Changing perspectives in pre-existing diabetes and obesity in pregnancy: maternal and infant short- and long-term outcomes

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Purpose of review
Climbing obesity rates in women have propelled the increasing prevalence of type 2 diabetes mellitus (T2DM) in pregnancy, and an increasing number of women with type 1 diabetes mellitus (T1DM) are also affected by obesity. Increasing recognition that an intrauterine environment characterized by obesity, insulin resistance, nutrient excess, and diabetes may be fueling the obesity epidemic in children has created enormous pressure to re-examine the conventional wisdom of our current approaches.

Recent findings
Compelling data in pregnancies complicated by diabetes, in particular those accompanied by insulin resistance and obesity, support a fetal programming effect resulting in increased susceptibility to metabolic disease for the offspring later in life. Recent data also underscore the contribution of obesity, lipids, and lesser degrees of hyperglycemia on fetal fat accretion, challenging the wisdom of current gestational weight gain recommendations with and without diabetes. The risks of adverse pregnancy outcomes in T2DM are at least as high as in T1DM and there remains controversy about the ideal glucose treatment targets, the benefit of different insulin analogues, and the role of continuous glucose monitoring in T1DM and T2DM.

Summary
It has become unmistakably evident that achieving optimal outcomes in mothers with diabetes is clearly impacted by ideal glycemic control but goes far beyond it. The intrauterine metabolic environment seems to have long-term implications on the future health of the offspring so that the effectiveness of our current approaches can no longer be simply measured by whether or not maternal glucose values are at goal.

Keywords
fetal programming, gestational weight gain, obesity, type 1 diabetes mellitus, type 2 diabetes mellitus

INTRODUCTION

The rising prevalence of maternal obesity, estimated at about one in three pregnant women, has resulted in rapidly increasing rates of type 2 diabetes mellitus (T2DM) as well as gestational diabetes mellitus (GDM) in addition to influencing pregnancy risk in many women with type 1 diabetes mellitus (T1DM) [1]. This perspective highlights major conceptual changes on the importance of the intrauterine environment in women with pre-existing diabetes and obesity on the long-term health of the offspring. It reviews the pregnancy outcomes in women with T1DM versus T2DM despite similar glycemic control, discusses our current understanding of glucose targets and the treatments we use to try to achieve them, and emphasizes the importance of preconception

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KEY POINTS

- An intrauterine environment that exposes the fetus to excess glucose, lipids, inflammation, growth factors, and cytokines may promote adipogenesis, alter appetite regulation, adversely affect pancreatic, renal, and hepatic development, and modify mitochondrial function, partly through epigenetic influences, resulting in long-term metabolic risk to the offspring.
- Maternal obesity commonly complicates pregnancies with GDM, T2DM, and even T1DM and independently increases the risk of adverse pregnancy outcomes including major malformations, preeclampsia, pregnancy loss, and stillbirth. As a result, pregnancy complications in T2DM are at least as common as in T1DM.
- The current IOM guidelines may be too liberal for women who are overweight or obese and less weight gain or no weight gain may be beneficial to improve pregnancy outcomes.
- Normal glucose levels in pregnancy are lower than usually recognized, but it is not clear whether targeting a lower glucose treatment threshold will improve pregnancy outcomes. Long-acting insulin analogues, insulin pumps, and continuous glucose monitors may have some advantages in achieving glycemic control, but pregnancy outcomes have yet to be convincingly improved by their use.
- Effective contraception until the A1C can be normalized and a healthier weight can be achieved may be more powerful in improving pregnancy outcomes than interventions during pregnancy itself.

counseling and effective contraception in women planning for pregnancy.

DIABESITY BEGETS DIABESITY: INTERGENERATIONAL INFLUENCE OF MATERNAL DIABETES, OBESITY, AND NUTRIENT EXCESS

The Developmental Origins of Health and Disease (DoHAD) hypothesis, now substantiated by extensive animal and human research, supports that both maternal nutrient deficiency as well as nutrient excess results in an acquired susceptibility to metabolic disease later in life which is programmed in utero and in early infancy [2–4]. 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 [5]. The evidence of this fetal programming effect has become one of the most compelling reasons why optimizing maternal glycemic control, identifying other nutrients contributing to excess fetal fat accretion, improving maternal insulin resistance and inflammation, 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. Epigenetics provides a conceptual framework of how metabolic factors (glucose, lipids, amino acids, growth factors, cytokines) in the intrauterine environment could alter DNA methylation and histone modification to change gene expression [6,7]. Such changes may modify number, growth, and function of many cells, promote adipogenesis, and later impact hypothalamic appetite regulation, pancreatic function, and alter mitochondrial and kidney function in the offspring. Even modest hyperglycemia in rats results in overweight offspring, changes in beta cell function possibly because of pancreatic islet exhaustion, and causes arterial hypertension, in part because of decreased nephron number [8]. There are also data in animal and nonhuman primate models to support that a maternal high-fat diet and obesity can influence the offspring's mesenchymal stems cells to differentiate along adipocyte rather than osteocyte pathways [9,10]. Further, this intrauterine environment invokes changes in the serotonergic system resulting in increased anxiety [11], affects neural pathways involved with appetite regulation, promotes lipotoxicity in the fetal liver and regulates gluconeogenic enzymes generating histology consistent with nonalcoholic fatty liver disease (NAFLD) [12,13], alters mitochondrial function in skeletal muscle, and programs beta cell mass in the pancreas [4,14–17].

In most cases of T2DM, GDM, and often in T1DM, the maternal metabolic environment is characterized by insulin resistance and inflammation, and both conditions increase fetal growth [18]. Maternal insulin resistance shunts all nutrient excess to the fetus including glucose, triglycerides (TGs), free fatty acids (FFA), and amino acids all of which can be used for fetal fat accretion and excess fetal growth. Furthermore, the placental transcriptome is a target of the altered environment of diabetic and obese pregnancies. Genes for lipids and amino acid transport are upregulated in the placentas of women with diabetes, as are genes for inflammatory pathways [19,20]. The Pima Indian population, which shares similar genetics and a postnatal environment, has demonstrated that offspring born to mothers who have T2DM or GDM have up to a six-fold risk of developing T2DM as a young adult

compared to an offspring born to the mother before she developed diabetes [21], strongly implicated non-genetic effects related to the intrauterine environment, and likely due to impaired insulin secretion and insulin sensitivity [22]. Similar patterns have been demonstrated with the effect of maternal obesity alone, as supported by data that siblings born before maternal bariatric surgery are at a much greater risk for obesity than siblings born after weight loss surgery [23]. Recently, Brumbaugh and our group demonstrated that newborns of obese GDM mothers also have evidence of increased intrahepatic fat at birth using NMR spectroscopy [24], possibly due to increased FFA flux across the placenta that is deposited in the liver, potentially increasing the risk for NAFLD later in childhood. This scenario creates enormous potential on a public health level for the incidence of T2DM to escalate as these children with impaired glucose tolerance become mothers themselves, perpetuating the cycle.

ROLE OF OBESITY ALONE IN ADVERSE PREGNANCY OUTCOMES: MORE THAN JUST THE GLUCOSE

By the most recent NHANES statistics, 56% of black women aged 20–39, 34–38% of Hispanic or Mexican American women, and 27% of white women are obese [1]. In addition to its association with multiple maternal complications, failed induction of labor, increased perinatal mortality, and lactation failure, maternal obesity independently increases the risk of first trimester and recurrent pregnancy losses and congenital malformations including central nervous system (CNS), cardiac, gastrointestinal defects, and cleft palate [25]. In fact, bariatric surgery has been shown to improve pregnancy outcomes in women with severe obesity [26], especially in the development of GDM, preeclampsia, macrosomia, and cesarean delivery. One study concluded that for every unit increase in BMI, the relative risk of a neural tube defect increased 7% [25]. Because so many women with T2DM or GDM are also obese, in addition to a growing number of women with T1DM, all of these complications increase the risk of poor pregnancy outcomes in these populations. Harmon and our group have shown that obese women with normal glucose tolerance have higher glycemic patterns throughout the day and night by continuous glucose monitoring (CGM) compared to normal weight women both early and late in pregnancy [27], despite a controlled diet. Interestingly, maternal TGs and FFAs were also higher in the obese women and were more strongly correlated with infant adiposity than maternal glucose, which is supported by other studies [28–30]. Women with obesity or diabetes complicated by obesity often have underlying hypertension, hyperlipidemia, and inflammation, all of which lead to increased oxidative stress and may explain some of the increased risk of congenital malformations in T2DM women, despite similar glycemic control compared to their normal weight T1DM counterparts.

The prevalence of childhood obesity is ~2.5 times higher in offspring of obese women compared to women with normal BMIs [31,32]. Importantly, the majority of large gestational age (LGA) babies(>90th percentile) are not born to mothers with diabetes or GDM but to overweight and obese mothers [33,34]. Pregnant women who are obese (maternal obesity) is also an independent risk factor for excess neonatal fat, a more important predictor of childhood adiposity, and a stronger risk factor than GDM in predicting offspring obesity by dual-energy X-ray absorptiometry (DXA) at 9 years of age 16 [33].

ARE IOM GUIDELINES FOR WEIGHT GAIN TOO LIBERAL AND ARE DIET AND PHYSICAL ACTIVITY INTERVENTIONS WORTH THE EFFORT?

The Institute of Medicine (IOM) published new gestational weight gain (GWG) guidelines in 2009 given the increasing recognition of the role of obesity on adverse pregnancy outcomes. The IOM did not offer any GWG guidelines specific to women with diabetes. Surprising to many, the IOM guidelines were minimally modified compared to the 1999 guidelines [35–37]. The guidelines were unchanged for underweight, normal weight (BMI 18.5–24.9: 25–35 lbs), and overweight (BMI 25–29.9: 15–25 lbs) women. For obese women, they recommended an upper limit to weight gain (BMI ≥30: 11–20 lbs) but provided no distinction for classes of obesity. Many experts voiced disappointment in the 2009 guidelines because there is much data to support lower GWG recommendations, especially for overweight and obese women [37,38]. The Harvard Project Viva studied 1044 mother–child pairs to study GWG and offspring adiposity at 3 years of age [39]. Women who gained according to the IOM guidelines still had a nearly four-fold increased risk of having a 3-year-old ≥95th percentile for weight compared to those who gained less than the guidelines recommended, but those who gained less than the recommended guidelines did not have an increased risk of delivering a small-for-gestational age (SGA) infant. Another study using this cohort [40] found that the lowest predicted prevalence of the five adverse outcomes (LGA, SGA, preterm delivery, postpartum weight retention, and childhood obesity) was associated with a weight gain of ~25 lbs in normal weight women, a weight

loss of ~3 lbs in overweight women, and a weight loss of ~17 lbs in obese women. Many other studies in the literature support no minimal or weight gain for obese women and even slight weight loss for Class II (BMI $\geq$ 35) or Class III (BMI $\geq$ 40) obese women [37,38,41] to avoid both SGA and LGA. Long-term childhood risk with excess GWG was evaluated [42] in nearly 5000 children of ages 14–22 from the 1979 National Longitudinal Survey of Youth and it was determined that GWG clearly increased LGA, postpartum weight retention, and child overweight but that SGA only decreased with GWG in underweight and normal weight mothers. The investigators recommended an optimal GWG of 11 lbs for overweight mothers but an optimal GWG of 0–11 lbs in obese mothers. It has been shown that although there is a clear relationship between GWG and birth weight in underweight and normal weight women, this relationship is not the case for obese women [37,43–45]. In a systematic review of outcomes of the 35 highest quality studies drawn from the report conducted for the Agency for Healthcare Research and Quality (AHRQ), the authors concluded that there was strong support between excessive weight gain and LGA but only strong support between inadequate weight gain and SGA in normal and underweight women [46]. The occurrence of SGA in overweight, obese, or women with diabetes is usually because of placental insufficiency from other maternal morbidities including vascular or renal disease or hypertension, and not related to weight gain. Further, the AHRQ encouraged the IOM to re-evaluate the GWG guidelines for overweight and obese women given these findings.

There are retrospective data in overweight GDM women that less GWG than the IOM guidelines results in a decreased need for insulin and lowers macrosomia (birth weight $\geq$ 4000 gm) [47] and that women who actually lose ~3 lbs between diagnosis of GDM and delivery have lower infant birth weights but no increase in SGA [48]. Further, recent data from retrospective cohort of 58 obese women with T2DM suggested that GWG less than 5 kg was associated with a lower LGA rate and less perinatal morbidity [49]. Targeting the diet has been modestly effective in minimizing excess GWG and physical activity interventions are safe, but compliance is low even though they have the potential to decrease LGA [50,51]. Women with GDM may benefit even more [52] and in a meta-analysis of seven studies using activity-based interventions in GDM women, five of seven showed improvement in glycemic control or limiting insulin use. In a recent review of the literature, this author [37] suggested that the lower limits of GWG be used for normal weight (25 lbs), overweight (15 lbs), and obese women (11 lbs), but that there are adequate data to support no GWG for women with a BMI more than 35. Further, overweight and obese women with diabetes are likely to benefit even more from lower GWG goals because GWG further worsens the insulin resistance of pregnancy, results in a higher postpartum weight retention, and leads to a higher prepregnancy BMI when going into the next pregnancy.

NORMAL GLUCOSE LEVELS IN PREGNANCY LOWER THAN EXPECTED AND LACK OF ROBUST TREATMENT TARGETS IN DIABETES

A recent careful review of the literature by Hernandez and our group demonstrated that normal pregnant women (BMI 22–28) during the third trimester have on average a fasting blood glucose (FBG) of 71 mg/dl; a 1-h postprandial glucose of 109 mg/dl; and a 2-h postprandial value of 99 mg/dl, which are much lower than typically appreciated and significantly lower than the current targets for glycemic control [53]. Gestational age and maternal BMI affect 'normal' glucose levels and a longitudinal study of 32 healthy, normal weight women between 16 weeks gestation and 6 weeks postpartum demonstrated a rise in mean glucose levels from 82 mg/dl at 16 weeks to 94 mg/dl at 36 weeks which was maintained at 6 weeks postpartum using CGM [54]. Two hour postprandial levels were increased rising from ~96 mg/dl at 16 weeks to a peak of 111 mg/dl at 36 weeks. As noted earlier in our series using CGM in normal and obese women, obese women have higher glycemic patterns throughout the day and night, early and late in pregnancy by an average of ~10 mg/dl compared to normal weight mothers [27], even when diet is carefully controlled.

Treatment targets for fasting and postprandial glucose levels in women with pre-existing diabetes or GDM have not been the subject of carefully randomized controlled trials. In a systematic review and meta-analysis, it was concluded that a FBG target of less than 90 mg/dl was associated with the most reduction in the risk of macrosomia (odds ratio 0.39); LGA (odds ratio 0.68); neonatal hypoglycemia (odds ratio 0.65); and preeclampsia (odds ratio 0.47), primarily from data in GDM women evaluated in the third trimester [55]. Data to support current postprandial targets of less than 140 mg/dl at 1h and less than 120 mg/dl at 2h are weaker because of significant heterogeneity between the studies and the lack of RCT comparing two or more thresholds and their impact on critical outcomes. These goals may need to be less aggressive in women with T1DM who have hypoglycemic unawareness. The fetus has no ability to increase its glucose

because of immature hepatic gluconeogenic capacity, and thus prolonged hypoglycemia can be life threatening to both the mother and the fetus with unknown neurodevelopmental consequences [18].

ARE PREGNANCY OUTCOMES WORSE IN T1DM COMPARED TO T2DM?

In many populations because of the rising obesity rate, T2DM has exceeded T1DM in women of childbearing age [18]. Pregnant women who have T2DM are at least as high of a risk of pregnancy complications as women with T1DM [56] because of additional risks of obesity, older age, a lower rate of preconception counseling, and the coexistence of the metabolic syndrome including hyperlipidemia, hypertension, and chronic inflammation [57,58]. In addition, because of the common occurrence of obesity, they may more often have undiagnosed sleep apnea with underlying pulmonary hypertension, be at higher risk for thromboembolism, and commonly have unsuccessful labor resulting in cesarean delivery. The causes of pregnancy loss seem to differ in women with T1DM versus T2DM with more pregnancy losses in T1DM because of major congenital anomalies or prematurity [58] compared to T2DM, when most were attributable to stillbirth or chorioamnionitis, suggesting that obesity plays a major role. In a recent cohort of 272 women with T2DM in the Netherlands with a mean BMI of ~32 and reasonable glycemic control, preterm birth was still ~20%, LGA occurred in about one-third, and the perinatal mortality rate was ~5% [56].

INSULIN TREATMENT OPTIONS AND UTILITY OF CGM

Increasingly, individuals with diabetes, especially those with T1DM and difficult-to-control T2DM are being managed with a flexible intensive self-management program in which they learn to dose their short-acting insulin to a premeal correction factor and carbohydrate to insulin ratio [18,59,60]. 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 [61] whereas fetal outcomes were similar. Long-acting insulin analogues such as Glargine and Detemir also seem to be safe [62,63] without evidence of an increased mitogenic effect from Glargine compared to neutral protamine Hagedorn (NPH). The efficacy and safety of Detemir have been confirmed in a multinational RCT involving 310 women [63] with no differences in maternal or neonatal outcomes, a slightly lower fasting glucose, but no difference in major and minor hypoglycemia rates and A1C's were similar. NPH is still often useful immediately before bedtime to take advantage of its 6–8-h peak to bring down fasting glucose levels, especially when the longer-acting insulins with a flatter profile are not successful in controlling the dawn effect associated with fasting hyperglycemia. There are no definitive studies favoring insulin pumps over multiple daily injections [64]. Randomized control trials of multiple daily injections versus the insulin pump generally showed equivalent glycemic control and perinatal outcome, but the pump can be especially useful for patients with nocturnal hypoglycemia or a prominent dawn phenomenon [64]. However, insulin delivery failure from a kinked catheter can result in DKA rapidly, which occurs at lower glucose levels in pregnancy [18], so it is optimal to start pump therapy before conception because of its steep learning curve and the rapidly changing insulin sensitivity in pregnancy requiring frequent changes to basal and bolus rates. The use of oral hypoglycemic agents in women with T2DM is likely to have a high failure rate because of the greater beta cell dysfunction and insulin resistance in this population (see Unresolved Controversies in GDM). A very small study of 28 women diagnosed with T2DM or early GDM were randomized to metformin versus insulin with 43% of the women in the metformin group requiring insulin therapy [65] and a larger trial adding metformin to insulin in women with T2DM (MiTY trial) is underway.

Using CGM technology may help identify periods of unrecognized hyper or hypoglycemia and certainly confirm glycemic patterns. In one study using intermittent blinded CGM in which the information was used by the health-care team to adjust insulin treatment, there was improved glycemic control in the third trimester and a reduction in macrosomia rates [66]. In another study of intermittent use of real-time CGM (where results are simultaneously displayed), there was no improvement of glycemic control or macrosomia [67]. It must be emphasized to the patient that the values displayed by CGM should not be used to dose insulin given the interstitial glucose values are dependent on the one preceding it, the physiological diffusion of blood into capillaries and separation to interstitial fluid creates a time measurement delay, and calibration errors are not infrequent [68]. In one study outside of pregnancy, the use of a closed-loop system, which uses computerized algorithms to link insulin delivery with CGM glucose levels in real time, resulted in less hypoglycemia [69] but use in pregnancy will require resolution of the current challenges of obtaining the necessary precision and developing effective and safe algorithms. There are no standardized approaches to

define and analyze the enormous amount of data offered by CGM to facilitate comparisons among research studies. A recent study from Hernandez and our group defines pregnancy-relevant CGM-derived glucose variables and offers a methodologic approach to characterize 24-h glycemic profiles for the study of fetal growth and neonatal adiposity [68].

CONCLUSION

Clearly, it is imperative that all women of childbearing age with diabetes receive preconception counseling about the critical importance of optimizing glycemic control (A1C < 6.5) to prevent major malformations which occur at ~5–8 weeks gestation [70,71], before most women know they are pregnant. For obese women with or without diabetes, eating a healthy diet and trying to achieve weight loss BEFORE pregnancy is critical given the importance of prepregnancy BMI in maternal and childhood outcomes. Providing effective birth control until women are ready to conceive has the power to reduce the malformation rate to that of the nondiabetic population [72]. There are no adequate breastfeeding studies in regard to milk composition or infant fat development as yet in T2DM and scant data in T1DM, but breastfeeding rates in these populations have recently been shown to be less than half of the rates seen in women without diabetes [73]. It has become evident that the optimal preconception, antepartum, and postpartum management of women with diabetes or obesity has far-reaching implications to the long-term health of both the mother and her offspring and that randomized trials which follow the mothers and infants through childhood, although expensive, are critical to positively impact the transgenerational effects.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012; 307:491–497.
2. Heerwagen MJ, Miller MR, Barbour LA, Friedman JE. Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. Am J Physiol Regul Integr Comp Physiol 2010; 299:R711–R722.
3. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet 2011; 378:169–181.
4. Nolan CJ. Normal long-term health for infants of diabetic mothers: can we achieve it? J Clin Endocrinol Metab 2013; 98:3592–3594.
5. Patti M-E. Intergeneration programming of metabolic disease; evidence from human populations and experimental animal models. Cell Moll Life Sci 2013; 70:1597–1616.
6. Lillycrop KA, Burdge GC. Epigenetic mechanisms linking early nutrition to long term health. Best Pract Res Clin Endocrinol Metab 2012; 26:667–676.
7. Pinney SE, Simmons RA. Metabolic programming, epigenetics, and gestational diabetes. Curr Diab Repor 2012; 12:67–74.
8. Mitanchez D, Burguet A, Simeoni U. Infants born to mothers with gestational diabetes mellitus; mild neonatal effects, a long-term threat to global health. J Pediatr 2014; 164:445–450.
9. Chen JR, Zhang J, Lazarenko OP, *et al.* Inhibition of fetal bone development through epigenetic down-regulation of HoxA10 in obese rats fed high-fat diet. FASEB J 2012; 26:1131–1141.
10. Symonds ME, Pope M, Sharkey D, *et al.* Adipose tissue and fetal programming. Diabetologia 2012; 55:1597–1606.
11. Sullivan EL, Grayson B, Takahashi D, *et al.* Chronic consumption of a high fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. J Neuroscience 2010; 30:3826–3830.
12. McCurdy CE, Bishop JM, Williams SM, *et al.* Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest 2009; 119:323–335.
13. Suter MA, Chen A, Burdine MS, *et al.* A maternal high-fat diet modulates fetal SIRT1 histone and protein deacetylase activity in nonhuman primates. FASEB J 2012; 26:5106–5114.
14. Sassone-Corsi P. When metabolism and epigenetics converge. Science 2013; 339:148–149.
15. Vrachnis N, Antonakopoulos N, Iliodromiti Z, *et al.* Impact of maternal diabetes on epigenetic modifications leading to diseases in the offspring. Exp Diabetes Res 2012; 2012:1–6.
16. Malcolm J. Through the looking glass: gestational diabetes as a predictor of maternal and offspring long-term health. Diabetes Metab Res Rev 2012; 28:307–311.
17. Portha B, Chavey A, Movassat J. Early-life origins of type 2 diabetes: fetal programming of the beta cell mass. Exp Diabetes Res 2011; 2011:1–16.
18. Keely E, Barbour LA. Management of diabetes in pregnancy. Endotext 2013; 1–46; Chapter 20.
19. Radaelli T, Lepercq J, Varastehpour A, *et al.* Differential regulation of genes for fetoplacental lipid pathways in pregnancy with gestational and type 1 diabetes mellitus. Am J Obstet Gynecol 2009; 201:209.e1–209.e10.
20. Aye IL, Powell TL, Jansson T. Adiponectin – the missing link between maternal adiposity, placental transport, and fetal growth? Placenta 2013; 34:S40–S45.
21. Dabelea DT. Crume, maternal environment and the transgenerational cycle of obesity and diabetes. Diabetes 2011; 60:1849–1855.
22. Kelstrup L, Damm P, Mathiesen ER, *et al.* Insulin resistance and impaired pancreatic B-cell function in adult offspring of women with diabetes in pregnancy. J Clin Endocrinol Metab 2013; 98:3793–3801.
23. Kral JG, Biron S, Simard S, *et al.* Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. Pediatrics 2006; 118:e1644–e1649.
24. Brumbaugh DE, Tearse P, Cree-Green M, *et al.* Intrahepatic fat is increased in the neonatal offspring of obese women with gestational diabetes. J Pediatr 2012; 162:930–936.
25. Watkins ML, Rasmussen SA, Honein MA, *et al.* Maternal obesity and risk for birth defects. Pediatrics 2003; 111:1152–1158.
26. Vrebosch L, Bel S, Vansant G, *et al.* Maternal and neonatal outcome after laparoscopic adjustable gastric banding: a systematic review. Obes Surg 2012; 22:1568–1579.
27. Harmon KA, Gerard L, Jensen DR, *et al.* Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. Diabetes Care 2011; 34:2198–2204.
28. Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, *et al.* Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 2008; 31:1858–1863.
29. Barbour L, Hernandez T, VanPelt R, *et al.* Change in fasting triglycerides from early to late gestation is highly predictive of neonatal adiposity. ADA Diabetes 2009; 58 (Supp 1):A84.
30. Whyte K, Kelly H, O'Dwyer V, *et al.* Offspring birth weight and maternal fasting lipids in women screened for gestational diabetes mellitus (GDM). Eur J Obstet Gynecol Reprod Biol 2013; 170:67–70.
31. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. Pediatrics 2004; 114:29–36.
32. Black MH, Sacks DA, Xiang A, *et al.* The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care 2013; 36:56–62.
33. Catalano PM, Farrell K, Thomas A, *et al.* Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr 2009; 90:1303–1313.
34. Catalano PM, McIntyre DH, Cruickshank JK; the HAPO Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome Study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012; 35:780–786.

35. Institute of Medicine (IOM). US, Subcommittee on nutritional status and weight gain during pregnancy. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: National Academy Press; 2009.
36. Rasmussen KM, Yaktine AL, eds.; Institute of Medicine and National Research Council Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight gain during pregnancy: reexamining the guidelines. Washington, DC, National Academies Press, 2009, 1–250.
37. Barbour LA. Weight gain in pregnancy: is more truly less for mother and child? J Obstet Med, June 2012; 5:58–64.
38. Blomberg M. Maternal and neonatal outcomes among obese women with weight gain below the new Institute of Medicine recommendations. Obstet Gynecol 2011; 117:1065–1070.
39. Oken E, Taveras EM, Kleinman KP, *et al.* Gestational weight gain and child adiposity at age 3 years. Am J Obstet Gynecol 2007; 196:322–328.
40. Oken E. Maternal and child obesity: the causal link. Obstet Gynecol Clin North Am 2009; 36:361–377.
41. Hinkle SN, Sharma AJ, Dietz PM. Gestational weight gain in obese mothers and associations with fetal growth. Am J Clin Nutr 2010; 92:644–651.
42. Margerison Zilko CE, Rehkopf D, Abrams B. Association of maternal gestational weight gain with short- and long-term maternal and child health outcomes. Am J Obstet Gynecol 2010; 202:574–578.
43. Bodnar LM, Siega-Riz AM, Simhan HN, *et al.* Severe obesity, gestational weight gain, and adverse birth outcomes. Am J Clin Nutr 2010; 91:1642–1648.
44. Artal R, Lockwood CJ, Brown HL. Weight gain recommendations in pregnancy and the obesity epidemic. Obstet Gynecol 2010; 115:152–155.
45. Herring SJ, Rose MZ, Skouteris H, Oken E. Optimizing weight gain in pregnancy to prevent obesity in women and children. Diabetes Obes Metab 2012; 14:195–203.
46. Siega-Riz AM, Viswanathan M, Moos, *et al.* A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. Am J Obstet Gynecol 2009; 201:339.e1–339.e14.
47. EunPark J, Park S, Daily JW, Kim SH. Low gestational weight gain improves infant and maternal pregnancy outcomes in overweight and obese Korean women with gestational diabetes. Gynecol Endocrinol 2011; 27:775–781.
48. Katon J, Reiber G, Williams MA, *et al.* Weight loss after diagnosis with gestational diabetes and birth weight among overweight and obese women. Matern Child Health J 2013; 17:374–383.
49. Asbjornsdottir B, Rasmussen SS, Kelstrup L, *et al.* Impact of restricted maternal weight gain on fetal growth and perinatal morbidity in obese women with type 2 diabetes. Diabetes Care 2013; 36:1102–1106.
50. Thangaratinam S, Rogozinska E, Jolly Ket al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: a meta-analysis of randomized evidence. BMJ 2012; 344:1–15.
51. Skouteris H, Clark-Hartley L, McCabe M, *et al.* Preventing excessive gestational weight gain: a systematic review of interventions. Obesity reviews 2012; 11:757–768.
52. Ruchat SM, Mottola MF. The important role of physical activity in the prevention and management of gestational diabetes mellitus. Diab Metab Res Rev 2013; 29:334–346.
53. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? Diabetes Care 2011; 34:1660–1668.
54. Siegmund T, Rad NT, Ritterath C, *et al.* Longitudinal changes in the continuous glucose profile measured by the CGMS in healthy pregnant women and determination of cut-off values. Eur J Obstet Gynecol Reprod Biol 2008; 139:46–52.
55. Prutsky GJ, Domecq JP, Wang Z, *et al.* Glucose targets in pregnant women with diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2013; 98:4319–4324.
56. Groen B, Links TP, van den Berg PP, *et al.* Similar adverse pregnancy outcome in native and nonnative Dutch women with pregestational type 2 diabetes; a multicenter retrospective study. ISRN Obstet Gynecol 2013; 361435:1–7.
57. Clausen TD, Mathiesen E, Ekbom P, *et al.* Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care 2005; 28:323–328.
58. Cundy T, Gamble G, Neale L, *et al.* Differing causes of pregnancy loss in type 1 and type 2 diabetes. Diabetes Care 2007; 30:2603–2607.
59. Mathiesen JM, Secher AL, Ringholm L, *et al.* Changes in basal rates and bolus calculator settings in insulin pumps during pregnancy in women with type 1 diabetes. J Matern Fetal Neonatal Med 2013; 27:724–728.
60. Ringholm L, Secher AL, Pedersen-Bjergaard U, *et al.* The incidence of severe hypoglycaemia in pregnant women with type 1 diabetes mellitus can be reduced with unchanged HbA1c levels and pregnancy outcomes in a routine care setting. Diabetes Res Clin Pract 2013; 101:123–130.
61. Lambert K, Holt RIG. The use of insulin analogues in pregnancy. Diabetes Obes Metab 2013; 15:888–900.
62. Lepercq J, JLin J, Hall GC, *et al.* Meta-analysis of maternal and neonatal outcomes associated with the use of insulin glargine versus NPH insulin during pregnancy. Obstet Gynecol Int 2012; 2012:649070.
63. Mathiesen ER, Hod M, Ivanisevic M, *et al.* Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin determir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care 2012; 35:2012–2017.
64. Castorino K, Paband R, Zisser H, Jovanovič L. Insulin pumps in pregnancy: using technology to achieve normoglycemia in women with diabetes. Curr Diab Rep 2012; 12:53–59.
65. Hickman MA, McBride R, Boggess KA, Straus R. Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial. Amer J Perinatol 2013; 30:483–490.
66. Murphy HR, Rayman G, Lewis K, *et al.* Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomized clinical trial. BMJ 2008; 337:1–l8.
67. Secher AL, Ringholm L, Andersen HU, *et al.* The effect of real-time continuous glucose monitoring in pregnant women with diabetes. A randomized controlled trial. Diabetes Care 2013; 36:1877–1883.
68. Hernandez TL, Barbour LA. A standard approach to continuous glucose monitor data in pregnancy for the study of fetal growth and infant outcomes. Diab Technol Therap 2013; 15:1–8.
69. Murphy HR, Elleri D, Allen JM, *et al.* Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. Diabetes Care 2011; 34:406–411.
70. Bell R, Glinianaia P, Tennant PWG, *et al.* Periconception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with preexisting diabetes: a population-based cohort. Diabetologia 2012; 55:936–947.
71. Tennant PWG, Glinianaia SV, Bilous RW, *et al.* Preexisting diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. Diabetologia 2014; 57:285–294.
72. Keely E. Preconception care for women with type 1 and type 2 diabetes – the same but different. Can J Diabetes 2012; 36:83–86.
73. Finkelstein SA, Keely E, Feig DS, *et al.* Breastfeeding in women with diabetes: lower rates despite greater rewards. A population-based study. Diabet Med 2013; 30:1094–1101.