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% (see section VIIIe). 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 weight gain recommendations should be consistent with the current Institute of Medicine (IOM) weight gain guidelines (65), (BMI <18.5, 28-40 lbs; BMI 18.5-24.9, 25-35 lbs; BMI 25-29.9, 15-25 lbs; BMI ≥ 30, 11-20 lbs) since both a higher maternal BMI and gestational weight gain independently increase the risk of LGA (66). However, there are many trials which support no weight gain for women with a BMI of ≥35 (67) with improved pregnancy outcomes and the lack of weight gain did not increase the risk for small for gestational age (SGA) infants in this BMI category. Further, targeting gestational weight gain (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 30-34.9) has been shown in many trials to decrease the risk of preeclampsia, Cesarean delivery, GDM, and most importantly, postpartum weight retention (67). Further, excess GWG has been shown to markedly increase the risk of postpartum weight retention and maternal obesity later in life. 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 (68,69,70) without appreciably increasing the risk of SGA (see section VIIIe). For obese women, ~25 kcal/kg rather than 30 kcal/kg is currently recommended. However (71) other investigators would argue for a lower caloric intake (1600-1800 calories/day) (72) 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 (63). 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 (73). 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 (61) 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 women with Type 1 DM and who are normal weight, 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 a carbohydrate to insulin ratio should estimate grams of carbohydrate with each meal. Preferably blood glucoses can be recording on the same food and beverage record for comparison of carbohydrate intake with glucose excursions.

There is a consensus that exercise is an important component of healthy lifestyle and it is recommended in pregnancy by ACOG, the ADA, and Society of Obstetricians and Gynaecologists of Canada (74,61,75,64). A large recent meta-analysis of all randomized controlled trials on diet and physical activity (76) which evaluated all 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 large-for-gestational age infants (LGA, >90th percentile). There was no increase in small-for-gestational-age 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. There is some data which suggested 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 (77). Babies who were slightly lighter 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) but the lighter neonates were the result of decreased body fat. These strategies have been less examined in women with Type 2 DM but are likely to be equally beneficial due to the effects of exercise on improving insulin resistance. As described in Section VIII, there is data in GDM women that exercise may decrease the need for insulin (78). 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.

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

Although historically, Type 1 DM has been more prevalent for women of child-bearing age, this is changing with increased obesity rates worldwide. The increase in the prevalence of Type 2 diabetes in individuals aged 30-39 years has been much higher compared to the increases in other age groups (79). In Canada, the number of women with pre-existing diabetes has increased 50% between 1996 and 2001 with Type 2 DM representing a growing proportion (80). In a large USA population based study, the proportion of women with Type 2 DM increased was 65% in 1988 (81).

Both women with Type 1 DM and Type 2 DM are at increased risk of poor obstetrical outcomes, and both can have improved outcomes with optimized care. (82,83). The White Classification (Table 1) was developed decades ago by Priscilla White at the Joslin Clinic to stratify risk of adverse pregnancy outcomes in women with Type 1 DM according to the age of the patient, duration of diabetes and from vascular complications of diabetes. Although recent evidence suggests that it 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 (84). Although it was never intended to be used in women with Type 2 DM, given the very low prevalence of this Type 2 DM in women of childbearing age decades ago when it was first established in 1949, many also apply it to this group of women. The American College of Obstetrics and Gynecology 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). Type 2 DM is sometimes considered milder, however women with Type 2 DM are at least as high of a risk of pregnancy complications as women with Type 1 DM. 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. (25,26,85). Furthermore, the causes of pregnancy loss appear to differ in women with Type 1 DM versus Type 2 DM. In one series comparing outcomes, >75% of pregnancy losses in women with Type 1 DM were due to major congenital anomalies or prematurity (85). In women with Type 2 DM, >75% were attributable to stillbirth or chorioamnionitis, suggesting that obesity plays a major role.

Preconception care for women with pre-existing diabetes is associated with improved outcomes (83,86). The importance of strict glycemic control, folic acid supplementation, discontinuation of potentially harmful medications, encouraging weight loss in overweight/obese women and optimization of associated medical conditions are all important components of preconception care. In order to reduce congenital anomalies, interventions need to be in place well before the diagnosis of pregnancy. All major organ systems are complete by 6 weeks after conception so any changes made after that have limited, if any, impact. Unfortunately many women do not plan their pregnancies or seek preconception care. There are certain maternal characteristics such as poor health literacy, smoking, being unmarried, lower family income and poor relationship with their provider that tend to predict lower likelihood of accessing preconception care (87). Women who attend specialized pre-pregnancy clinics for preconception

counseling do have improved outcomes vs. non-attenders, but those that access the clinics tend to be the lowest risk women. (87).

a. Reducing risk of congenital anomalies

Hyperglycemia is a known teratogen whether occurring from Type 1 DM or Type 2 DM (88) and can result in complex cardiac defects, CNS anomalies such as anencephaly and spina bifida, skeletal malformations and genitourinary abnormalities (89,90). A systematic review of 13 observational studies of women with Type 1 DM and Type 2 DM 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 (91). Women with a normal HgbA1c at conception and during the first trimester have no increased risk while women with a HgbA1c of 10-12% or a fasting blood glucose >260 mg/dl have up to a 25% risk of major malformations (92,93) Most organizations recommend women achieve a HgbA1c of less than 6.5-7% prior to conception.. (94,30) For some women hypoglycemic unawareness will prevent them from safely obtaining a HgbA1c of <7%, so that individual targets must be set.

The mechanism of glucose induced congenital anomalies has not been fully elucidated. (95) 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 (96)

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

Women with Type 2 DM are more likely to be treated for dyslipidemia and hypertension. Chronic hypertension occurs in 13-19% of women with Type 2 DM and many of these will be prescribed an ACE-inhibitor or Angiotensin receptor blocker. (97) 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. The data on teratogenicity of statins for treatment of hypercholesterolemia is also conflicting and is based on animal, not human, studies. (98) and may be the focus of a multicenter trial to determine if this class of drugs could decrease preeclampsia due to its favorable effect of vascular endothelial growth factor in animal studies. Ideally statins should be stopped prior to pregnancy, but definitely at diagnosis of pregnancy.

b. Treatment options in achieving glycemic control

All women with Type 1 DM and Type 2 DM should target a HgbA1c of <6.5-7% preconception when possible. For women on oral agents it must be decided whether to switch to insulin prior to pregnancy, even in women who are achieving the target HgbA1c < 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 gestational diabetes. 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. (99,100,101) There is minimal data on thiazolidinediones or metiglanides and no data on incretin-based therapies (DPP-4 inhibitors and GLP-1 analogues). It is recommended that women with Type 2 DM who are actively trying to become pregnant should be switched from oral 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 and oral hypoglycemic agents are highly likely to fail given the insulin resistance of pregnancy and increasing demands on the pancreatic islet cells to produce much more insulin. 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 (30)

Metformin is sometimes used pre-conception and throughout the first trimester in women with polycystic ovary disease not for glycemic control but to improve fertility and prevent early miscarriage. A recent systematic review of these trials did not show any teratogenic effect of metformin when used in women with PCOS (101). 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. 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. (102,64).

Insulin therapy must be individualized. Increasingly, individuals with diabetes, especially those with Type 1 DM, 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 carbohydrate to insulin ratio (103) Lispro and Aspart have been used in multiple trials in pregnancy and are superior to regular insulin with improvement in postprandial glycemia with reduced hypoglycemia.(104,105,106) while fetal outcomes were similar.

Although there is less safety data on the use of long acting insulin analogues in pregnancy they do appear to be safe. (104) 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. (107). Early case reports raised concern over progression of retinopathy with Glargine, however recent studies in the non-pregnant population have not borne this out. 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. (108,109). There were no differences in any of the maternal or neonatal outcomes. Overall glycemic control was slightly better with Detemir, with lower fasting glucose, less risk of maternal hypoglycemia and slightly reduces HgbA1c levels.

The insulin pump is gaining favor in the treatment of Type 1 DM in pregnancy. In a non-randomized trial, 24 women began insulin pump therapy during pregnancy and were compared to 12 women using the pump before pregnancy and 24 women treated with multiple insulin injections. There was no deterioration of glycemic control and maternal and perinatal outcomes were similar (110). However, 2 of the 24 women who began using the pump in pregnancy developed ketoacidosis due to pump failure compared to no cases of ketoacidosis in the two other groups. However, disadvantages 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(111). 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.

c. 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 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. (112,113). 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. (114). In 179 pregnancies in women with Type 1 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%), moderate to severe background retinopathy (30% versus 3.7%), and a trend for those women who had the greatest fall in HgbA1c (114). The risk of progression of retinopathy is most pronounced in women with more severe pre-existing proliferative retinopathy, chronic hypertension, preeclampsia, and poor glycemic control prior to pregnancy. (30). Proliferative retinopathy may also progress during pregnancy, especially in women with hypertension or poor glycemic control early in pregnancy (115).

Women with Type 1 DM and Type 2 DM should have ophthalmological assessments before conception. Laser photocoagulation for severe nonproliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy (30,61) 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. In women with severe untreated proliferative retinopathy, vaginal delivery with the Valsalva maneuver has been associated with retinal and vitreous hemorrhage. As assisted second-stage delivery or cesarean delivery should be considered (61)

Diabetic Nephropathy/Chronic Kidney Disease

Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (116,117,118,119,120,121) 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 (119,120,121,122,123,124), Those with more severe renal insufficiency (creatinine >1.5 mg/dl) have a 30-50% risk of a permanent pregnancy-related decline in GFR. (125). 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 Type 1 DM and nephropathy, maternal and obstetric outcomes were strongly dependent on the degree of maternal renal function (126). 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 gms. 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 is conflicting information on whether first-trimester exposure to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (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 (127). 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. 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. Women who are taking ACE-inhibitors or angiotensin receptor blockers should be counseled that these agents are contraindicated in the 2nd and 3rd trimester of pregnancy. Women who are actively trying to get pregnant should be switched to calcium channel blockers, methyldopa, hydralazine, or selected B-adrenergic blockers which includes 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 (128)

Cardiovascular disease

Although infrequent,, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes and the increasing prevalence of Type 2 DM with associated hyperlipidemia, hypertension, and inflammation is further increasing the prevalence of CVD. 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 (61,129)

Due to the increase 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. An EKG should be done preconception for any woman with diabetes >35 (61). 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 oils, 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.

d. Associated autoimmune thyroid disease

Women with Type 1 DM 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 (130,131) Women with positive TPO antibodies should have their TSH checked each trimester (Table 2) since the demands of pregnancy can unmask decreased thyroid reserve from Hashimoto's thyroiditis. Thyroid hormone requirements increase by 30-50% in most women, often early in pregnancy due to increase in thyroid binding globulin stimulated by estrogen. For those women on thyroid hormone replacement prior to

pregnancy, it should be expected that requirements may increase during pregnancy. A TSH of >2.5-3.0 is considered abnormal in the first trimester, especially when associated with TPO antibodies and > 3-3.5 in the 2nd and 3rd due to the thyrotropic influence of hCG (130,131).

VI. MANAGEMENT OF PRE-EXISTING DIABETES DURING PREGNANCY

a. 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. (see above). Poor control later in pregnancy increases the risk of intrauterine fetal demise, macrosomia, cardiac septal enlargement in the fetus, perinatal death, and metabolic complications in the newborn. Target glucose values for fasting and postprandial times should be discussed with the patient. Current guidelines are that pre-meal whole blood glucose should be 70-95 mg/dl, the 1 hour postprandial glucose <130-140mg/dl and the 2 hour glucose <120mg/dl (30,63). 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 3rd trimester (FPG ~71 +/- 8 mg/dl; 1 hr PP ~109 +/- 13 mg/dl; 2 hr 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 Type 1 DM showed less preeclampsia with glucose targets of fasting <5.1 mmol/L (92 mg/dl), preprandial <6.0 mmol/L (108 mg/dl) and 1 hour postprandial <7.8 mmol/L (140 mg/dl) (132). A HgbA1c should be done at first visit and every 1-3 months thereafter depending on whether it is normalized. Additional labs and exams recommended for women with preexisting diabetes are listed in Table 2.

Increasingly, pregnant women with Type 1 DM 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 carbohydrate to insulin ratio (103). Type 1 DM patients usually require 3-4 injections per day or an insulin pump to achieve adequate control during pregnancy and multiple injections with short acting insulin analogs are often needed in women with Type 2 DM as well. 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. (133) Thus, for some women it may be necessary to take meal time insulin 30 minutes prior to the meal.

Basal insulin may be provided as two doses of NPH or with one of the long acting analogues - Glargine or Detemir. 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 p.m. dose of NPH usually needs to be moved to before bedtime to avoid nocturnal hypoglycemia and prevent fasting hyperglycemia. Although women with Type 2 DM 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 Type 2 DM and GDM in a randomized study (134)

Maternal hypoglycemia is common and often severe in pregnancy in women with Type 1 DM. 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% (135). 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, but diabetic women who have gastroparesis or hyperemesis gravidarum are at the greatest risk for daytime hypoglycemia. In a series of 84 pregnant women with Type 1 DM, hypoglycemia requiring assistance from another person occurred in 71% of patients with a peak incidence at 10-15 weeks gestation (136). One third of subjects had a least one severe episode resulting in seizures, loss of consciousness, or injury. There is also data to suggest that the counter-regulatory hormonal responses particularly growth hormone and epinephrine to hypoglycemia are diminished in pregnancy (137,138). This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control preconception and by the use of analogue insulins (139,106,140). The risk of hypoglycemia is also present in pregnant women with Type 2 DM (141), but tends to be less so than in women with Type 1 DM. 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 (142). Exposure to hypoglycemia in utero may have long-term effects on the offspring including neuropsychological defects (142) so intensive efforts must be made to avoid it. Women with Type 1 DM 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 Type 1 DM can be reduced often without significantly increasing HgbA1c levels and is a priority given hypoglycemic unawareness worsens with repeated episodes and can result in maternal seizures and rarely maternal death. (143).

By 20 weeks of gestation, peripheral insulin resistance increases 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 Type 1 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%. (144).

There are no definitive studies favoring continuous subcutaneous insulin infusion (insulin pump) over multiple daily injections (see Section IV). (145) Randomized control trials (RCTs) of multiple daily injections versus the insulin pump generally showed equivalent glycemic control and perinatal outcome and the pump can be especially useful for patient with nocturnal hypoglycemia or a prominent dawn phenomenon (145). As noted in Section IV, 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 noted in Section IV, neither glyburide or metformin are approved for use in pregnancy for pre-existing diabetes and are likely to have high failure rates for these women given the high insulin secretion demands and worsening insulin resistance in pregnancy. However, for women with preexisting diabetes who will not be managed with insulin, either agent or both is certainly better than no treatment at all and use is unlikely to result in adverse outcomes from the agents themselves unless hyperglycemia is inadequately controlled.

b. Monitoring

Pregnant women with diabetes must do frequent self-glucose monitoring in order to obtain 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 diabetic women need to monitor their post-meal and fasting glucoses regularly (146) and women with Type 1 DM or Type 2 DM using a flexible intensive insulin regimen also need to monitor their pre-meal glucoses. Preprandial 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 measurements determine if the insulin to

carbohydrate ratios are effective in meeting targets and optimal control is associated with less macrosomia, metabolic complications in the fetus, and possibly preeclampsia. (132,147). Due to the increased risk of nocturnal hypoglycemia with any intensive insulin therapy, glucose monitoring during the night is often necessary given the common occurrence of hypoglycemic unawareness with the achievement of tight control.

Continuous glucose monitoring systems (CGMS) may help identify periods of hyper- or hypoglycemia (148) and certainly confirm glycemic patterns. (149). In one study using intermittent blinded CGMS 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. (148). In another study of intermittent use of real time CGMS (where glucose results are simultaneously displayed) there was no improvement of glycemic control or macrosomia. (150) It must be stressed to the patient that the values displayed by CGMS should not be used to dose insulin given the interstitial glucose values are dependent on the one 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, CGMS 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 CGMS to facilitate comparisons among research studies. A recent study offers one approach for the study of fetal growth and infant outcomes (151). In one study outside of pregnancy, the use of a closed-loop system which uses computerized algorithms to link insulin delivery with CGMS glucose levels in real time, resulted in less hypoglycemia. (152). Whether closed loop systems will become available for clinical use in pregnancy remains to be seen given the current challenges of obtaining the necessary precision in measurements and developing effective and safe algorithms.

c. 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 (153,154). 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 glucosuria at lower serum glucoses. Any pregnant woman with Type 1 DM 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.

In a study of 20 consecutive cases of DKA, only 65% of fetuses were alive on admission to the hospital (154). 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. Causes of DKA in pregnancy are often different with infection less common as a precipitant (155). 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. Beta agonist therapy, 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(156). 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 2nd and 3rd 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 (154).

d. Hypertensive Disorders in Pregnancy

Women with diabetic nephropathy are at extremely high risk of developing preeclampsia which often leads to prematurity and intrauterine growth restriction. 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) (157) 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 (122), however suboptimal hypertensive control has been associated with preterm delivery (158). 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 (61), 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 (158). Although outside of pregnancy achieving a BP < 120/80 is renoprotective, 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 of superimposed preeclampsia given this risk is so high in women with pre-existing 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, Clonidine, or Labetalol can all be used (157). ACE-Inhibitors and Angiotensin Receptor blockers 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.

e. Fetal Surveillance

Still birth rates are increased in women with Type 1 DM and Type 2 DM, especially those with poor glycemic control, vascular complications, hypertension, or nephropathy who are at the highest risk for abnormal placentation and fetal overgrowth. Women with gestational diabetes requiring medications or who have suboptimal glycemic control may also have an increased risk of fetal loss. Fetal hypoxia and cardiac dysfunction secondary to poor glycemic control are probably the most important pathogenic factors in stillbirths among pregnant diabetic women (159).

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 HbA1c was elevated (>6.5-7.0) during the first trimester. Women with Type 1 DM can be at risk for macrosomic infants (due to excess delivery of nutrients to the fetus from poor glycemic control) or intrauterine growth restriction (IUGR) 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 (see Section III). 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. (18) This abnormal growth is usually in a characteristic pattern of head to body disproportion. The fetus exhibits advanced growth in the abdominal circumference measurement due to excessive subcutaneous fat, compared to the head measurement. This places the mother at an increased risk for cesarean section

due to difficult delivery of the baby's enlarged abdomen. This abnormal growth pattern can be seen between 29-32 weeks. Increasingly, fetal criteria and growth patterns by ultrasound at this time are dictating the aggressiveness of maternal glycemic treatment rather than simply using mother's glucoses as the goal for therapy (160,161).

In addition to fetal ultrasound, antepartum fetal monitoring including fetal movement records, the nonstress test, and the biophysical profile are usually recommended for women with pregestational diabetes with initiation of testing typically at 32-34 weeks. However, due to the increased risk of uteroplacental insufficiency and intrauterine fetal demise in patients with longstanding Type 1 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 (157).

f. 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. (162). 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 cesarean delivery (C-section) may be recommended for obstetric indications such as severe preeclampsia with an unfavorable cervix, estimated fetal weight >4500 grams, history of a C-section, or fetal distress. If there are no obstetric indications for a cesarean delivery, a vaginal delivery is encouraged in women with diabetes due to the higher risk of infectious complications, thromboembolism, and delayed recovery with cesarean delivery. 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. 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. (163). Despite the lack of evidence, many clinicians will at least increase fetal surveillance if insulin requirements drop in third trimester.

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. However, insulin requirements postpartum drop dramatically and most women need only ~1/3 to 1/2 of their previous 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 who may have a further decline in insulin requirements.

VII. 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 Type 1 DM). It has been demonstrated that the majority of women with pre-existing diabetes, even those who have been extremely compliant and who have had optimal glycemic control during pregnancy, have a dramatic worsening of their glucose control after the birth of their infant (164). 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.

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 Type 1 DM often need to decrease their insulin 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 (165). For women on an insulin pump, the postpartum basal rates can be preprogrammed prior to delivery to allow a seamless transition to the lower doses following delivery.

Women with Type 1 DM have been reported to have a 25% incidence of postpartum thyroiditis (166). 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.

a. Breastfeeding

Breastfeeding should be encouraged for all women. However, it may even have more benefits for women with pregestational diabetes and their children. (167) Although the association is weak, it does appear that breastfeeding reduces the likelihood of Type 1 DM in offspring.(168,169) For women with Type 2 DM, especially those with a high pre-pregnancy BMI or excessive gestational weight gain, 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 . (170,171) Women with both Type 1 DM and Type 2 DM have lower rates of breastfeeding despite good intentions..(172,173). For women with Type 2 DM, there has been a reluctance to reintroduce oral agents during the breast feeding 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 milk and may be safe (174). Very low Metformin levels were detected in breast milk in 3 studies with very low or undetectable serum levels in the infant (175). 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 Type 1 DM who are breastfeeding will need lower basal insulin doses than women who are not breastfeeding. (176). Breast feeding 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.

Statins should not be started if the woman is nursing due to inadequate studies in nursing 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.

b. Contraception

It should be documented at every visit that women are using or have been offered an effective birth control method. 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 (177). 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. (178). 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. Low dose combined oral contraceptives and the Nuva Ring have been shown to be effective and to have minimal metabolic effects in women with diabetes, however their use in women with known micro- or macrovascular disease is more controversial. (179). Implantable progestational 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 Type 1 DM or Type 2 DM 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 maternal 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 (180).

VIII. GESTATIONAL DIABETES

a. Prevalence and Pathophysiology:

The prevalence of GDM is rapidly rising and ranges from 3-14% of pregnancies throughout the world (using ACOG criteria) and is highest in ethnic groups that have a higher incidence of Type 2 DM (Hispanic Americans, Native Americans, and Pacific Islanders;). 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 abnormalities in at least 3 aspects of fuel metabolism: insulin resistance, impaired insulin secretion, and increased hepatic glucose production (7). The beta cell defects reflect the spectrum of B-cell defects that leads to diabetes in nonpregnant individuals (181). 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 TNF α were increased (182). 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 (181,183). Investigators have also shown more pronounced insulin resistance during pregnancy in GDM patients compared to women with normal glucose tolerance, that may contribute to hyperglycemia in addition to defects in insulin secretion (7,1,181).

Although diabetes usually remits after pregnancy, 30-50% of women diagnosed with GDM go on to develop Type 2 DM later in life, particularly if obesity is present. GDM shares many of the characteristics of Type 2 DM. Both are aggravated by increasing obesity and age, suggesting that the components of insulin resistance and decreased insulin secretion, which lead to GDM, may be common to Type 2 DM. Thus, pregnancy is a "stress test for the development of glucose intolerance and GDM may represent an unmasking of the genetic predisposition of Type 2 DM 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 in pregnancy and GDM. 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 γ expression in adipose tissue, a target for thiazolidinediones (5). There is also 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 (184).

b. Risks to the Mother and Infant with Gestational Diabetes

The immediate risks to the mother with GDM are an increased incidence of cesarean delivery (~30%), preeclampsia (~20-30%), and polyhydramnios (~20%) which can result in preterm labor(59, 64);. The long-term risks to the mother are related to recurrent GDM pregnancies and the substantial risk of developing Type 2 DM. Women with GDM represent a group of patients with an extremely high risk (~50%) of developing Type 2 DM 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 Type 2 DM (especially Latin-American women), or who demonstrate impaired glucose tolerance or fasting glucose at 6 weeks postpartum, have the highest risk of developing Type 2 GDM (64). Latino women with impaired glucose tolerance postpartum have up to an 80% risk of developing Type 2 DM within five years and should be targeted for primary prevention (185). 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 (see Section III) . In Pima Indians, the incidence of childhood Type 2 DM 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 Type 2 DM after pregnancy (186), underscoring the importance of the intrauterine environment. Thiazolididiones, metformin, and lifestyle modifications have all been demonstrated to decrease the risk of developing Type 2 DM in GDM women who have impaired fasting glucose or glucose intolerance postpartum (187,188).

The risks to the infant from gestational diabetes (macrosomia, metabolic abnormalities in the newborn, immature lung maturation, and cardiac hypertrophy), are similar to women with Type 1 DM or Type 2 DM if poorly controlled (Section III), 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 (64). 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 (Section III).

c. 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 recently published demonstrating the benefit in identifying and treating GDM (189,190). 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, self blood glucose monitoring (SBGM), and insulin therapy as needed versus routine care and the results of the 2 hr 75 gram oral glucose tolerance test (OGTT) were blinded to practitioners and subjects . Entry criteria included women whose FBG was less than 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. Furthermore, maternal quality-of-life evaluation at 3 months postpartum revealed lower rates of depression and higher improved health status cores in the intervention group (189).

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 (190). 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, SBGM, 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 hr 100 gm OGTT were included. Furthermore, an additional 931 women with normal results on the 3 hr 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).

There is also new compelling data that the risk of adverse maternal-fetal outcomes from maternal carbohydrate intolerance is along a graded continuum (191,55). 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 (Hyperglycemia and Adverse Pregnancy Outcomes), the largest ever conducted in pregnant women, enrolled 25,505 pregnant women at 15 centers in nine countries (191). All underwent a 2 hr 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 >90 th 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 hr 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 hr or 2 hr value. The results also indicated a strong and continuous association with these outcomes and maternal glucose levels below those diagnostic of GDM.

d. Diagnosis of Gestational Diabetes—Lack of Consensus

The previous definition of GDM as a glucose-intolerant state with onset or first recognition during pregnancy (64) was recently challenged by the International Association of Diabetes in Pregnancy Study Group (IADPSG) and ADA (192). 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 HgbA1c is ≥ 6.5 , the IADPSG and ADA recommended that GDM be only diagnosed if the glucose intolerance was identified in pregnancy AND women did not qualify for pre-existing (overt) diabetes. The IADPSG and 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: HgbA1c of ≥ 6.5 ; FBF ≥ 126 , or random glucose ≥ 200 , which are the same criteria for diabetes outside of pregnancy.

The ADA also adopted the IADPSG recommendations to diagnose GDM at lower glucose thresholds that 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-hr OGTT traditionally used by ACOG. However, adopting the new ADA criteria will result in a tripling of the prevalence of GDM (estimated to be 18% of the pregnant population) compared to the 5-6% currently estimated prevalence using the ACOG criteria (Table 3). This prevalence could be even higher in some ethnic groups (Hispanic Americans, Native Americans, Pacific Islanders, and Asian Americans).

The Carpenter and Coustan diagnostic criteria continue to be used by the majority of 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 [(64)]. 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 ; 2 hour ≥ 165 ; 3 hour ≥ 145) which results in ~50% decrease in the diagnosis of GDM compared to the Carpenter and Coustan criteria. If the 100 gm 3-hour OGTT test is performed and only 1 value is abnormal, a repeat 100 gm 3-hour test should be performed 1 month later because a single elevated value increases the risk of LGA, and one third of patients ultimately meet the diagnostic criteria for GDM when performed 3-4 weeks later. 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.

However, the ADA adopted the IADPSG recommendations based on the HAPO trial which showed that a single value (fasting of ≥ 92 , a 1 hour of ≥ 180 , OR 2 hour of ≥ 153) on a 75 gm 2 h-OGTT resulted in a 1.75 increased risk of LGA and should be the basis for the diagnosis resulting in an estimated 18% prevalence. Critics complained that a 2.0 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 (193,194). 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 (195). 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. There is also debate about early screening of high risk women for GDM (see below) given the ADA abandoned the use of a 50 gm glucose challenge (1 hour glucola) to screen women, which continues to be used by ACOG.

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. Women meeting any of the following criteria should be tested early which include obesity, personal history of GDM (recurrence rate of 30-50%) previous macrosomic infant (>9 lbs), or known impaired glucose metabolism. Other risk factors include women with significant glycosuria, family history of diabetes in a first degree relative, or polycystic ovary syndrome (PCOS). ACOG recommends that high risk women be screened on their first prenatal visit with a 50 gm glucose load and if the value at 1 hour exceeds 30-140 mg/dl, a diagnostic 3-hr 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 (196,64). 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 new ADA criteria does not use a 50 gm glucola for screening. They advocate that high risk women be tested on the first prenatal visit with a HgbA1c OR a FBG OR a 75 gm 2-hr OGTT, primarily to rule out overt diabetes. If women make criteria for overt diabetes (HgbA1c ≥ 6.5 ; FBG ≥ 125 ; or random glucose ≥ 200), a diagnosis of pre-existing rather than GDM should be made. If a fasting glucose of ≥ 92 is demonstrated, a diagnosis of

GDM can be made. A 75 gm 2-hour OGTT to determine whether the 1 hour or 2 hour values exceed or equal 180 or 153, respectively, is optional and not mandated on all high risk women **early** in pregnancy.

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/ADA criteria since a practitioner can choose whether to obtain a HgbA1c, fasting glucose, or 75 gm 2-hour OGTT **early** in pregnancy. Some practitioners are recommending that a HgbA1c of ≥ 5.7 be used to diagnose GDM early since this level diagnoses prediabetes outside of pregnancy. However, a HgbA1c of 5.7 or greater was not given as an optional criteria by either IADPSG or the ADA to diagnose GDM. Further, studies outside of pregnancy have demonstrated that the HgbA1c is the least sensitive test to diagnosis either prediabetes or diabetes, especially given that anemia is common in pregnancy and the HgbA1c 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 (195). 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%). This raises the question as to whether early diagnostic testing recommended by the ADA for high risk women will miss many women with only impaired glucose tolerance, since administering the 75 gm 2-hour OGTT is optional **early** in pregnancy (women can be screened with EITHER a HgbA1c or a FBG). Both ACOG and the ADA agree that if initial testing is normal (using their different recommendations), repeat testing should be performed at 24 to 28 weeks gestation using either the 100 gram 3-hour OGTT (ACOG) or the 75 gram 2-hour OGTT (ADA).

According to ACOG, women who have NO risk factors do not require screening or diagnostic testing at 24-28 weeks but this category is limited to women meeting ALL of the following criteria: age under 25 years, normal weight before pregnancy, member of an ethnic group with a low prevalence of GDM, no known diabetes in first-degree relatives, no history of abnormal glucose tolerance, and no history of poor obstetric outcome or macrosomic infant (> 9 lbs). Most obstetricians advocate for universal screening because there are few women who meet all of these criteria. The ADA recommends diagnostic testing at 24-28 weeks for everyone with the 75 gm OGTT (there is no screening using a 1 hr 50 gram glucose challenge).

Currently there is no consensus about the adoption of the ADA criteria over the ACOG criteria. The NIH held a Consensus Conference in March of 2013 (197). They acknowledged that the HAPO data 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/ADA criteria and such adoption could markedly increase cost of treatment. Further, there was a concern that adopting the IADPSG/ADA 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/ADA 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. (53).

The NIH also underscored the concerns that there is considerable variability in the 2 hr 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 BW 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 in Section III, 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 benefit. Disappointingly, the 4-5 yr 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 pit the diagnostic criteria against each other to determine whether implementation and treatment based on the new IADPSG/ADA 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 from 1 institution to the next is extremely confusing for patient management as well as for clinical research trials for which a number of diagnostic criteria could be used.

Screening and Diagnosis of GDM Outside the U.S.

Although it was hoped that the HAPO trial would influence all countries to adopt the IADPSG/ADA criteria using a 75 gm OGTT, the lack of consensus has resulted in diagnostic criteria differing in most other countries. (30) Outside of the U.S., most countries use the WHO one-step 75 gram OGTT (fasting ≥ 126 mg/dl/7.0 mmol/L or 2 hr ≥ 140 mg/dl/7.8 mmol/L; (198) rather than either the ACOG 2 step screen and diagnostic 100 gm OGTT test or the ADA 75 gm 1 step test.

International Association of Diabetes and Pregnancy Study Groups (IADPSG) and ADA 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;

HgbA1c ≥ 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

e. 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 (146) modest carbohydrate restriction to ~45%-50% of total calories may be helpful to blunt the postprandial glucose excursions, however a growing concern is 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 (36,71). 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 (62). 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 (199). 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 non-alcoholic fatty liver disease (NAFLD) (44). 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 (200) 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 (201), consistent with the recommendations discussed in Section IV for women pre-existing diabetes or obesity. The caloric intake and weight gain recommendations are also consistent with what is recommended in women with obesity or Type 2 DM as in Section IV. However, there are two studies suggesting that weight gain <IOM recommendations for overweight GDM women may decrease insulin requirements, Cesarean delivery, and improve pregnancy outcomes without appreciably increasing SGA (69,70). Further, a third study suggesting that slight weight loss (mean of 1.4 kg) in overweight GDM women decreased BW without increasing SGA (68).

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 (see section IV) and the same considerations apply. 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 (78). In most successful studies (3 times/wk), insulin need \downarrow 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 (202,74). 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 may also have long lasting benefits for the GDM patient who clearly has an appreciable risk of developing Type 2 DM in the future.

f. Medical Treatment Options

Metformin

The largest experience with Metformin has been in GDM women later in pregnancy (203). In the randomized, controlled Metformin in Gestation (MiG) trial (203), 751 women with GDM were randomized to Metformin versus insulin. Due to concerns about the possible risk of fetal lactic acidosis since Metformin is a cousin to phenformin, women with fetal anomalies, gestational hypertension, preeclampsia, fetal growth restriction, and ruptured membranes were excluded. Metformin did not appear to increase any adverse outcomes, although it was associated with a slight increase in preterm birth. Importantly, 46% of the women in the Metformin group required supplemental insulin to achieve adequate glycemic control. In another smaller RCT, Metformin had a 32% failure rate and these women were more obese, had higher FBG levels, and exhibited an earlier need for pharmacologic treatment (204). The offspring in the MiG trial are being followed for evidence of any long-term effects. A follow-up report of the infants in the MiG trial (205) 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 (206). 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 (207). 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 (208).

Metformin is concentrated in the fetal compartment with umbilical artery and vein levels being up to twice those seen in the maternal serum (209,99) 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. Although the ADA recommends that continuing Metformin beyond first trimester, especially in patients with pre-existing diabetes, should be studied in the context of a trial, ACOG recently states that insulin and oral medications are “equivalent” in efficacy, although they acknowledge that 20-45% of women fail Metformin alone necessitating that insulin be added (64).. They also suggest a role for counseling women that although current data do not demonstrate any adverse short term outcomes, long term outcomes have yet to be studied. 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 (63) due to a number of randomized controlled trials (210,211) and was recently supported by ACOG (64). . In some trials, maternal glycemic control, macrosomia, neonatal hypoglycemia, and neonatal outcomes were not different between groups (210) although in others, there was a significantly greater rate of macrosomic infants in the glyburide group (212,213). Although it was initially thought not to appreciably cross the placenta or significantly affect fetal insulin levels, a recent publication using HPLC mass spectrometry suggested a modest amount does cross. (214,99). Starting doses of 2.5 q.d. to b.i.d before meals are used in most studies and titrated up to a maximal dose of 10 mg b.i.d. A RCT compared the efficacy of metformin with glyburide for glycemic control in gestational diabetes (211). In the patients who achieved adequate glycemic control, the mean fasting and 2-hour postprandial blood 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 than the failure rate of glyburide when used in the management of gestational diabetes.

(211.) 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 are limited to after 24 weeks gestation so the effect on embryogenesis was not studied but there are no convincing reports that is a teratogen. Its use in women with Type 2 DM has not been adequately studied. Given it has been shown to have a high failure rate in women diagnosed with GDM < 24 weeks (215) 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 even a 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 recent data suggests that serum concentrations with usual doses are lower in pregnant women (214). 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 early a.m. hypoglycemia in light of its 3-4 hour peak (similar to Regular insulin). For women who have postprandial glucoses well controlled by Glyburide but have inadequate control of their fasting glucoses, adding NPH before bedtime (~8 hour peak) to the Glyburide can sometimes be useful. If both postprandial and fasting glucoses remain elevated, the patient should be switched to insulin. There are no sufficient data available on thiazolidinediones, metglitinide inhibitors, and incretins and such agents should only be used in the setting of approved clinical trials and their teratogenicity 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.

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

Although there is little 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 abdominal circumference (AC) relative to the biparietal diameter (BPD) i.e. body to head disproportion, the rate of fetal macrosomia can be decreased (216). This fetal based strategy (160, 161) 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 (192). Gestational diabetes can often be treated with twice daily injections of NPH and Regular insulin but occasionally postprandial glycemic excursions are so excessive that three times daily mealtime injections of Lispro or Aspart are necessary.

g. 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 who are not taking medical therapy but who have suboptimal glycemic control should be considered for fetal surveillance at ~32-34 weeks gestation (213). However, there is no consensus regarding antepartum testing in women with well-controlled GDM (64). 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 [160, 161], especially if fundal height is difficult to measure or it would influence treatment.

Delivery is usually recommended between 39-40 weeks unless glycemic control is very poor or there is an obstetric indication for earlier delivery. 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 (217)

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 (218). An estimated fetal weight of > 4500 grams on ultrasound carries a significantly increased risk for shoulder dystocia (60). It is recommended that women with GDM be counseled regarding the option of a scheduled cesarean delivery (64) and some experts would consider this option for an estimated fetal weight of >4250 grams with evidence of body to head disproportion.

h. 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 6-12 weeks postpartum. 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 Type 2 DM (219). Hyperglycemia generally resolves in the majority of patients during this interval but up to 10% of patients will fulfill criteria for Type 2 DM. 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 \geq 100 mg/dl). A 75 gm 2 hour glucose tolerance test is recommended by the ADA, CDA and Fifth International Workshop since most women with impaired glucose intolerance will be missed if only a FBG is checked (220). 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 (221). A 2 hour value of at least 200 mg/dl establishes a diagnosis of diabetes and a 2 hour value of at least 140mg/dl but less than 200 mg/dl makes the diagnosis of impaired glucose tolerance. Utility of using the HgbA1c postpartum to predict the subsequent occurrence of Type 2 DM in women with a history of GDM remains to be studied and may be affected by glycemic control during pregnancy if done before 3 months postpartum (222). The importance of diagnosing impaired glucose intolerance lies in its value in predicting the future development of Type 2 DM. In one series which mainly studied Latino women, a diagnosis of impaired glucose tolerance was the most potent predictor of the development of Type 2 DM in women with a history of GDM; 80% of such women developed diabetes in the subsequent 5-7 years (185). Intensified efforts promoting diet, exercise and weight loss should be instituted in these patients.

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 Type 2DM. The rate of Type 2 DM 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 (223). 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. (224,187,181). However, using thiazolidinediones for the purpose of preventing the development of Type 2 DM 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 (188). A total of 349 subjects had a history of GDM, and such a history conferred a 74% hazard rate to the development of Type 2 DM compared to women without a history of GDM. In the placebo arm, women developed Type 2 DM 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 make criteria for metabolic syndrome, achieving postpartum weight loss, and instituting aggressive interventions beginning with lifestyle changes to decrease insulin resistance for primary prevention of Type 2 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. 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 (64).

Breastfeeding

Women who breastfeed appear to have a lower incidence of developing Type 2 DM and it also appears to decrease the risk of developing infant obesity and impaired glucose tolerance (225). 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 (226). Recent studies that included GDM women have also shown it to decrease the risk of childhood obesity (227,171). 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 (228). 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 (229). Calcium intake should be at least ~1500 mg per day since exclusive breast-feeding for an extended period of time can cause a modest decrease in bone density.

Contraception

The same contraception choices recommended for preexisting diabetes apply for women with GDM with the possible exception of Depo-Provera injections (see Section VIIb). Although combined oral contraceptives do not appear to influence the development of Type 2 DM, Depo-Provera was shown in one trial to increase the subsequent risk of developing Type 2 DM in women with GDM, but this was largely due to the weight gain associated with its use (179). Effective contraception is critical given there is data that recurrent pregnancies in women with GDM appear to increase the risk of later development to Type 2 DM, 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.

IX. CONCLUSION

The obstetric outlook for pregnancy in women with pre-existing diabetes has potential to improve as rapid advances in diabetes management, fetal surveillance, and neonatal care emerge. However, the greatest challenge to face is the growing number of women developing GDM and Type 2 DM as the obesity epidemic increases and obesity-related complications exert a further deleterious effect. The development of Type 2 DM in the mother of GDM women 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 CV disease in addition to that of her offspring and offers the potential to decrease the intergenerational risk of obesity and diabetes.

Figure 1. Hernandez

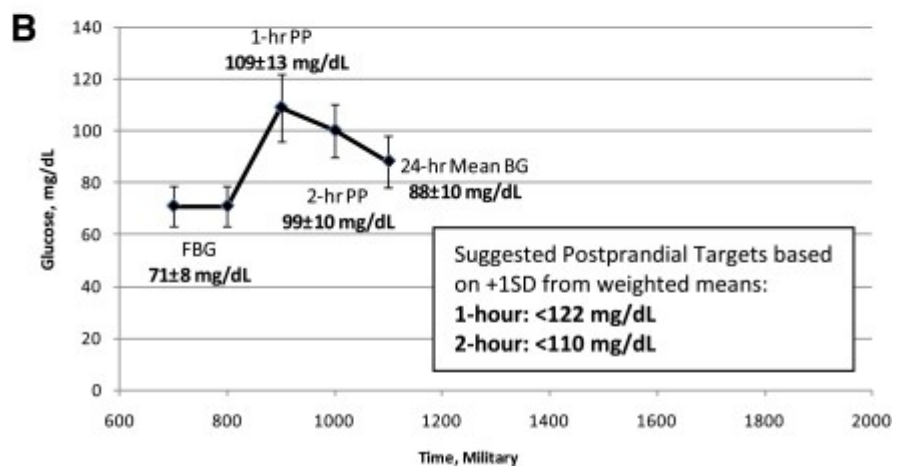
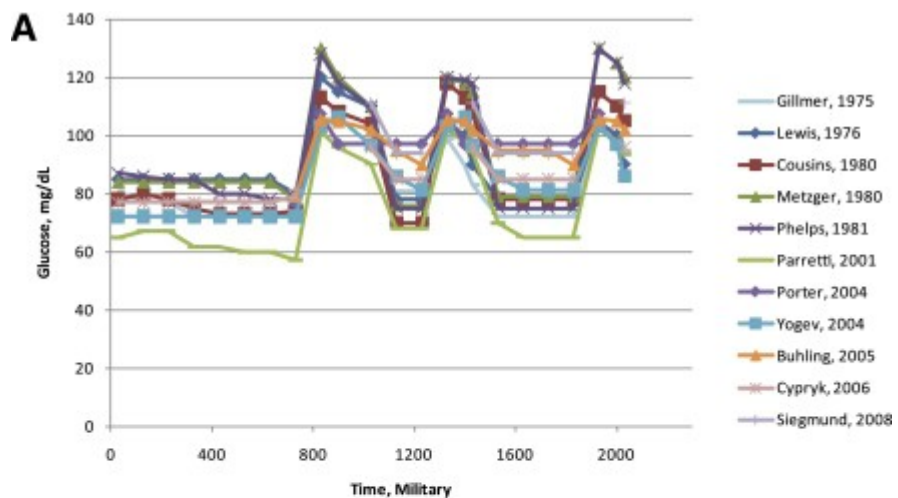


Table 1

Modified White Classification of Pregnant Diabetic Women				
Class	Diabetes onset age (yr)	Duration (yr)	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

Table 2

Evaluation of Women with Preexisting Diabetes in Addition to Prenatal Labs	
HgbA1c	Initially and every 1 – 3 months Especially in Type 1 DM; Consider TPO antibodies and repeat
TSH	TSH very trimester if + TPO antibodies
TGs	Repeat if borderline due to doubling in pregnancy
ALT;AST	To evaluation for non alcoholic fatty liver disease and as baseline preeclampsia labs
CR; Urine albumin or protein	If abnormal, obtain 24 hr urine for protein and estimated CrCl Repeat Prot/Cr ratio or 24 hr urine every 1 – 3 months if significant proteinuria
Ferritin, B12	Obtain for anemia or abnormal MCV, especially B12 if Type 1
Baseline preeclampsia labs	Consider Uric Acid; Obtain CBC with platelet count in addition to AST, ALT, BUN, Cr, 24 hr urine for protein, Cr
EKG	For women ≥35 or CV risk factors; Consider further evaluation if indicated
Dilated Retinal Exam	Every 1-6 months according to risk of progression

Table 3

SCREENING FOR GESTATIONAL DIABETES

American College of Obstetrics and Gynecology (ACOG)

Low Risk Status: Low risk status requires no glucose testing, but this category is limited to those women meeting all of the following criteria:

- Age <25 years
 - Weight normal before pregnancy
 - Member of an ethnic group with a low prevalence of GDM
 - No known diabetes in first-degree relatives
 - No history of abnormal glucose tolerance
-
- No history of poor obstetric outcome or macrosomic infant

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. Women meeting any of these criteria should be tested early:

- Obesity
 - Personal history of GDM or previous macrosomic infant
 - Family history of diabetes in a first degree relative
-
- Polycystic ovarian disease (PCOS)

CRITERIA FOR A POSITIVE 50 gm GLUCOLA CHALLENGE per ACOG

Glucose > 140 mg/dl (7.8 mmol/l): Identifies ~80% of women with GDM at the cost of performing a 3 hr 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 hr 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

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