Diabetes Mellitus, Obesity, and the Placenta

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THE HEALTH PROBLEM—IS THE PLACENTA INVOLVED?

Obesity and type 2 diabetes mellitus (T2DM) have become escalating global health problems. In 2016 worldwide obesity, defined by a body mass index \( \geq 30 \text{ kg/m}^2 \), had a prevalence of 13.1% among the age group 18+ years compared with 5.3% in 1980.¹ Importantly obesity is a major risk factor for T2DM, hence the number of people with diabetes mellitus, about 90% of whom are T2DM, has risen from 108 million in 1980 to 422 million in 2014. This represents an 8.5% global prevalence of diabetes mellitus among adults over 18 years in 2014.² Projections of the International Diabetes Federation expect this number to increase to about 500 million in 2045.³

Derangements of the maternal glucose-insulin axis as in pregestational (type 1 diabetes mellitus [T1DM] and T2DM) and gestational diabetes mellitus (GDM) and maternal obesity increase the risk of both mother and offspring to develop obesity and T2DM later in life. Thus, an obese pregnant woman or a woman with T1DM, T2DM, or GDM confers a risk for the offspring to become obese and also to later develop T2DM. Female offspring born to such a pregnancy may themselves become pregnant when already overweight or obese, which in turn increases the risks for the

KEYWORDS

- Insulin
- Glucose
- Placental development
- Fetal phenotype
- Sexual dimorphism
- Stress

KEY POINTS

- Maternal metabolic and inflammatory changes in first trimester may alter placental development and determine placental trajectories ultimately contributing to fetal and neonatal phenotype.
- Placental phenotype in diabetes and obesity and molecular responses to environmental perturbation are sexually dimorphic with more plasticity in the placenta of a female fetus.
- The consequences of the manifold placental changes, observed at the end of pregnancy, associated with diabetes and/or obesity on fetal development are unclear. Indeed, they may constitute adaptive responses to the altered maternal-fetal milieu to maintain a homeostatic environment for the fetus.

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next generation. This sequence constitutes a self-perpetuating cycle that contributes to the obesity and T2DM epidemic that we are seeing.\textsuperscript{4,5}

For this reason obesity in the youth is especially alarming. In Europe more than 20% of children are overweight or obese by the age of 10 years.\textsuperscript{6} Epidemiologic evidence demonstrates that being born with excessive adiposity (often described as “macroscopic” or large for gestational age at birth) strongly associates with overweight or obesity in youth, commonly with features of the metabolic syndrome. These associations are independent of ethnicity and genetics and are likely mediated through epigenetic changes,\textsuperscript{7–10} which may be induced by fetal hyperglycemia, hyperinsulinemia, or other metabolic disturbances in fetal development. For example, offspring born to obese women not only store more triglycerides, but also have a greater number of adipocytes by the age of 2 years.\textsuperscript{11} Hence, the evidence suggests that excessive fat deposition in utero resulting in offspring being born with excess capacity for adipose storage contributes to the epidemic of obesity and T2DM. This raises the question of how the placenta, as the nutrient gatekeeper between mother and fetus, contributes to excessive neonatal adiposity.

**EARLY PREGNANCY EVENTS**

Although screening for GDM commonly occurs at gestational weeks 24 to 28, women who are subsequently diagnosed with GDM may be hyperglycemic earlier at weeks 9 to 10.\textsuperscript{12} Moreover, women with pregestational diabetes, especially those with T1DM, are hyperglycemic very early in pregnancy despite marked improvement in the management of glycemia in nonpregnant adults. This distinguishes diabetes from obesity early in pregnancy, because obese pregnant women are normoglycemic and hyperinsulinemic.\textsuperscript{13}

The rate of growth of the placenta is most rapid in the first trimester\textsuperscript{14} and during this period placental tissues are most sensitive to environmental perturbation. Both hyperglycemia and hyperinsulinemia likely contribute to alterations in placental growth.\textsuperscript{15,16} Notably, the early placenta exhibits more plasticity than later in pregnancy, secondary to lower average DNA methylation.\textsuperscript{17} Placental volume (a marker of growth) at around week 11 to 13 is associated with neonatal birth weight category. At the end of the first trimester placentas of neonates born large for gestational age have a greater volume than placentas of neonates born appropriate for gestational age.\textsuperscript{18} Although higher birthweight is a poor indicator of neonatal adiposity, a proportion of large for gestational age neonates may have accumulated excess fat during intrauterine growth. Furthermore, placental volume at week 14 and volume changes between gestational weeks 14 and 17 each correlate with fetal anthropometric parameters, including abdominal circumference, at week 36\textsuperscript{19} (Fig. 1).

Because, in the first trimester, insulin receptors are primarily located at the syncytiotrophoblast surface, elevated insulin levels may directly signal to affect placental growth and metabolism. Interestingly, the area under the insulin curve after an intravenous glucose tolerance test (GTT) performed at 12 to 14 weeks’ gestation, is associated with placental weight at the end of gestation, whereas the area under the insulin curve of a GTT performed before conception or at around week 34 to 36 is not.\textsuperscript{16} This indicates that metabolic events in early gestation influence placental formation, program placental growth, and development, and suggests a role for maternal insulin in these processes. In line with this reasoning, fetal growth, which is related to placental growth and function, is determined by events in early pregnancy.\textsuperscript{20}

We recently proposed a model linking early placental growth and maternal metabolic changes, primarily of the glucose-insulin axis, with excessive fat accumulation...
The mechanism by which glucose/insulin may stimulate early placental growth has remained elusive. It may involve stimulating fusion of cytotrophoblast with syncytiotrophoblast, thereby expanding the trophoblast compartment responsible for nutrient transport to the fetus. Insulin, through activation of syncytiotrophoblast protein kinase B, induces matrix-metalloproteinase 14 (MMP14), an enzyme located on the surface of cytotrophoblasts. MMP14 contributes to the trophoblast fusion process. MMP14 is also upregulated in pregnancies with T1DM, likely induced by maternal insulin levels, as MMP14 levels correlate with the average daily insulin dose, a proxy measure for circulating insulin levels, in the first trimester of these women.

Similar mechanisms expanding the trophoblast compartment may be operative in obese women in whom tumor necrosis factor α (TNF-α) enhances MMP14 levels. Conversely, insulin seems to play a lesser role in obese versus lean women because of trophoblast insulin resistance, which is inferred from a reduced insulin effect on trophoblast gene expression. Hence, exposure to elevated insulin levels in early pregnancy desensitizes insulin signaling pathways in obese women.

Extracellular hyperglycemia activates mitochondrial activity in various cell types and this enhances generation of reactive oxygen species (ROS), therefore, mitochondria and their dysfunction may contribute to placental maladaptation in diabetes and obesity. Several genes regulating mitochondrial metabolism are downregulated in the first trimester trophoblast of obese compared with nonobese women. However, in vitro studies commonly use 21% oxygen, which creates a state of hyperoxia that likely overwhelms cellular antioxidative defense mechanisms. Notably, when first trimester trophoblasts were incubated at lower physiologic oxygen tension, hyperglycemia increased ROS levels, but independent of mitochondrial activity, suggesting nonmitochondrial generation of ROS.

Changes in oxygen tension in the intervillous space are a physiologic response to remodeling of the spiral arteries in decidua and a key driver of early placental development. Any changes in spiral artery remodeling associated with maternal diabetes, obesity, or both, will affect oxygen concentration delivered to the intervillous space,
which in turn induces placental adaptive responses. In pregnancies complicated with T1DM the placenta shows signs of enhanced oxidative stress attributed to altered oxygen tension in the intervillous space. Support for this notion comes from in vitro experiments with isolated primary trophoblasts in which increasing oxygen tension, but not hyperglycemia or TNF-α increased oxidative stress, are markers. However, TNF-α may be harmful by enhancing inflammatory cytokines and chemokines in trophoblasts from early gestation. The consequences of these early placental changes for fetal growth are unclear. Historically, T1DM was accompanied by an early growth delay of the placenta and fetus associated with small for gestational age neonates, owing to problems with implantation and remodeling of the decidual arteries. In recent years, improvement in preconceptional and maternal glycemic control have alleviated these problems. However, neonates born to T1DM pregnancies are still at risk for complications, but not for overgrowth or large for gestational age. An attractive hypothesis that needs testing is that maternal insulin contributes to overgrowth of the fetus resulting in neonates with excessive adiposity.

LATER IN PREGNANCY

The fetus is generally exposed to metabolic alterations before the time of GDM testing. Fetal fat depots are present from week 14 onward, and increased fetal adiposity can be detected as early as gestational weeks 17 to 20, well before the usual time of screening for diagnosis of GDM. This fact emphasizes the important role of the first half of pregnancy (cf. above), and early fetal hyperinsulinemia, as a key driver of lipogenesis, which contributes to large for gestational age neonates.

Fetal hyperglycemia early in gestation, but also elevated fetal concentrations of other insulin secretagogues, such as leucine and arginine, may contribute to stimulating the fetal pancreas at this time. The resulting fetal hyperinsulinemia steepens the maternal-fetal glucose concentration gradient with subsequent increased glucose flux to the fetus, the so-called “fetal glucose steal.” Enhanced transplacental transfer of glucose or insulin secretagogues early in gestation may associate with diabetes, obesity, or both.

AT THE END OF PREGNANCY

Multiple placental changes associated with maternal diabetes, obesity, or both, have been described at the end of pregnancy and extensively reviewed. Some of them are listed in Table 1, which provides a summary of well-established findings.

At present, no framework has been conceptualized describing how any or all of these changes contribute to the excessive fetal fat accumulation characteristic of these pregnancies. We have recently proposed that, alternatively, the placental changes reflect adaptive responses to ultimately protect the fetus from the adverse intrauterine environment. This paradigm shift then assigns the placenta, at least late in pregnancy, the role of an innocent bystander in determining the fetal/neonatal phenotype in pregnancies complicated by pregestational, gestational diabetes, and/or maternal obesity. This concept is supported by data demonstrating that maternal-to-fetal transfer of glucose and fatty acids are not increased in such complicated pregnancies, whereas previously this critical placental function has been regarded as unfavorably altered in conditions of maternal overnutrition, therefore, contributing to neonatal adiposity.

The concept discussed above firmly places the fetal glucose-insulin axis at the center of fetal fat accumulation, which leads to the neonatal phenotype seen in pregnancies...
with maternal diabetes mellitus, obesity, or both. However, there has been an ongoing debate about the potential contribution of maternal lipids in particular fatty acids to the process. Maternal triglycerides are hydrolyzed on the surface of the syncytiotrophoblast by endothelial lipase to release free fatty acids. An increased maternal triglyceride concentration is often associated with diabetes and obesity leading to elevated free fatty acid concentrations on the maternal side of the placenta. These fatty acids are taken up by the syncytiotrophoblast and, after re-esterification, stored as lipid droplets. When there are excessive maternal fatty acids trophoblast storage capacity may be overwhelmed and fatty acids spill over to reach the fetal circulation. The proportion of maternally derived fatty acids in the total fetal fatty acid pool is unknown, but overall transplacental transfer is notably low (2%–3%).

**EFFECTS OF PREVENTIVE MEASURES ON THE PLACENTA**

The conclusion from the evidence presented above is that, in late gestation, the placenta contributes little to determining the neonatal phenotype associated with
Pregnancies complicated by maternal diabetes, obesity, or both. Following on from this interventions to prevent the development of this phenotype will have to concentrate on the mother and have to begin before or as early as possible in pregnancy. Dietary supplementation of mothers with n-3 long-chain polyunsaturated fatty acids did not alter offspring fat at up to 1 year. However, it affected the placental transcriptome in a sexually dimorphic manner with a greater number of transcripts altered by the intervention in placentas of female compared with male fetuses. Many women with GDM are vitamin D deficient, which confers some risk for developing GDM. Dietary supplementation of mothers with n-3 long-chain polyunsaturated fatty acids did not alter offspring fat at up to 1 year. However, it affected the placental transcriptome in a sexually dimorphic manner with a greater number of transcripts altered by the intervention in placentas of female compared with male fetuses. Many women with GDM are vitamin D deficient, which confers some risk for developing GDM. This has led to intervention studies using vitamin D supplementation to prevent GDM and, hopefully, also reduce the accompanying adiposity in the offspring. These trials have, however, not been successful, but may have altered placental function in several ways given the broad range of vitamin D effects on the placenta. Analysis of placental samples from women undergoing this intervention may provide useful information about potential compensatory mechanisms, which may have precluded a beneficial intervention effect on the fetus and neonate.
A lifestyle intervention that reduced sedentary behavior in pregnant obese women has been shown to successfully reduce neonatal adiposity. Although the effects of physical activity on the placenta have been documented, the role of reducing sedentary behavior for placental development and function has not yet been studied.

AREAS FOR FUTURE RESEARCH

Despite enormous research efforts, a large number of gaps still limit our understanding of the effects of maternal metabolic derangements on placental development and function and the consequences for the growing fetus. Therefore, future research should focus on closing some of these gaps to improve our understanding to ultimately allow establishment of conceptualized frameworks for the dialog between mother, placenta, and fetus in these pregnancies. Listed below are some areas of research priorities we have identified. They agree with published suggestions in this field, but the selection is of course biased.

- How is first trimester placental development and function affected by metabolic changes and the inflammatory environment associated with maternal adiposity/obesity, pregestational diabetes, or hyperglycemia short of a GDM diagnosis?
- How do these placental changes track throughout pregnancy and how do they determine fetal growth and development and neonatal outcome?
- GDM is a heterogeneous condition characterized not only by changes in insulin resistance, insulin secretory defects, or a combination of the 2, but also by other metabolic changes. Likewise, obesity is not a homogeneous entity, because a subgroup of obese women is regarded metabolically healthy, that is with normal metabolism. Future research will have to use a more detailed phenotypic characterization of women to define subtypes of placental responses to these conditions.
- Sexual dimorphism in the placental transcriptome has been well established at the whole tissue and cellular level and may explain some of the sex dependency of changes in maternal diabetes and obesity. However, much less is known about the structural and functional consequences of these differences in gene expression. Their further characterization will help understand (1) how evolutionary pressure has facilitated development of placental phenotypes and (2) how the placenta may contribute to programming offspring phenotype and subsequent sex-dependent developmental changes in childhood.
- Although much research has focused on studying placental response to maternal changes, little efforts have been made to describe the placental contribution to the maternal metabolic and inflammatory responses. We proposed a bidirectional interaction with maternal signals affecting placental development and function, especially in early pregnancy, and that these placental changes then feed back to the maternal system through placental-specific signals. These signals may include hormones, such as placenta-specific growth hormone, chorionic gonadotropin, placental lactogens, and others, as well as placentally derived microvesicles, which may all contribute to maternal adaptation to pregnancy.
- Enhanced fat accretion in the fetus may result from increased transplacental fatty acid transfer. However, the fetus is capable of de novo fatty acid synthesis using glucose as precursor and indeed an overabundance of fetal glucose is present in pregnancies with maternal diabetes, obesity, or both. The contribution of maternally derived fatty acids to fetal fat accretion is unclear, but is thought to be small based on its limited transfer and the further reduction of free fatty acid transfer in...
GDM and obesity.\textsuperscript{50,51} Although oxidative stress and mitochondrial function in the placenta has been well studied, endoplasmic reticulum stress has not received the same attention. Lipotoxicity was demonstrated in the placenta in maternal obesity,\textsuperscript{77,78} but its consequences for placental function remain unknown.\textsuperscript{79}

- The fetus in diabetic pregnancy is often low in oxygen, as reflected by increased red blood cell count and cord blood erythropoietin. How metabolic changes in the placenta affect partitioning of oxygen is unclear. In addition, transplacental iron transfer may be altered to facilitate fetal generation of the various fetal hemoglobins, but details and regulatory mechanisms are unknown.

- Placental microvesicles are secreted into the fetal circulation, but their role is unknown.\textsuperscript{80,81} They may constitute important signals targeting various fetal organs and thus contribute to phenotypic and functional changes, which may emerge only in the neonatal period and thereafter.

- A further important area of future research will include deciphering the role of the placenta, if any, in determining offspring phenotype in childhood. The association of placenta alkaline phosphatase with adiposity in children at the age of 4 and 6 to 7 years\textsuperscript{82} suggests such a role, but future efforts will need to demonstrate causality and unravel underlying mechanisms.

Collectively, while an enormous amount of data has been accumulated over the past 70 years related to the placenta and fetus in the setting of maternal diabetes mellitus and obesity, we are far from understanding the role of the placenta in determining the immediate, but even more so the long-term consequences of these conditions for the mother and, predominantly, for the offspring.

DISCLOSURE

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