Placental Transfer of Maternal Obesity: Identifying the Gatekeeper

Jennifer J. Adibi[1,2] and Yaqi Zhao[1]

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261; and [2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania 15261

The trend is undeniable by which the prevalence and dosage of lipid exposures are rising within the fetal environment. Approximately one-third of women of reproductive age were obese, as defined by a body mass index $\geq$30 kg/m^2, in 2014. Every year, there is a steady 2% increase in this estimate (1). At some point, maternal adiposity is no longer an exposure but an evolutionary force that has implications for the future of the species (2).

In the shorter time framework, maternal obesity in pregnancy is a risk factor for adverse outcomes that include hypertension, preeclampsia, gestational diabetes, large for gestational age (>90th percentile at birth), miscarriage and stillbirth, delayed and complicated labor, and even a higher risk of some neural tube defects (1). It is not clear if these effects are explained by direct lipotoxicity vs a more intelligent mechanism that involves an interplay of maternal, placental, and fetal physiology. Understanding the common underpinnings will help to unify the diverse strains of mechanistic and health outcome research.

Given the necessity of fat as a source of energy and nutrition for brain growth and reproduction, it is not intuitive that fat would also be directly toxic to fetal cells. Alas, in high doses fat is toxic and can directly damage fetal organs (3). Fat can also induce inflammation in the placenta (4). Another idea in maternal obesity research is that the fetus does not experience lipotoxicity directly but senses maternal fat indirectly and alters its own developmental program accordingly (5, 6). According to the Predictive Adaptive Theory, these adaptations are beneficial to the fetus if the *in utero* and *ex utero* environments match. In obesogenic environments, such as the United States, they are mismatched due to the endless supply of calories. Offspring of obese women unfortunately do not have the ability to recalibrate after birth and suffer from poor outcomes, including diabetes, obesity, cardiovascular disease, subfertility, and behavioral issues (V. Calabuig-Navarro, personal communication, April 2017). Hence, examples in modern human history where excess maternal lipids confer an advantage have not been identified.

In this issue of *Endocrinology*, Calabuig-Navarro *et al.* (7) lay out potential fates for maternal lipids, rigorously and comprehensively addressing the role of the placenta. The placenta is a fetal organ that physically buffers the fetus from the maternal environment. It may also be the intelligent mechanism that reconciles the interests of the fetus with the reality of the maternal environment. In this article, the authors describe four physiologic pathways for maternal lipids involving the placenta: (1) They can be esterified and stored in placental tissue, (2) they can undergo β-oxidation in the mitochondria (a cellular organelle responsible for energy production), (3) they can undergo β-oxidation in the peroxisome (a cellular organelle that shortens the long-chain fatty acids before sending them to the mitochondria), and/or (4) they can be transferred to the fetus.

The authors measured a complex cascade of endpoints (Table 1) to understand the role of the placenta in mediating the effects of maternal obesity on neonatal adiposity. The study design was observational and restricted to the end of pregnancy when fetal programming and growth are close to complete. Early pregnancy biologic samples were not available. The authors overcame this limitation partially by isolating viable trophoblasts from a separate, but analogous, cohort to conduct *in vitro* tests of maternal obesity–related differences in lipid esterification and to

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Table 1. A Cascade of Measures in Pregnant Women/Neonate/Placenta Triads To Understand the Role of the Placenta in Mediating the Effects of Maternal Obesity on the Neonate

Temporal sequence	Construct	Measure
1	Maternal pre-pregnancy characteristics	Age,[a] race,[a] parity[a]
2	Maternal adiposity (obese vs nonobese)	Body mass index below or above 30 kg/m^2
3	Maternal physiologic response to pregnancy	Weight gain, plasma glucose, plasma insulin, plasma homeostatic model assessment-insulin resistance, plasma free fatty acids
4	Fetal-placental sex	Sex of baby at birth[a,b]
5	Placental function (*in vivo*, *in vitro*)	Tissue content of lipids, placental tissue and mitochondrial messenger RNAs, membrane lipids, number of mitochondria, *in vitro* measures of fatty acid esterification and oxidation, placental weight at birth
6	Maternal-placental-fetal exchange via cord blood	Insulin, glucose, homeostatic model assessment-insulin resistance, free fatty acids, carnitine, acylcarnitine (lipid oxidation intermediates)
7	Neonatal adiposity	Birthweight, length, lean body mass, fat mass, percentage fat

[a]Evaluated as a potential confounder.

[b]Evaluated as a potential effect modifier.

compare the effects of lipids on mitochondrial vs peroxisomal fatty acid oxidation capacity.

Judging by the timing of labor and birth size, overall placental function was comparable between the obese and lean mothers. The differences played out at the molecular and cellular levels. The obese women had 17% higher lipid content in their placental tissue at birth. Obesity was associated with higher lipid esterification and storage as compared with women of normal weight. This was most strongly demonstrated by significantly lower concentrations of long-chain fatty acids and lipid oxidation intermediates in the placentas of obese women. Mitochondrial function was lower in the obese women, which was compensated for by an increase in peroxisome fatty acid oxidation. These cross-sectional findings were confirmed by the behavior of the isolated trophoblasts cultured *in vitro*.

In a clinical trial in which this same group of investigators randomized obese pregnant women to long-chain fatty acid supplements, the converse effect was observed (8). They effectively lowered placental lipid content and esterification, tipping the long-chain fatty acid transfer equation in the favor of the fetus—another sign of placental intelligence.

The placentas in this study buffered the lipid environment of the mother, minimizing lipotoxicity to the fetus. After adjusting for maternal factors and weight gain in pregnancy, the fat-free mass was slightly higher in the babies born to obese mothers. In all babies taken together, placental lipids explained 8% of the variability in the neonatal fat mass. The effect was in the negative direction, suggesting that the placenta possibly overcorrected.

The magnitude of the differences reported in this study was generally small, and fetal sex differences in these placental functions were not detected. The ability of the species to reproduce is not impeded to a large degree in the face of maternal obesity. The potentially more impactful issues, which this research points to, are changes taking place at the level of mitochondrial function, insulin sensitivity in the neonate, and availability of essential building blocks.

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Address all correspondence and requests for reprints to: Jennifer J. Adibi, ScD, 130 Desoto Street, Parran Hall 5132, Pittsburgh, Pennsylvania 15261. E-mail: adibij@pitt.edu.

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