MINI-REVIEW
Diabesity 2022, Volume 0, Number 0: 00-00

Trophoblast Changes in Maternal Obesity

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ABSTRACT

Maternal obesity has become a common metabolic dysfunction among reproductive age women affecting at least 1 in 5 women. Pregnancy complicated with maternal obesity is associated with adverse outcomes to both mother and the fetus. Maternal obesity increases the risk of adverse pregnancy outcome including preeclampsia, fetal growth restriction and overgrowth and stillbirth. Recent studies show that children born to obese mother have increased adiposity and are vulnerable to develop metabolic syndromes later in their life. Placenta, which plays an important part during pregnancy and fetal development has become a major research focus of scientists around the world for its impact on fetal health. Increased evidence suggest that a maternal obesogenic environment influences placental normal function and in turn programs the developing fetus towards adverse health outcomes in adult life. Here, we briefly discuss how maternal obesogenic environment impacts placental functions and influence child health later in life.

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Acknowledgement
The project described was supported by Revision Award from Agriculture Research Division, Institute of Agriculture Natural Resources, Nebraska Center for Prevention of Obesity Diseases, the National Institute of General Medical Sciences Grant (P20GM104320 to SKN) and the University of Nebraska-Lincoln. The contents of this manuscript are solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

1. Introduction

Obesity is a chronic metabolic dysfunction, consequent of excessive accumulation of fat and presents itself as a health hazard over time[1]. According to world health organization, individuals with a body mass index (BMI) over 25 kg/m^2 are defined as overweight and a BMI over 30 kg/m^2 are considered obese. Globally, the prevalence of obesity among children and adults between the ages of 5-19 has increased from 4% in 1975 to 18% in 2016. By 2016, close to 1.9 billion adults worldwide were overweight, among which 650 million were obese[2,3]. While the exact etiology behind overweight or obesity is not fully understood, a complex interplay of individual biology, genetics and environmental factors have been attributed to a chronic state of positive energy balance and obesity development[4]. Chronic overweight or obesity has been positively associated with increased risk for the future development of metabolic complications including type 2 diabetes, cardiovascular diseases, osteoarthritis, liver and kidney dysfunctions and also some forms of cancer[5].

2. Maternal Obesity

Since the incidence of obesity has increased worldwide in the last few decades, it is not surprising that there is an increased predominance of obesity among women of reproductive age. Maternal obesity has become a serious obstetric health challenge in developed and developing countries and its prevalence is influenced according to region and ethnicity[6]. Obesity during pregnancy has been linked with elevated risk of developing obstetric complications like gestational diabetes, hypertension, pre-eclampsia, postpartum hemorrhage, stillbirth, and fetal growth restriction[7]. Additionally, maternal obesity can have considerable impact on fetal health through in utero programming and have been shown to influence child health status even after birth and later in life[8]. Many studies have positively corelated increased maternal BMI with greater adiposity and increased inflammatory cytokines in neonates and elevated risks of developing type 2 diabetes, coronary heart diseases and obesity during child- and adulthood[9-12]. Thus, pregnancy complicated by obesity has become a daunting health crisis with a significant impact on the health of next generation.

Placenta plays an important role in establishing a successful pregnancy, and as such ensuing a successful pregnancy and proper fetal development is very much dependent on placental functions. The dual nature of placenta makes it a barrier and a bridge between the mother and developing fetus. Placenta controls the flow of nutrients, hormones, growth factors, cytokines, inflammatory mediators and mediates oxygen exchange[13]. As such ensuring a successful pregnancy and adequate fetal development is very much dependent on the proper placental functions. Although the exact mechanism connecting maternal obesity and adverse fetal outcome remains elusive, the role of placenta is unmistakable. Here, we will focus on how maternal obesity induce placental structural and functional alterations and influence offspring health *in utero* and later in life.

3. The Human Placenta

Early in pregnancy, after the implantation,

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blastocyst differentiates into inner cell mass (giving rise to fetus proper) and trophectoderm, which develops into trophoblast and placental tissue[14]. Placenta acts as vascular interface between maternal and fetal circulatory systems and is composed of multiple cell types, of which trophoblasts are major type. Extravillous trophoblasts carry out remodeling of uterine vasculature, a crucial step in successful pregnancy establishment, by invading maternal spiral artery and replacing resident endothelial and smooth muscle cells, a process known as trophoblast invasion[15]. The remodeling of intrauterine vasculature results in low resistance and high capacitance spiral arteries, making it suitable for nutrient transport between the mother and developing embryo, thus ensuring proper fetal growth[16]. Many obstetric complications including pre-eclampsia, fetal growth restriction develop due to changes in placental architecture as result of inadequate trophoblast invasion. Maternal obesity is characterized by changes in the circulating levels of nutrients, growth factors, hormones, inflammatory mediators; all of which support placental growth during first few weeks of pregnancy. It is likely that, changes in these soluble mediators in an obesogenic environment could potentially affect placental structure and functions and program the developing fetus towards future adverse health outcomes. Described below are specific placental functions and its changes in maternal obesity.

3.1. Alterations in placental metabolism and hormonal regulation during obesity

A characteristic feature of normal pregnancy is increased glucose metabolism to promote placental and fetal growth and increased insulin release[17]. Obese pregnant women have been shown to have 50-60% higher post-prandial insulin compared to pregnant women of normal weight[18]. A study conducted by Catalano et al. found children born to obese mothers had greater percentage of body fat and were insulin resistant in comparison to children born to lean women[9]. Hyperinsulinemia during maternal obesity activates placental glucose and amino acid transporters, thereby enriching placental insulin and mammalian Target of Rapamycin (mTOR) activity, which could possibly contribute to increased placental growth, enhanced fetal nutrient delivery, and accelerated fetal growth[19, 20].

Another common feature of maternal obesity is hyperlipidemia. The effect of fatty acids primarily relies on the chain length and their saturation levels. For example, obesity associated physiologic levels of palmitic (16:0) and stearic acid (18:0) induces apoptotic cell death in trophoblasts, while oleic acid (18:1) not only stimulates mTOR signaling and amino acid uptake but protects against palmitic and stearic acid induced trophoblast death in cultured human primary trophoblasts and trophoblast cell lines[21,22]. These so called lipotoxic saturated fatty acids have been shown to reduce invasiveness of trophoblast *in-vitro* by inducing autophagic defects while unsaturated fatty acids protect against the effects of saturated fatty acids[23]. Multiple placental omics studies have revealed enrichment of lipid metabolic pathways in pregnancies complicated by maternal obesity. Transcriptomic analysis of term placenta from obese women is associated with decreased expression of unique lipid metabolic transcripts and increased expression of lipid-droplet associated proteins[24-26].

Maternal obesity has also been reported to be associated with low adiponectin, elevated leptin and increased concentration of insulin-like growth factor 1 (IGF-1) levels in plasma, possibly influencing placental development and fetal growth. In a mouse model of maternal obesity during pregnancy, low levels of maternal adiponectin, increased placental insulin signaling, nutrient transfer and fetal growth were observed [27]. Similarly, elevated maternal leptin levels in obese pregnant women are shown to be positively corelated with fetal insulin resistance[9]. Further, increased IGF-1 during maternal obesity is a known promoter of trophoblast proliferation and increases glucose and amino acid uptake in primary trophoblast cells and trophoblast cell lines and could positively impact placental growth and fetal overweight[28-30].

3.2. Obesity associated changes in placental pro- and anti-inflammatory cytokines

Obesity has often been associated with chronic low-grade inflammation. During normal pregnancy, levels of most cytokines in maternal circulation increases across pregnancy due to placental cytokine secretion[31]. Accumulated evidence from many studies report, maternal obesity further increases the circulating levels of pro-inflammatory cytokine such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, and C-reactive protein[32-34]. A study by Radaelli et al. showed a positive correlation between increased IL-6 and fetal adiposity[35]. Studies on cultured trophoblast show TNF-α and IL-6 alter placental functions involving lipid and amino acid transport and cellular metabolism,

potentially impacting placental function during obesity[36]. Moreover, maternal obesity has been shown to activate Signal Transducer and Activator Of Transcription 3 (STAT3) and p38 mitogen activated protein kinase mediated inflammatory pathways in placenta[37,39]. Although the role of placental inflammation induced changes in trophoblast function has been established, the exact mechanisms linking inflammatory mediator to placental dysfunction and fetal health during maternal obesity remain elusive.

3.3. Altered placental signaling during maternal obesity

As described above, maternal obesity induces changes in the levels of growth hormones, soluble mediators, cytokines and nutrient in maternal circulation. Increased levels of these factors are believed to impact intracellular signaling pathways modulating overall placental functions. For example, obese placenta show enrichment of insulin/IGF, PPARγ and RXR signaling and reduced AMPK activity resulting in altered fatty acid and glucose metabolism, nutrient transport to fetus and trophoblast invasion[39,40].

3.4. Oxidative stress in maternal obesity

Individuals with obesity often have higher levels of reactive oxygen species (ROS) compared to non-obese individuals and show signs of oxidative stress. Similarly, maternal obesity has been associated with increased levels of ROS in the placenta along with increased levels of malonaldehyde, nitric oxide, carbonylated proteins, superoxide and low glutathione concentration suggesting an oxidative stress [41]. Oxidative stress in the placenta is postulated to be due to the increased metabolism of glucose and fatty acids. Further, maternal obesity is complemented with increased glutathione concentration and superoxide dismutase activity, possibly leading to impaired mitochondrial function and lower ATP production with placental damage[42]. Additionally, higher levels of maternal lipids and placental ROS combined with dysfunctional mitochondria could result in increased production of oxidized lipids including lipid peroxides, oxidized cholesterols and lipoproteins and may affect normal trophoblast functions.

3.5. Altered placental nutrient transport in maternal obesity

There is evidence which suggest a key determinant of placental and fetal overgrowth during maternal obesity is enrichment of transporters for glucose, fatty acids and amino acids in the placenta of obese women. GLUT1, which mediate glucose uptake in placenta is shown to be enriched in obese mothers[43]. System A transporter, which is a major amino acid transporter, is positively corelated with increased birth weight in a cohort of normal and obese mothers[39]. Similarly, placental taurine transporter activity has been shown to be negatively associated with maternal obesity[7]. Moreover, maternal obesity has been shown to be associated with differential expression of fatty acid transporters. Fatty acid receptors like FATP1 and FATP4 are decreased, while upregulation of FATP6 and FAT/CD36 has been observed in the placenta from obese mother compared to lean mother[44]. Further research is needed to fully understand the factors which regulate placental fatty acid transporters expression under normal and obesogenic environment.

Conclusion

Maternal obesity has become a serious health concern over the years with significant challenges to maternal and neonatal health and later life metabolic complications. Increasing evidence supports the belief that altered placental function resulting from altered maternal physiology during obesity increases the risk of disease like obesity, diabetes, and cardiovascular complication in adult life. Newer studies have provided with evidence that placenta influences fetal brain development and adverse neurodevelopmental etiology in obstetric complications[45]. Thus, understanding placental functions under normal and pathological conditions could provide with much needed boost to underpin the molecular mechanism of developmental programming and help prevent adverse health outcomes in adult life.

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