Large-for-Gestational-Age Neonates in Type 1 Diabetes and Pregnancy: Contribution of Factors Beyond Hyperglycemia

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REVIEW

Despite significant reductions in serious adverse perinatal outcomes for women with type 1 diabetes in pregnancy, the opposite effect has been observed for fetal overgrowth and associated complications, such as neonatal hypoglycemia, shoulder dystocia, and admission to the neonatal intensive care unit. In addition, infants born large for gestational age (LGA) have an increased lifetime risk of obesity, diabetes, and chronic disease. Although exposure to hyperglycemia plays an important role, women who seemingly achieve adequate glycemic control in pregnancy continue to experience a greater risk of excess fetal growth, leading to LGA neonates and macrosomia. We review potential contributors to excess fetal growth in pregnancies complicated by type 1 diabetes. In addition to hyperglycemia, we explore the role of glycemic variability, prepregnancy overweight and obesity, gestational weight gain, and maternal lipid levels. Greater understanding of the stimuli that drive excess fetal growth could lead to targeted management strategies in pregnant women with type 1 diabetes, potentially reducing the incidence of LGA neonates and the inherent risk of acute and long-term complications.

The relationship between type 1 diabetes in pregnancy and adverse perinatal outcomes is universally recognized. Early in pregnancy, women with type 1 diabetes have an increased risk of miscarriage and a greater likelihood of their fetus having congenital malformations, and prepregnancy planning with optimization of glycemic control reduces these risks (1). Later in pregnancy, women with type 1 diabetes are more likely to experience preeclampsia, preterm birth, induction of labor, cesarean section, and delivery complications (2). Of note, babies born to women with type 1 diabetes have significantly higher rates of being large for gestational age (LGA) (birth weight >90th percentile for gestational age and sex), macrosomia (birth weight >4,000 g or 8 lb 13 oz), and neonatal hypoglycemia (3).

Hyperglycemia is believed to be the underlying cause for many of the adverse fetal, neonatal, and maternal outcomes in pregnancies complicated by type 1 diabetes; however, in women with well-controlled diabetes, an increased incidence of perinatal complications still is observed (4). In particular, the rates of LGA neonates and macrosomia remain high, experienced by up to 50% of women (5), and suggest that hyperglycemia may not be the only driver of fetal overgrowth for women with type 1 diabetes or that it may act in concert with other factors that lead to fetal hyperinsulinemia and excess fetal weight gain.

Knowledge about the clinical implications of LGA or macrosomia has increased over the past two decades, with a broader appreciation of the effect of fetal programming on the metabolic health of the offspring. Elevated birth weight may be associated with a greater risk of obesity, type 2 diabetes, and chronic disease in later life (6).

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Furthermore, LGA neonates still experience higher rates of acute perinatal complications than their appropriate-weight counterparts, including neonatal hypoglycemia, shoulder dystocia, and admission to the neonatal intensive care unit (7).

The St. Vincent declaration of 1989 set a 5-year target to reduce the risk of adverse perinatal outcomes for women with type 1 diabetes to the level of women without diabetes (8). Despite many advances in diabetes management and therapy, this target has not been attained. In light of the continuing high incidence of LGA and macrosomic infants and their greater risk of acute and chronic complications, we evaluated the factors beyond hyperglycemia associated with the risk of fetal overgrowth in type 1 diabetes and pregnancy, with a particular focus on the possible roles of glycemic variability, prepregnancy BMI, gestational weight gain, and maternal lipid levels (Fig. 1). This review describes pertinent studies on the topic of fetal growth in pregnancy complicated by type 1 diabetes but does not intend to include an exhaustive list of all literature on this subject. First, we briefly review the role of maternal hyperglycemia in excess fetal growth.

MATERNAL GLYCEMIA

Glycemic Control and Hyperglycemia

Initially described by Pedersen (9), maternal hyperglycemia in the second and third trimesters of pregnancy can promote excess fetal weight gain through stimulation of fetal hyperinsulinemia. Fetal insulin production enhances glucose utilization in insulin-sensitive tissues, such as liver, heart, skeletal muscle, and adipose tissue, and fetal hyperinsulinemia leads to the expansion of adipocytes and increased fat tissue deposition. Early maternal hyperglycemia, such as that experienced by women with type 1 diabetes in the late first trimester and beginning of the second trimester, may prime the fetus toward elevated insulin production, and this coincides with the gestational age at which fetal fat accretion begins (10,11).

A continuous relationship exists between maternal fasting plasma glucose and birth weight, with a similar association seen for HbA_{1c} (12,13). In addition, we recently observed that HbA_{1c} in type 1 diabetes and pregnancy is significantly and positively correlated with fetal abdominal circumference in the second and third trimesters and that HbA_{1c} >6% (42 mmol/mol) later in pregnancy is associated with an increased risk of neonates being born LGA (14), similar to the findings of Maresh et al. (3). As well as fasting plasma glucose and overall hyperglycemia, elevated glucose levels during specific periods of the day (late morning and afternoon in the second trimester and evening in the third trimester) are associated with LGA neonates in women with type 1 diabetes (15). Thus, the latest American Diabetes Association guidelines recommend that to reduce the risk of LGA neonates, HbA_{1c} should be targeted to 6–6.5% (42–48 mmol/mol) during pregnancy and maintained at <6% (42 mmol/mol), if possible, avoiding hypoglycemia. Although the target HbA_{1c} of 6% (42 mmol/mol) is considered tight glycemic control for type 1 diabetes, the average HbA_{1c} in pregnant women without diabetes is 5% (31 mmol/mol) in late pregnancy (16). The difference between 5% (31 mmol/mol) and 6% (42 mmol/mol) (1% [11 mmol/mol]) corresponds to a higher average circulating glucose of ~1.6 mmol/L (~29 mg/dL) in type 1 diabetes. Moreover, 19% of women with type 1 diabetes who maintain their HbA_{1c} <5.5% (37 mmol/mol) in the third trimester have LGA neonates compared with 52% of women with HbA_{1c} >6.4% (46 mmol/mol) (17).

Although maternal hyperglycemia leads to a significant risk of excess fetal growth, several studies have found no association between maternal glycemic control and fetal overgrowth or that a reduction in hyperglycemia completely ameliorates the risk of infants being born LGA. For example, use of real-time continuous glucose monitoring (CGM) was associated with improved glycemic control and reduced the incidence of fetal overgrowth and neonatal hypoglycemia, yet the proportion of neonates who were born LGA remained high at 53% (18). Likewise, closed-loop insulin pump technology improved glycemic control with less time spent in hyperglycemia; however, LGA births occurred in 81% of offspring (19). Fetal hyperinsulinemia is recognized as the main causal factor for excess fetal growth, yet the association between fetal insulin levels and maternal glucose levels generally is not strong enough to explain all of the variation seen (20). Thus, abnormal maternal glycemia may account for some but not all of the risk of LGA neonates in type 1 diabetes and pregnancy. In other instances, either small perturbations in glycemic control leading to mild maternal hyperglycemia throughout pregnancy sufficiently stimulate excess fetal growth in type 1 diabetic pregnancy or elements outside hyperglycemia play a causative or contributory role.

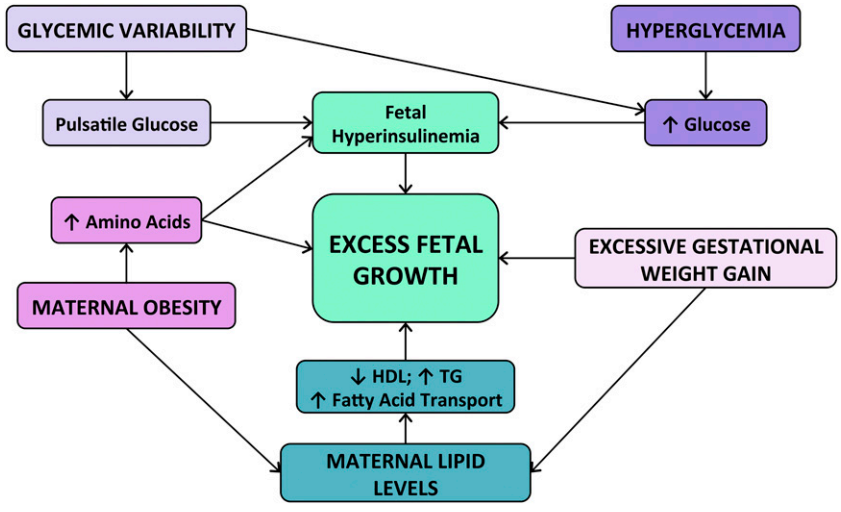

Figure 1—Contribution of maternal factors to fetal overgrowth in type 1 diabetes in pregnancy and possible mechanisms of action. Additional cross talk between pathways may occur through as-yet unidentified mechanisms. TG, triglyceride.

Glycemic Variability

Glycemic variability (GV), or acute fluctuations in blood glucose levels, occurs frequently in individuals with type 1 diabetes, despite acceptable glycemic control reflected by HbA_{1c}. The optimal method of

detection of GV is through the analysis of CGM data, and CGM is an accurate technique for assessing glucose levels in pregnancy complicated by type 1 diabetes (21). Of note, women with type 1 diabetes in pregnancy experience greater GV than those with gestational diabetes mellitus (GDM) (22), with both significant intra- and interday variability in glucose (23). Furthermore, CGM is a more robust indicator of the time spent in hyperglycemia in pregnancy than HbA_{1c} (24). A small study of women with and without preexisting diabetes found that average 3-day maternal glucose levels were not associated with birth weight, but a significant positive correlation between hyperglycemic excursions and birth weight centile was observed (25).

In addition to identifying transient periods of hyperglycemia, CGM data can be used to derive summary measures of GV, which is relevant in pregnancy because higher indices of GV in the second and third trimesters have been associated with LGA neonates for women with type 1 diabetes (15). Furthermore, increased GV was predictive of asymmetrical fetal growth and associated with an increased risk of macrosomia, which was attributed to fluctuations in glucose rather than to time spent in hyperglycemia per se (26). In our center, we have observed that the combination of elevated GV and HbA_{1c} >6% (42 mmol/mol) in the late second trimester of type 1 diabetic pregnancy was associated with LGA neonates (27). In addition, women who had LGA neonates had a significantly greater J-index (a measure of GV that incorporates both the mean and the SD of glucose to describe overall glycemia and variability) between 24 and 28 weeks of gestation. Examples of CGM traces for women with type 1 diabetes are provided in Fig. 2, showing low, moderate, and high levels of mean glucose and GV (27).

Of note, reductions in hyperglycemia and GV, specifically the SD of glucose and mean amplitude of glycemic excursions for women with type 1 diabetes who used real-time CGM, have led to a lower risk of LGA neonates (18). However, the absolute reductions in HbA_{1c}, SD of glucose, and mean amplitude of glycemic excursions from baseline to 34 weeks of gestation for women in the real-time CGM group were 6.83% to 6.35% (51 to 46 mmol/mol), 3.1 to 2.2 (55.8 to 36.9 mg/dL), and 6.0 to 4.2 mmol/L (108 to 75.6 mg/dL), respectively. Although clinically significant, this may not have been a sufficient decrease in overall glucose levels or GV to mitigate fetal overgrowth because 53% of neonates in the real-time CGM group were, nonetheless, born LGA.

The use of short-term glycemic markers in pregnancy rather than HbA_{1c} has been

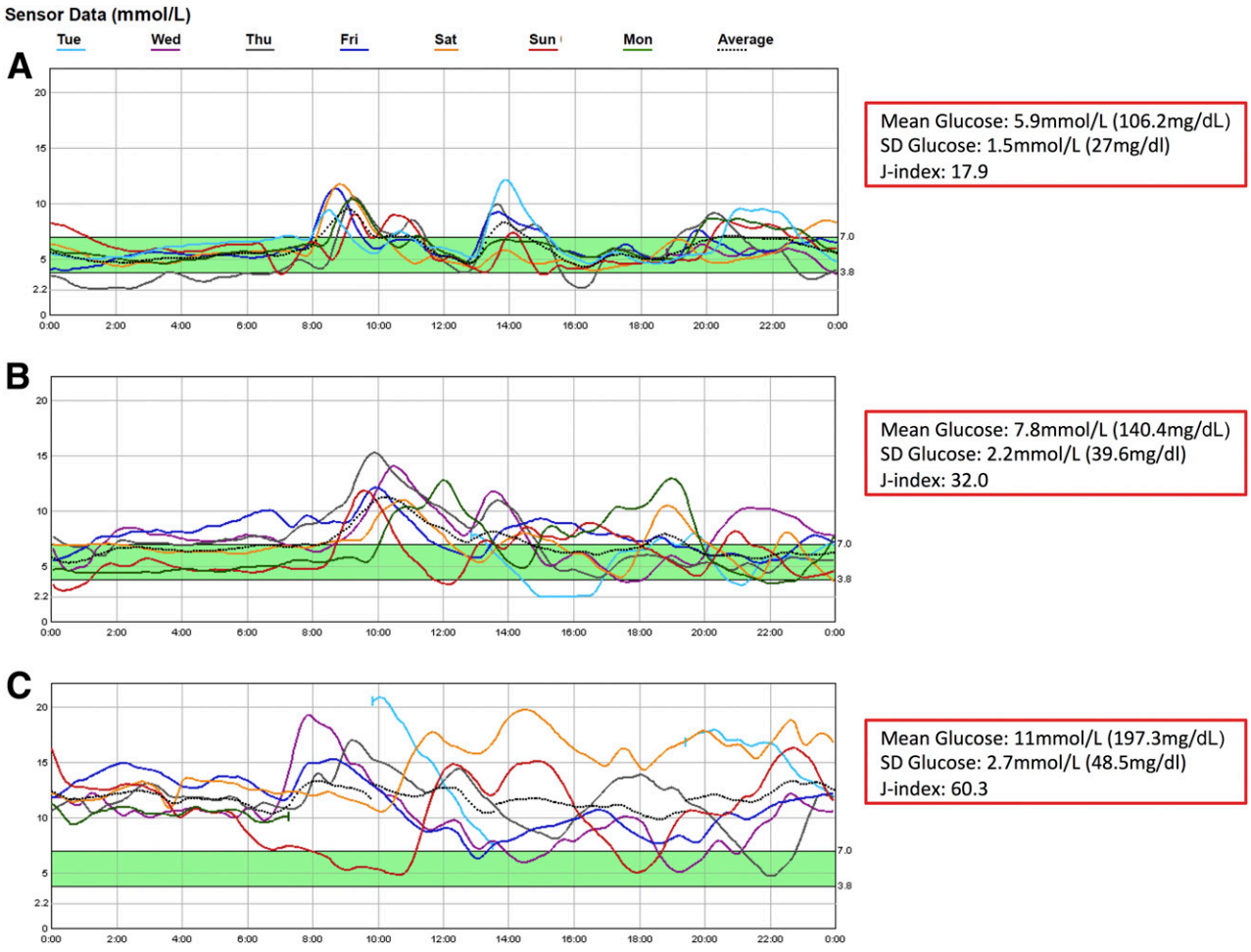

Figure 2—Examples of CGM traces carried out between 24 and 28 weeks of gestation in women with type 1 diabetes in pregnancy (27). *A*: Low mean glucose with low GV. *B*: Moderate mean glucose with moderate GV. *C*: High mean glucose with high GV. GV indicated by SD of glucose and J-index.

suggested because they can more accurately reflect glucose excursions that occur over weeks rather than months (28), which could be more relevant during gestation. Third trimester 1,5-anhydroglucitol, a short-term marker of glycemic control that is significantly correlated with measures of GV, was a better predictor of LGA neonates than HbA_{1c} measured at the same time point in pregnancy in women with type 1 diabetes (29). Furthermore, a study of diabetes complicating 85 pregnancies (including 37 women with type 1 diabetes) showed that 1,5-anhydroglucitol is inversely correlated with birth weight and may be a useful adjunct to HbA_{1c} in the assessment of women with diabetes at risk for fetal overgrowth (30). Another marker of recent glucose exposure (2–4 weeks) is glycated albumin, and higher levels of glycated albumin and HbA_{1c} 1 month before birth have been associated with LGA neonates in GDM and preexisting diabetes in pregnancy (31). Additional studies are required to determine the utility of glycated albumin compared with HbA_{1c} in type 1 diabetes and pregnancy.

Exposure to short-term periods of hyperglycemia, in addition to chronic hyperglycemia, may contribute to fetal hyperinsulinemia, leading to a weight-promoting environment in utero. This is supported by evidence that glucose excursions are more predictive of macrosomia than HbA_{1c} (32), and third trimester peaks in glucose predict excess fetal growth (17). In addition, animal models have demonstrated that pulsatile glucose rather than chronic hyperglycemia leads to higher fetal insulin production (33). Short-term measures of glucose fluctuations, such as GV indices calculated from CGM data, 1,5-anhydroglucitol, and glycated albumin, may be more sensitive indicators of glucose patterns sufficient to increase fetal weight gain. Another hypothesis is that increased GV enhances oxidative stress and endothelial dysfunction (34). Oxidative stress is greater in pregnancies complicated by type 1 diabetes than by GDM, yet levels of breakdown products associated with oxidative stress are higher in both forms of diabetes in pregnancy than in nondiabetic pregnancy (35). Furthermore, a relationship between endothelial dysfunction in women with type 1 and type 2 diabetes—specifically elevated soluble E-selectin—and fetal overgrowth has been demonstrated (36). Additional research to elucidate the contribution of GV to oxidative stress and/or endothelial dysfunction in type 1 diabetes in pregnancy and the possible effects on fetal growth in experimental models or clinical studies would be of benefit. Moreover, future studies should determine whether reducing glycemic excursions in type 1 diabetes in pregnancy contribute to lower rates of LGA neonates.

PREPREGNANCY BMI AND GESTATIONAL WEIGHT GAIN

Prepregnancy BMI and Maternal Obesity

The rise in obesity worldwide has led to a higher incidence of elevated prepregnancy BMI in women of reproductive age. Of note, even in the absence of diabetes, prepregnancy obesity increases the likelihood of fetal overgrowth (37,38). Furthermore, the increased birth weight observed in neonates born to obese mothers is attributable to greater fat mass than lean mass because the higher supply of nutrients promotes fetal hyperinsulinemia, leading to increased neonatal adiposity (39,40).

Traditionally, type 1 diabetes has been associated with a lean body type; however, the number of pregnant women with type 1 diabetes who have a BMI in the overweight (>25 kg/m^2) or obese (>30 kg/m^2) range has been increasing (41). For example, a study in Sweden found that the rate of overweight and obesity among pregnant women with type 1 diabetes is ~45% greater than for pregnant women without type 1 diabetes (42). These results have been mirrored in Ireland (43), Australia (41), and Finland (44), where maternal BMI has been independently associated with a higher likelihood of macrosomia together with third trimester HbA_{1c} (44). In fact, the combination of elevated BMI and type 1 diabetes in pregnancy has a synergistic effect, and the presence of both factors is estimated to increase the risk of LGA neonates by 13-fold (42).

Maternal obesity may compound hyperglycemia in type 1 diabetes to augment the fetal nutrient supply, yet elevated fetal abdominal circumference as early as 18 weeks of gestation is associated with higher maternal BMI rather than glycemic control (45). Furthermore, a prepregnancy BMI >30 kg/m^2 was an independent risk factor for LGA neonates in women with either type 1 or type 2 diabetes in pregnancy (46). The relationship between maternal body weight and fetal overgrowth appears to be linear because the likelihood of neonates being born with a ponderal index (birth weight in grams per length in cubic centimeters) >90th percentile was higher for obese than for overweight women with type 1 diabetes (42). Similarly, higher prepregnancy BMI compounded poor maternal glycemic control to increase the risk of neonatal LGA, yet the interaction among maternal BMI, hyperglycemia, and fetal overgrowth is restricted to women with a BMI >23 kg/m^2 (47).

Gestational Weight Gain

In addition to the trend toward overweight and obesity, gestational weight gain is increasing in women with type 1 diabetes (1). The Institute of Medicine gestational weight gain guidelines recommend the optimal targets for weight gain in pregnancy on the basis of prepregnancy BMI and further categorize weight gain as insufficient, appropriate, or excessive (48). As is the case in pregnancies not complicated by diabetes, excessive gestational weight gain in type 1 diabetes heightens the risk of macrosomia (49). Although women with type 1 diabetes who become pregnant at a greater body weight or gain excessive weight in pregnancy tend to have a higher HbA_{1c} (47,50), the relationship between accelerated fetal growth and excess gestational weight gain in type 1 diabetes remains significant after controlling for glycemia (51) and adjustment for prepregnancy BMI in pre-GDM (51,52). In addition, no difference in prepregnancy BMI has been found between women with type 1 diabetes who did or did not have LGA neonates, yet excessive gestational weight gain and HbA_{1c} in the first and third trimesters were independent predictors of LGA (53). Excessive gestational weight gain also may be a risk factor for asymmetrical fetal growth in women with type 1 diabetes because for every 1-lb increase in maternal weight during gestation, the likelihood of having an asymmetrically LGA infant (birth weight >90th percentile for gestational age, race, and sex) increases by 4% (54).

Possible Mechanisms

The mechanisms underpinning the contribution of maternal obesity and gestational weight gain to fetal overgrowth in type 1 diabetes in pregnancy have not

been fully determined. Excess maternal weight either before or during pregnancy could compound hyperglycemia through increased insulin resistance. However, weight gain itself is a known significant risk factor for LGA in nondiabetic pregnancy (55), and this association persists in type 1 diabetes in pregnancy, even when tight glycemic control is achieved. In addition, maternal obesity induces insulin resistance in the fetus (56), which has been postulated to contribute toward greater neonatal fat mass (9,55).

Additional nutrients (separate from glucose) crossing the placenta may contribute to excess fetal growth. Fetal hyperinsulinemia has long been recognized to be stimulated by amino acids in addition to glucose and leads to increased fetal adiposity and birth weight (57,58). Moreover, some macrosomic infants born to mothers without diabetes are hyperinsulinemic (55). Excessive gestational weight gain is associated with higher levels of circulating fatty acids (59), and in lean women with type 1 diabetes, fetal weight correlates with plasma amino acid levels (58). Furthermore, a positive relationship between maternal BMI and cord blood amino acid levels has been observed independent of maternal fasting plasma glucose (60). With the increase in obesity in pregnant women with type 1 diabetes, amino acid transfer across the placenta may be greater (61), and fatty acid transfer may be upregulated (as evidenced in obese women with type 2 diabetes [62]) (Fig. 1).

Another potential mediator of fetal weight gain is leptin, a hormone secreted from adipocytes that suppresses appetite. Paradoxically, leptin levels are increased in obese individuals who are thus considered to be leptin resistant, and similarly, obese pregnant women have higher levels of leptin than their lean counterparts (63). Leptin may be a surrogate marker that mirrors an underlying metabolic process responsible for excess fetal growth. In addition, in women with type 1 diabetes, type 2 diabetes, and without diabetes, maternal BMI significantly correlates with fetal leptin levels, as has third trimester HbA_{1c} (in women with pre-GDM alone) (64). Cord blood leptin levels are higher in neonates of women with type 1 diabetes than in women with GDM or without diabetes, and higher leptin levels have been associated with increased birth weight and LGA neonates (65). Furthermore, despite no difference in maternal HbA_{1c} during pregnancy, these infants are more likely to be overweight or obese at 7 years of age (66). Fetal leptin levels also are correlated with fetal IGF-1, a key regulator of fetal growth, and a significant positive association exists between cord blood IGF-1 and neonatal adiposity in pregnant women without diabetes (67).

In summary, in addition to hyperglycemia, weight gain above the recommended rates in pregnancy contributes to excess fetal weight gain and macrosomia, possibly through fetal overnutrition and hyperinsulinemia, together with alterations in adipokine levels. These data suggest that interventions targeting both maternal blood glucose levels and body weight may result in the best environment for the growing fetus, and prepregnancy planning in type 1 diabetes could comprise management of glycemia and weight before pregnancy (1,68), with an ongoing focus on these parameters during gestation. Our review of the evidence for such management strategies is shown in Table 1.

MATERNAL LIPID LEVELS

Fatty acids are an important source of fuel for the growing fetus, particularly in later gestation, and are vital for normal retinal and neural development (69). Consequently, maternal circulating lipid levels increase throughout pregnancy, and the gestational rise in lipids observed for women with type 1 diabetes is similar to that seen in nondiabetic pregnancy (70).

Recently, low HDL levels throughout type 1 diabetic pregnancy were associated with LGA neonates, as were higher triglycerides in the first and third trimesters (71). Of note, these relationships were independent of maternal prepregnancy BMI, gestational weight gain, and HbA_{1c}, suggesting a separate role for lipids in modulating fetal growth. Similarly, Göbl et al. (72) observed that elevated triglycerides and low HDL levels in the third trimester are predictive of LGA neonates in women with pre-GDM. Furthermore, type 1 diabetes has been shown to lead to increased placental triglyceride concentrations and a greater fetal-to-maternal triglyceride ratio, indicating an augmented transfer of lipids across the placenta (73). This finding has been confirmed by microarray analyses demonstrating an upregulation of genes related to lipid pathways in the placentas

Table 1—Modifiable maternal factors and possible management strategies to target individual factors

Modifiable factor	Management strategy	Evidence*
Hyperglycemia	Maintaining HbA_{1c} <6.5% (48 mmol/mol) or <6% (42 mmol/mol), where possible, before and throughout gestation	Strong (3,18). Many studies have demonstrated that lower HbA_{1c} in type 1 diabetes in pregnancy can reduce the incidence of LGA neonates.
GV	Reducing frequent excursions in blood glucose levels	Minimal (18,26,27). Additional prospective clinical studies are required.
Maternal obesity	Losing weight before pregnancy to achieve a BMI <25 kg/m^2	Moderate (42,44). Studies are yet to be carried out in type 1 diabetes in pregnancy.
Gestational weight gain	Minimizing weight gain throughout pregnancy to keep in line with Institute of Medicine guidelines (48)	Moderate (47,49). Studies are yet to be carried out in type 1 diabetes in pregnancy.
Maternal lipid levels	Lowering maternal triglyceride levels through dietary manipulation	Minimal (72,73). Further prospective clinical studies are required.

The aim of reducing the incidence of LGA neonates in type 1 diabetes in pregnancy are outlined. *The evidence is graded as minimal, moderate, or strong, where minimal indicates that supporting literature includes mechanistic or associative studies only, moderate indicates minimal evidence along with evidence in studies outside type 1 diabetes in pregnancy, and strong indicates minimal and moderate evidence as well as direct evidence from studies in type 1 diabetes in pregnancy.

of type 1 diabetic pregnancies, specifically fatty acid uptake and transport (74). Moreover, venous cord blood levels of fatty acids are significantly increased in pregnancies complicated by type 1 diabetes compared with nondiabetic pregnancies (75).

We hypothesize that an enhanced supply of fatty acids to the fetus, in conjunction with fetal hyperinsulinemia, accelerates the incorporation of fatty acids into adipocytes, leading to greater fetal adiposity. Szabo and Szabo (76) were the first to suggest that maternal free fatty acids cross the placenta to the fetal circulation where they are taken up by developing adipocytes, and fatty acids, rather than glucose, are the primary cause of fetal adiposity. In addition, women with an elevated prepregnancy BMI have alterations in placental genes that regulate fatty acid transport, which were suggested to affect fetal metabolism (77) and further underscore the importance of reducing overweight and obesity before pregnancy as well as minimizing gestational weight gain to decrease the availability of circulating lipids and fatty acid transport across the placenta. Interventions to reduce maternal lipid levels may result in lower levels of excess fetal growth; however, a study of a low-cholesterol diet during pregnancy for women without diabetes found no effect on birth weight (78). To our knowledge, no published studies have investigated the effect of a lipid-modulating diet on birth weight outcomes in women with type 1 diabetes in pregnancy; additional work to determine the possible effect of weight loss before pregnancy or a diet lower in triglycerides on fetal overgrowth may be warranted.

CONCLUSIONS

The management of type 1 diabetes in pregnancy centers on insulin therapy to maintain tight glycemic control and achieve HbA_{1c} levels close to the normal range. Minimizing hyperglycemia reduces the risk of fetal abnormalities and adverse perinatal outcomes, yet disappointingly does not always ameliorate excess fetal growth. This has short-term consequences for mothers and babies as well as long-term implications for adverse metabolic health in future life. Evidence derived from CGM suggests that acute glycemic fluctuations, in addition to chronic hyperglycemia, may contribute to fetal hyperinsulinemia and accelerated fetal growth; thus, reducing GV could prevent excess fetal weight gain, but large prospective studies are required to confirm this. Moreover, the utility of HbA_{1c} in type 1 diabetes and pregnancy is unclear, and the use of short-term glycemic markers may play a role in identifying women with type 1 diabetes at risk for delivering LGA neonates. Prepregnancy maternal obesity and gestational weight gain in type 1 diabetes exacerbate the effects of maternal hyperglycemia on fetal overgrowth, and more interventional studies are needed to determine whether strategies to reduce weight before pregnancy or minimize gestational weight gain ameliorates the risk of LGA neonates. Furthermore, decreasing maternal triglyceride levels in both early and late pregnancy could lower the transfer of fatty acids across the placenta, thereby reducing fetal overgrowth. Type 1 diabetes in pregnancy should be viewed as a dysregulated metabolic state that requires a multifaceted approach to the management of maternal risk factors. Although obtaining target glucose levels before and during pregnancy remains important, optimal management of type 1 diabetes in pregnancy challenges us to move beyond a glucose-centric approach.

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