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Review

From fatalism to mitigation: A conceptual framework for mitigating fetal programming of chronic disease by maternal obesity

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ABSTRACT

Prenatal development is recognized as a critical period in the etiology of obesity and cardiometabolic disease. Potential strategies to reduce maternal obesity-induced risk later in life have been largely overlooked. In this paper, we first propose a conceptual framework for the role of public health and preventive medicine in mitigating the effects of fetal programming. Second, we review a small but growing body of research (through August 2015) that examines interactive effects of maternal obesity and two public health foci – diet and physical activity – in the offspring. Results of the review support the hypothesis that diet and physical activity after early life can attenuate disease susceptibility induced by maternal obesity, but human evidence is scant. Based on the review, we identify major gaps relevant for prevention research, such as characterizing the type and dose response of dietary and physical activity exposures that modify the adverse effects of maternal obesity in the offspring. Third, we discuss potential implications of interactions between maternal obesity and postnatal dietary and physical activity exposures for interventions to mitigate maternal obesity-induced risk among children. Our conceptual framework, evidence review, and future research directions offer a platform to develop, test, and implement fetal programming mitigation strategies for the current and future generations of children.

Contents

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Introduction

An increasing proportion of U.S. children are born to obese mothers, reaching 20% in 2009 (Fisher et al., 2013). The offspring have a three-fold greater risk of obesity (Yu et al., 2013) suggesting that we are in the midst of an escalating intergenerational obesity cycle (Dabelea and Crume, 2011). Existing strategies to curb intergenerational obesity focus on pregnancy and infant health (Nader et al., 2012; Perez-Escamilla and Kac, 2013). In this paper, we evaluate an emerging complimentary strategy: *mitigation* of maternal obesity-induced chronic disease susceptibility in childhood and adolescence, prior to reproduction.

Maternal obesity induces alterations in prenatal development that "programs" increased susceptibility to obesity and cardiometabolic conditions in offspring (Frias and Grove, 2012; Lawlor et al., 2012). Because of the powerful associations between adverse intrauterine exposures and later disease in offspring, it is tempting to assume a fatalistic interpretation in which programmed risk is perceived as irreversible after early life (Skogen and Overland, 2012; Vickers and Sloboda, 2012). However, programmed disease manifests primarily in the context of adverse exposures encountered in childhood, adolescence, or adulthood (Bagby, 2007). These exposures may include factors such as physical inactivity, poor diet, smoking, or psychosocial stress. Reducing postnatal adverse exposures represents a potential opportunity to mitigate the adverse intrauterine effects of maternal obesity.

In this paper, we first describe a conceptual framework for the role of public health and preventive medicine in mitigating the intergenerational cycle of obesity by preventing key postnatal exposures. Second, we review animal and human studies that consider how maternal obesity interacts with diet or physical activity in childhood, adolescence, or adulthood to alter risk for later disease and identify potential future directions for human research. Third, we discuss implications for interventions seeking to mitigate the deleterious effects of fetal programming in the current and future generations of children.

I. Fetal programming prevention and mitigation in the intergenerational cycle of obesity: conceptual framework

Consider a lineage of disease (Fig. 1), starting with the presence or absence of a "first hit" during prenatal development. In this paper, we focus on an individual's gestation within an obese or normal intrauterine environment. The detrimental effects of maternal obesity on the developing fetus are indicated by a red star. Maternal obesity-induced alterations increase susceptibility to obesity and disease in the offspring (Dabelea and Crume, 2011; Frias and Grove, 2012) which they carry throughout their life. After birth, offspring encounter "second hits" (Bagby, 2007) — postnatal nutritional, environmental, psychosocial, and behavioral factors that drive obesity and disease.

A. Fetal programming prevention: preventing the first hit

Compared with children born to normal weight mothers, those born to mothers who are obese have greater risk of obesity and cardiometabolic disease (Boney et al., 2005; Dabelea et al., 2008; Lau et al., 2014; Yu et al., 2013). Infants born to obese, nondiabetic mothers have elevated adiposity and insulin resistance emerging as early as birth (Catalano et al., 2009). Experimental animal research is consistent with human studies and has begun to provide understanding of the biologic mechanisms underlying intergenerational patterns (Ainge et al., 2011). Examples of these mechanisms include impaired appetite regulation (Breton, 2013; Kirk et al., 2009), low skeletal muscle mass with impaired glucose regulation (Bayol et al., 2014; Du et al., 2010), and dysfunctional lipid metabolism (McCurdy et al., 2009; Pruis et al., 2014).

Interventions in girls and women who are pregnant or about to become pregnant offer hope for preventing fetal programming (Macaulay et al., 2014; Nader et al., 2012; Perez-Escamilla and Kac, 2013) (the first hit) and reducing the number of individuals in the left side of Fig. 1 (obese mother). Promising approaches include preconception weight loss (Catalano and deMouzon, 2015) among women who are obese prior to pregnancy and, among all women, appropriate gestational weight gain, and healthy diet and physical activity before and during pregnancy (McDonald et al., 2015; Muktabhant et al., 2015; Rooney and Ozanne, 2011). Perinatal interventions are active areas of research, but to date have yielded only modest improvements in maternal health (Catalano and deMouzon, 2015; Guelinckx et al., 2010; Kinnunen et al., 2007; Poston et al., 2013; Wolff et al., 2008) and it is too soon to evaluate their effects on long-term offspring health.

B. Fetal programming mitigation: preventing the second hit

While preventing fetal programming exposures (first hit) remains an important area of practice and research, we propose that the course of intergenerational obesity has progressed beyond the stage in which we can focus solely on prenatal health. In 2009, 20.5% of children were born to women who were obese, with greater proportions in minority groups (e.g., 29.2% in African Americans) (Fisher et al., 2013). Resolving the obesity epidemic requires mitigation of programmed susceptibility in children who have already experienced a maternal obesity first hit, which comprises an increasing proportion of all births (Fisher et al., 2013).

We define the term *fetal programming mitigation* as the attenuation of disease processes after fetal programming has occurred. Mitigation concerns infants and children as they grow into adolescents and adults on the *left side* of Fig. 1 (obese mothers). We hypothesize that preventing second hits can minimize clinical risk factors (e.g., insulin resistance) and prevent or delay disease progression into clinical disease (e.g., diabetes). Fetal programming mitigation would thus reduce the manifestation of programmed risk in any given generation and, upon childbearing, prevent a first hit in the subsequent generation.

While healthy infant feeding practices such as breastfeeding and optimal complimentary feeding (Thompson, 2013) offer early opportunity for reducing obesity risk, less attention has been paid to strategies designed to prevent the second hit in childhood or beyond. Pharmacologic or nutritional therapeutic agents that mitigate fetal programming