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The impact of maternal obesity during pregnancy on offspring immunity

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ABSTRACT

In the United States, approximately 64% of women of childbearing age are either overweight or obese. Maternal obesity during pregnancy is associated with a greater risk for adverse maternal–fetal outcomes. Adverse health outcomes for the offspring can persist into adulthood, increasing the incidence of several chronic conditions including cardiovascular disease, diabetes, and asthma. Since these diseases have a significant inflammatory component, these observations are indicative of perturbation of the normal development and maturation of the immune system of the offspring in utero. This hypothesis is strongly supported by data from several rodent studies. Although the mechanisms of these perturbations are not fully understood, it is thought that increased placental inflammation due to obesity may directly affect neonatal development through alterations in nutrient transport. In this review we examine the impact of maternal obesity on the neonatal immune system, and potential mechanisms for the changes observed.

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1. Introduction

Obesity is defined as the accumulation of excess body fat and is traditionally reported by the body mass index (BMI), which is a calculation of weight (kg) divided by height (meters) squared. Healthy individuals have BMI values >19 and <25 kg/m^2 whereas persons with a BMI $\geq$ 25 kg/m^2 are considered overweight and those with a BMI $\geq$ 30 kg/m^2 meet the criteria for obesity. Obesity is a metabolic disease that results in a chronic low-grade inflammation (Wellen and Hotamisligil, 2005; Schmatz et al., 2010; Calder et al., 2011; Gregor and Hotamisligil, 2011), characterized by high levels of inflammatory mediators such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα). More importantly, excess weight/adiposity is associated with several comorbidities including: diabetes, cardiovascular disease, pulmonary complications, and cancer (Segula, 2014) resulting in decreased life expectancy (Grover et al., 2015). According to the Centers for Disease Control and Prevention (CDC), as of 2012, 69% of the adults aged 20 years and older in the United States have a BMI > 25, and 35.1% are obese (Flegal et al., 2012). The American Heart Association estimates that in 2013, 154.7 million people were overweight, and of these, 78.4 million were obese (Go et al., 2013). Unfortunately, the rates of obesity are expected to continue to rise (Centers for Disease C and Prevention, 2010).

2. Clinical impact of maternal obesity on maternal health

It is generally believed that a high BMI entering pregnancy, and excess weight gain during pregnancy can exacerbate the natural inflammatory state associated with pregnancy resulting in detrimental health outcomes for the mother (Schmatz et al., 2010; Sacks et al., 2004). A retrospective study by Leung et al. that assessed adverse outcomes associated with maternal obesity in a cohort of 29,303 Chinese women between 1995 and 2005, found that high maternal BMI assessed during the first antenatal visit correlated with increased rates of preeclampsia, gestational diabetes (GDM), caesarean section, and preterm delivery (Leung et al., 2008). Similarly, a study of 6959 singleton pregnancies from 2001 to 2005 by Gaillard et al., in the Netherlands found that maternal obesity prior to pregnancy and excessive weight gain during pregnancy were both associated with increased incidence of preeclampsia, GDM, hypertension, and caesarean section despite adjusting for

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familial and lifestyle factors (Gaillard et al., 2013). A third retrospective study of 30,298 subjects from 2004 to 2011 by Scott-Pillai et al. also reported similar outcomes in the UK, and showed that these risks are further exacerbated as BMI (measured during first pre-natal visit) increases above 35 (Scott-Pillai et al., 2013).

3. Maternal environment and origin of disease

The "origins of fetal and infant disease hypothesis," was first proposed in 1990 by Dr. Barker to serve as an explanation for the increase in coronary heart disease in western countries (Barker, 1990, 2000). In 2001, Drs. Hale and Barker expanded the "origins of fetal and infant disease hypothesis" into the "thrifty phenotype" hypothesis, which was based on the observations that children born to undernourished women during famine were better able to survive than children born to normally nourished women. This adaptation, while beneficial in times of famine, became a disadvantage when conditions became plentiful and children became predisposed to obesity and impaired glucose tolerance (Hales and Barker, 2001; Vaag et al., 2012). This theory was further expanded by Dr. Barker in 2002 into the "Fetal Origins of Adult Disease" (FOAD) based on the observation that children who were small at birth/infancy, as a result of intrauterine growth restriction in undernourished mothers, subsequently underwent accelerated weight gain in childhood and experienced higher incidence of coronary heart disease, type 2 diabetes, and hypertension as adults compared to normal birth weight children (Calkins and Devaskar, 2011; Barker et al., 2002). The FOAD proposes that changes in the gestational milieu directly impact fetal growth and development (Calkins and Devaskar, 2011; Dover, 2009), and consequently disease incidence later in life (Aagaard-Tillery et al., 2008). Two cornerstones of the FOAD hypothesis are developmental plasticity and compensatory growth (Barker et al., 2002). Developmental plasticity refers to changes in neural connections during development as a result of in utero environment. Compensatory growth, or "catch-up growth", is accelerated growth following a period of slowed development. Therefore, adaptations acquired in utero during limited nutritional intake were later detrimental in the adult offspring or when food became plentiful.

Although the initial Barker hypothesis focused primarily on nutritional deficiencies and low birth weight, there is evidence that over-nutrition also alters in utero programming (de Boo and Harding, 2006). The "fetal over-nutrition hypothesis" was developed based on epidemiological evidence that greater maternal adiposity, (self-reported/measured pre-pregnancy/first antenatal visit weight), increased lifetime risk of type 2 diabetes (Dabelea and Pettitt, 2001) and obesity (Lawlor et al., 2007) in the offspring. In the latter study, both maternal and paternal BMIs were taken before pregnancy, and the child's BMI was assessed at birth, 5 years, and 14 years. Only maternal BMI had an effect on offspring BMI, which wasn't evident until 14 years of age.

Taken together, there is strong evidence that in utero instruction by maternal nutritional environment can influence growth rate and disease risk during adulthood (Calkins and Devaskar, 2011; de Boo and Harding, 2006; Lawlor et al., 2007; Leddy et al., 2008). A fetus can adapt its physiology and metabolism to the supply of nutrients crossing the placenta (Leddy et al., 2008). Excess supply of nutrients can lead to permanent changes in metabolism, behavior and appetite regulation in offspring resulting in adverse health outcomes later in life (O'Reilly and Reynolds, 2013). In summary, this phenomenon is known as "early-life programming" which recognizes that events in utero have long term influences on risks of disease later in life (O'Reilly and Reynolds, 2013).

4. Clinical impact of maternal obesity in offspring

Increased incidence of stillbirths, abnormal growth, cardiac defects, and neural tube defects has been reported in the offspring of obese women after adjustment for various factors including age, familial and lifestyle factors, and ethnicity (Leung et al., 2008; Gaillard et al., 2013; Scott-Pillai et al., 2013; Catalano and Ehrenberg, 2006; McMahon et al., 2013) and Table 1). Furthermore, children born to women who enter pregnancy in an obesogenic state are at higher risk for several adverse long-term health outcomes including increased incidence of obesity (Leibowitz et al., 2012), cognitive development deficits and ADHD (Buss et al., 2012), type-2 diabetes (Barker et al., 1993; Morgan et al., 2010), cardiovascular disease (Reynolds et al., 2013; Forsen et al., 1997), cancer (Silver et al., 2015), and greater all-cause mortality (Reynolds et al., 2013) in comparison to children born to lean mothers. A Finnish study of coronary heart disease found that men born to mothers with a high BMI (assessed at time of labor admission) experienced a higher incidence of coronary related deaths (Forsen et al., 1997). A prospective cohort study in the Netherlands, utilizing data from the Generation R study in which growth and development, behavior, asthma childhood disease and genetics were documented from fetal life until young adulthood, found that high maternal pre-pregnancy BMI was associated with adverse cardiometabolic profiles in the offspring (Gaillard et al., 2014). Adverse cardiovascular outcomes were detected despite the exclusion of women with both pre-pregnancy, and pregnancy complications including diabetes/GDM (Reynolds et al., 2013; Forsen et al., 1997; Gaillard et al., 2014). In addition to cardiovascular disease, the periconceptional environment affects gene expression for at least 10 years and may result in lifelong increased risk of cancer in the offspring (Silver et al., 2015). Finally, increased incidence of childhood asthma and wheezing is emerging as a common adverse health outcome for the offspring of mothers with a pre-pregnancy BMI > 30 or excessive weight gain during pregnancy following adjustment for sex of child, maternal age, smoking, maternal history of asthma/allergy, maternal BMI, and maternal weight gain during pregnancy (Forno et al., 2014; Harpsoe et al., 2013; Kumar et al., 2010). The immune system plays a critical role in the pathogenesis of cardiovascular disease (Hansson and Hermansson, 2011), asthma (Homer and Elias, 2005; Kips, 2001; Kon and Kay, 1999), and diabetes (Wellen and Hotamisligil, 2005). Since maternal obesity is associated with increased incidence of these diseases, it is highly likely that maternal obesity disrupts normal development and maturation of the offspring's immune system in utero.

5. Overview of the immune system

The immune system is our first line of defense against microbial infection and cancer. It is composed of leukocytes that secrete various immune molecules such as cytokines, chemokines, immunoglobulins, and complement proteins in order to eliminate pathogens as well as mediate cell-to-cell communication. The immune system can be divided into two main branches: innate and adaptive immunity (Murphy et al., 2012). The innate immune branch is composed of neutrophils, eosinophils, basophils, natural killer (NK) cells, monocytes/macrophages, and dendritic cells (DCs); as well mucosal barriers and antimicrobial peptides (Parkin and Cohen, 2001). These cells can distinguish self from invading pathogens by expressing pattern recognition receptors (PRR) that recognize pathogen associated molecular patterns (PAMPs). Signaling through these PRRs results in signaling cascades that culminate in the production of cytokines, chemokines and complement proteins that can interfere with pathogen replication and recruit additional