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Editorial

Legacy of Maternal Obesity

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Abstract

Maternal obesity and consumption of high-fat diet can influence fetal development and growth. Placental inflammation leads to molecular alterations in different tissues in the off spring. Hypothalamic tissues can show early changes in the expression of neuropeptides, which contribute to damages in metabolic control and energy homeostasis. Inflammation of the placenta can affect orexigenic/anorexigenic neuropeptides, reward system, and energy expenditure, which in turn contribute to obesity and diabetes in the offspring. These changes can be caused by epigenetic mechanisms and can be passed on from the mother to the offspring.

Introduction

Obesity constitutes a growing health problem throughout the world. Prevalence of obesity in women of child bearing age [1] and in children is worrying because both increase the risk of metabolic diseases in the later life of the offspring. Human and animal studies have shown that changes in early life can have deleterious effects in adult life. These findings have increased the interest in the effects of maternal obesity on disease risk in the offspring [2-4].

The effect of maternal over nutrition during fetal development increases the risk of diseases in the offspring during its adult life. Different types of stress during critical periods of early development permanently alter an organism's physiology and metabolism. This phenomenon is called metabolic programming and has originated from fetal hypothesis proposed by Barker [5].

However, some important questions need to be answered regarding metabolic imprinting. These include understanding the role of gestation and lactation in the ill outcomes observed in the offspring and whether maternal obesity or High-Fat Diet (HFD) consumption during gestation and/or lactation could affect differently fetal development and result in metabolic damage in the offspring. Most studies have used animal models in which obesity is induced by feeding HFD during gestation and/or lactation. Therefore, it is impossible to establish the direct relation between metabolic damage in the offspring and maternal obesity and HFD consumption during pregnancy. However, despite the difficulty in the interpretation of results from these models, most studies have shown damages in different metabolic pathways and tissues. Maternal obesity and HFD consumption are associated with fatty liver [6,7] micro RNA expression modulation [8,9], insulin resistance [6,10], and cognitive disruption [11,12].

Hypothalamic tissue controls food intake, energy expenditure, reward system, and peripheral metabolism. Molecular changes in fetal and adult hypothalamus are related to maternal HFD consumption during pregnancy. Gupta and colleagues [13] showed increased mRNA levels of proopiomelanocortin, melanocortin receptor-4, neuropeptide Y, and agouti-related polypeptide in fetal hypothalamus from rats [13]. Up regulation of the orexigenic system can increase food intake and body weight. For example, increased expression of orexigenic neuropeptides in the postnatal period can induce high intake of milk during breastfeeding, thus contributing to excessive weight gain. Moreover, in mice, perinatal exposure to HFD can produce a more deleterious response to HFD challenge in later life even after an interval of normal diet in mice [14], suggesting permanent molecular alterations. Epigenetic modifications in DNA can result in permanent changes in the expression profile of genes related to metabolism and energy homeostasis.

Epigenetic modifications have been described in genes associated with reward, which can affect preference for palatable foods [15]. Expression of both μ-opioid receptor and preproenkephalin was increased in the nucleus accumbens, prefrontal cortex, and hypothalamus of mice born to dams that consumed HFD [15]. Moreover, mice born to HFD–fed dams during pregnancy and lactation showed hypomethylation in the dopamine reuptake transporter promoter region, μ-opioid receptor, and preproenkephalin. Reduced methylation of CpG in the promoter region permits the binding of a transcription factor to DNA and increases gene expression.

Maternal obesity and HFD consumption during pregnancy and/or lactation alter the levels of hormones (leptin and insulin), nutrients (fatty acids and glucose), and inflammatory cytokines [6,16] in the blood. This can affect the environment of the developing offspring. Some authors have shown proinflammatory components in the placenta of humans [17], rats [18], and sheep [19] in response to HFD consumption and obesity. However, uterine changes and embryonic inflammation precedes placentation. A study has shown that in rats, gene expression in the blastocyst at 4.5 days postcoitum is clearly influenced by maternal obesity. The same study has shown that placental inflammation increases due to the accumulation of ectopic lipids and expression of lipid metabolic genes in the uterus [18]. In contrast, a recent study has shown that obese dams show macrophage infiltration in the adipose tissue and liver but reversal of obesity-induced inflammation during gestation [20].

Initially, these findings may seem contradictory. However, pregnancy induces metabolic changes in the mother to ensure passage of nutrients to the fetus; therefore, reducing the availability of fatty acids and glucose in the maternal adipose tissue. HFD consumption during pregnancy increases placental transport of amino acids, glucose, and fatty acids [21], thus contributing to proinflammatory

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environment and ectopic lipid accumulation. Saturated fatty acids can activate toll-like receptor 4 (TLR4) and stimulate cytokine expression. Cotyledonary tissue obtained from obese pregnant mothers showed increased expression of TLR4 and macrophage markers (CD11b, CD14 and CD68) [19]. Larger and colleagues [22] have shown that high levels of IL-6 stimulate fatty acid accumulation in human primary trophoblast cells. This can contribute to excessive nutrient transfer in conditions associated with elevated maternal IL-6, such as obesity and gestational diabetes [22]. Although the precise mechanism is unknown, a recent study has shown that palmitic acid-mediated placental inflammation in human placenta choriocarcinoma cell line requires JNK signaling and recruitment of early growth response protein-1 (EGR-1) on cytokine promoters [23].

Although controversial, increased lipid circulation seems to be a mediator of fetal programming [24-26]. Epigenetic modifications (histone acetylation and methylation) and altered expression of enzymes that regulate histone and DNA methylation in the placenta have been observed in the off springs of dams who are fed HFD during pregnancy [26,27]. Monitoring of maternal blood lipid profile during gestation and breast milk composition during lactation is important to avoid permanent changes in the fetus that are caused by placental inflammation because gestational and lactational periods are important for neurogenesis and neuronal plasticity.

In summary monitoring of maternal nutrition and weight gain during the perinatal period is important to prevent metabolic disorders in the offspring. Furthermore, this paves a way for research in appropriate nutrition of obese mothers to prevent placental inflammation and metabolic complications in the offspring.

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