Molecular and Cellular Endocrinology 435 (2016) 7–19

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Persistent influence of maternal obesity on offspring health: Mechanisms from animal models and clinical studies

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ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form
30 June 2016
Accepted 1 July 2016
Available online 5 July 2016

Keywords:
Maternal obesity
Development programming
Epigenetics
Metabolism

ABSTRACT

The consequences of excessive maternal weight and adiposity at conception for the offspring are now well recognized. Maternal obesity increases the risk of overweight and obesity even in children born with appropriate-for-gestational age (AGA) birth weights. Studies in animal models have employed both caloric excess and manipulation of macronutrients (especially high-fat) to mimic hypercaloric intake present in obesity. Findings from these studies show transmission of susceptibility to obesity, metabolic dysfunction, alterations in glucose homeostasis, hepatic steatosis, skeletal muscle metabolism and neuroendocrine changes in the offspring. This review summarizes the essential literature in this area in both experimental and clinical domains and focuses on the translatable aspects of these experimental studies. Moreover this review highlights emerging mechanisms broadly explaining maternal obesity-associated developmental programming. The roles of early developmental alterations and placental adaptations are also reviewed. Increasing evidence also points to changes in the epigenome and other emerging mechanisms such as alterations in the microbiome that may contribute to persistent changes in the offspring. Finally, we examine potential interventions that have been employed in clinical cohorts.

1. Introduction

The pivotal role of intrauterine experience in shaping the trajectory of health and disease susceptibility in later-life is now widely recognized and has permeated most disciplines of medicine. In the 1980s, Prof. David Barker and his colleagues proposed the 'fetal origins of adult disease' hypothesis in an attempt to explain the relationship between *in utero* growth and adult cardiovascular disease. Barker's initial findings identified a correlation between maternal under-nutrition during gestation and increased offspring cardiovascular disease risk later in life. This concept has burgeoned into what is now recognized broadly as the Developmental Origins of Health and Disease (DoHAD) paradigm to describe how environmental factors broadly during critical periods of development can influence offspring gene expression and phenotypic outcomes and modulate adult health. While many people in the world are faced with undernutrition, the increasing prevalence of overweight and obesity is a growing global health issue with persistent long-term consequences in terms of co-morbidities such as diabetes and metabolic disease. According to the 2013 Global Burden of Disease Study, 37% of men and 38% of women worldwide are overweight or obese (body mass index (BMI) of 25 kg/m^2 or greater), and approximately 2.1 billion people are overweight (Ng et al., 2014). In the United States, the prevalence of overweight and obesity is considerably greater, as 68.8% of adults have a BMI of 25 kg/m^2 or greater and 35.7% of US adults are considered obese. More alarming is the fact that over 60% of pregnancies in the United States are in women who are either overweight or obese at conception (Ogden et al., 2014). Maternal obesity during pregnancy adversely affects the immediate health of both the mother and offspring (King, 2006; Catalano, 2010) and it is widely recognized that maternal obesity leads to developmental programming of excessive weight and adiposity in the offspring (Catalano, 2003). While there are many studies documenting that obesity-associated conditions such as excessive gestational weight gain and gestational diabetes also have long-term effects on offspring health and development, this review will focus on the impact of maternal obesity on offspring health and development in both translational experimental and clinical domains and provide insights into

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http://dx.doi.org/10.1016/j.mce.2016.07.001
0303-7207/

emerging mechanisms of this cycle of obesity propagation (Fig. 1).

1.1. Effects of maternal obesity on reproduction and fertility

Maternal obesity is associated with a number of adverse reproductive outcomes. Obese women have decreased rates of spontaneous pregnancy, longer time to conception, and are at higher risk of miscarriage, preeclampsia, gestational diabetes mellitus (GDM) and congenital birth defects compared to normal weight women. In addition, obese women experience poorer outcomes of fertility treatment and often require higher doses of ovulation-inducing agents. While obesity can affect endometrial receptivity, a study of over 45,000 assisted reproductive embryo transfers demonstrated that a higher BMI correlated with reduced likelihood of successful pregnancy when autologous oocytes were used, but not when oocytes from lean donors were used (Luke et al., 2011; Maheshwari et al., 2007). These data suggest that oocyte quality is a critical factor in determining reproductive outcome (Brewer and Balen, 2010). Specifically, obesity is associated with decreased oocyte acid transport proteins, increased lipid content, and increased production of reactive oxygen species secondary to mitochondrial dysfunction and these disruptions in oocyte metabolism manifest as meiotic defects, organelle dysfunction (mitochondrial and ER) and epigenetic alterations that act in concert to diminish oocyte quality and reproductive potential (Gu et al., 2015; Jungheim and Moley, 2010; Luzzo et al., 2012; Turner and Robker, 2015). Obesity is also associated with changes in ovarian granulosa cells and the follicular fluid surrounding the oocyte. Granulosa cells from obese mice have increased rates of apoptosis and decreased mitochondrial function (Wu et al., 2010), and obese women have increased follicular fluid triglyceride levels that presumably contribute to oocyte lipotoxicity and reduced fertilization rates (Robker et al., 2009). Thus, perturbations in oocyte metabolism might contribute to diminished reproductive potential in obese women. More importantly, animal studies demonstrate that exposure to maternal obesity increases inflammatory gene expression in the peri-implantation blastocyst (Shankar et al., 2011).

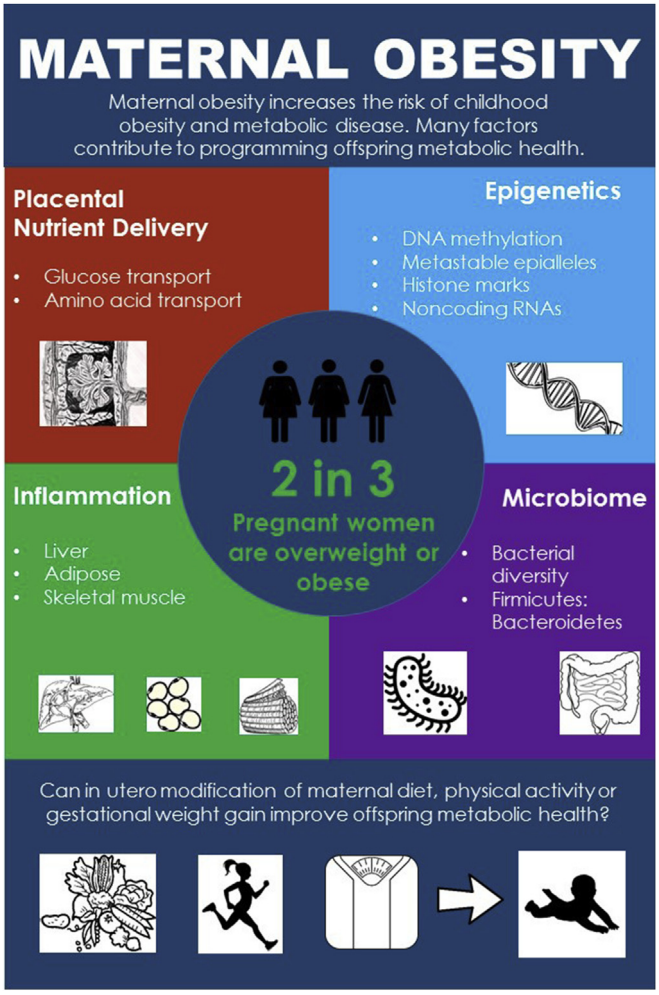

Fig. 1. Maternal obesity related factors contributing to fetal metabolic programming.

1.2. Pregnancy-associated changes in maternal metabolism

There are many maternal physiological and anatomical adaptations to pregnancy that begin early after conception to accommodate the nutritional needs of the growing fetus. During pregnancy there is an increase in fluid retention, blood volume expansion, increase in heart rate, decrease in peripheral vascular resistance, changes in thyroid function/hormone production, increase in basal metabolic rate, and a number of other important adaptations. These maternal pregnancy-associated physiological changes include endocrine and metabolic adaptations, many of which are driven via placental-derived hormones. Placental factors including steroids and hormones mediate both maternal recognition of pregnancy and orchestrate adaptations necessary for a healthy pregnancy at the local and systemic levels. Late in gestation, maternal fuel utilization switches from carbohydrate to fat usage to ensure a continuous supply of glucose and amino acids to the growing fetus (Herrera, 2000; Sivan et al., 1997). Pregnancy is associated with increased insulin secretion (Ernst et al., 2011), partially via hypertrophy and hyperplasia of pancreatic β-islet cells. Early in pregnancy insulin sensitivity is increased, but starting in the 2nd trimester, women become increasingly insulin resistant as pregnancy progresses, due in part to the release of placental hormones including cortisol, prolactin, human placental lactogen, and progesterone. Increasing insulin resistance in the mother maintains nutrient flow to the growing fetus, whereas prolactin and placental lactogen counterbalance this resistance and prevent maternal hyperglycemia by driving expansion of the maternal population of insulin-producing beta cells. Downstream of prolactin signaling, serotonin synthesis within the β-cells is required for this expansion (Kim et al., 2010; Ohara-Imaizumi et al., 2013).

Mechanistically, several factors contribute to the development of insulin resistance in pregnancy; insulin is less able to phosphorylate the insulin receptor (IR) on skeletal muscle, adipose and skeletal muscle expression of IRS-1 is decreased and adipose and skeletal muscle expression of the regulatory p85α subunit of PI3-K is increased (Barbour et al., 2007). Placental-derived TNFα and leptin seem to play important roles in modulating maternal skeletal muscle and hepatic insulin sensitivity. While fasting and postprandial insulin levels are increased in pregnancy, fasting glucose levels are lower due to increased plasma volume (dilution effect), increased tissue glycogen storage, increased peripheral glucose utilization, and increased fetal glucose consumption. Moreover, hepatic glucose production is increased to compensate for the increase in insulin secretion, but this compensation is incomplete and unable to sustain adequate glucose production. Hence, the net result of insulin resistance and hypoglycemia in late pregnancy is increased maternal lipolysis and increased circulating free fatty acids, which may in turn further contribute to insulin resistance in pregnancy. Early on in pregnancy there are measurable differences in insulin sensitivity in obese compared to lean women and though