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REVIEW ARTICLE

Maternal Obesity: Lifelong Metabolic Outcomes for Offspring from Poor Developmental Trajectories During the Perinatal Period

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The prevalence of obesity in women of reproductive age is increasing in developed and developing countries around the world. Human and animal studies indicate that maternal obesity adversely impacts both maternal health and offspring phenotype, predisposing them to chronic diseases later in life including obesity, dyslipidemia, type 2 diabetes mellitus, and hypertension. Several mechanisms act together to produce these adverse health effects including programming of hypothalamic appetite-regulating centers, increasing maternal, fetal and offspring glucocorticoid production, changes in maternal metabolism and increasing maternal oxidative stress. Effective interventions during human pregnancy are needed to prevent both maternal and offspring metabolic dysfunction due to maternal obesity. This review addresses the relationship between maternal obesity and its negative impact on offspring development and presents some maternal intervention studies that propose strategies to prevent adverse offspring metabolic outcomes.

Key Words: Developmental programming, Dietary intervention, Fetal programming, Maternal obesity, Metabolic syndrome, Offspring phenotype.

Introduction

Obesity rates have increased exponentially worldwide to almost epidemic proportions (1−3). The World Health Organization (WHO) has declared obesity as one of the top ten adverse health risk conditions in the world. Worldwide, 1.5 billion people are either overweight with a body mass index (BMI) >25 kg/m^2 or obese (BMI >30 kg/m^2) (3). The recent rise in obesity rates is associated with the interaction between genes, physical activity and changes in dietary habits (4) including augmented consumption of foods that are either industrial processed or dense in energy (5).

Obesity and overweight are prevalent in women of reproductive age (6−12). In Mexico the predominance is 32.4% (6,8), in the United States 35.5% (10), in Brazil 16.1% (9), in the United Kingdom 33% (11), in Ghana 37.1% (7) and in China 16% (12). Maternal obesity can result in negative metabolic disorders for both the mother (13,14) and the offspring (Figure 1) (13,15−17). The link between maternal obesity and adverse offspring health consequences are complex and likely involves alterations in glucose and lipid metabolism as well as altered leptin levels in obese women (18−20). This review will focus on metabolic aspects of maternal obesity and the effect on their offspring and how modifications of maternal lifestyle can improve maternal and fetal outcomes.

Glucose and Lipid Metabolism During Pregnancy

During pregnancy the mother adapts her metabolism to support fetal growth and development (20−22). Such adaptations are divided in two metabolic stages. Stage one includes the first two thirds of pregnancy where a predominantly anabolic condition is observed in which insulin secretion allows maternal body fat accumulation (20−23) as seen in pregnant women (24) and rats (25,26). During late gestation (second stage), the catabolic metabolism (20−22,27) is characterized by an insulin resistance state to direct maternal energy to the fetus (21,28,29). Therefore,

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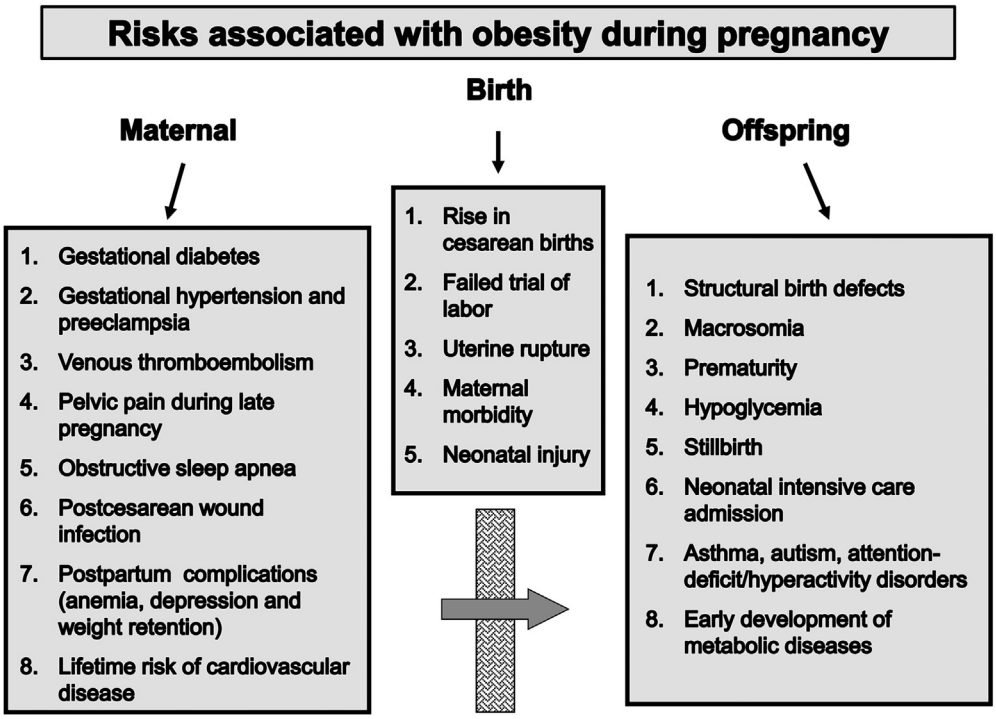

Figure 1. Maternal and offspring risks associated with obesity during pregnancy.

maternal energy reserves stored during the first trimester of pregnancy play an important role in the maternal metabolic adaptations that permit her to fulfill fetal demands in late pregnancy (21,22,30).

Glucose is the most important fetal energy substrate (21,22,28). The fetus uses >50% of the total maternal glucose turnover (31,32). Maternal hypoglycemia observed during late pregnancy is the consequence of improved glucose utilization by the placenta and fetus. The constant glucose supply depends on increased maternal hepatic gluconeogenesis (21,33) which, in late gestation, depends on the type of the substrate; for example, glycerol is metabolized faster than alanine (34, 35).

Regarding maternal lipid metabolism, body fat accumulation during the first part of gestation is due to hyperphagia (21), increased lipogenesis (27,36) and decreased hepatic lipoprotein lipase (LPL) activity (37). During late pregnancy, there is a reduced uptake of circulating triglycerides (38) and increased adipose tissue lipolysis. Glycerol and free fatty acids are released into the circulation and captured by the liver (Figure 2A) (21,36,39). They are then converted into their active forms, acyl-CoA and glycerol-3-phosphate, respectively, so they can be re-esterified and synthesized into triglycerides released into circulation (21,22,38,39), increasing maternal plasmatic very-low-density lipoproteins (VLDL) at the highest concentrations (40). In addition to increased lipolysis and decreased LPL activity, the increase in estrogens concentration (39) and insulin resistance state (41) may also contribute to the increased VLDL-triglyceride levels during pregnancy (Figure 2A). Under fasting conditions glycerol is used for glucose synthesis and free fatty acids are metabolized in the liver by β-oxidation of acetyl-CoA and ketone bodies (21,35). Ketone bodies are important alternative energy substrates for the fetal brain because lipids are not readily transported across the placenta (21,36,39).

Long-chain polyunsaturated fatty acids (LC-PUFAs) are important to the fetus. However, due to the limited capacity of the fetus to modify the structure of essential LC-PUFAs, their long-chain derivatives have to be transferred from the mother to the fetus through the lipoprotein receptors and fatty acid binding proteins in the placenta in appropriate amounts to enable normal fetal development, especially of the eyes and nervous system (42).

Effect of Maternal Obesity on Fuel Metabolism During Pregnancy

Obese women have higher energy supplies and metabolic rates during pregnancy than non-obese women (43). The physiological insulin resistance observed in late normal pregnancy is magnified in pregnant women with obesity and diabetes (20,44). These condition expose the fetus to exaggerated levels of metabolic fuels such as glucose and lipids (Figure 2B) (20,45–47). A recent study shows that high glucose levels diminish placental mitochondrial