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Minireview

Maternal inflammation, growth retardation, and preterm birth: Insights into adult cardiovascular disease

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ABSTRACT

The "fetal origin of adult disease Hypothesis" originally described by Barker et al. identified the relationship between impaired in utero growth and adult cardiovascular disease risk and death. Since then, numerous clinical and experimental studies have confirmed that early developmental influences can lead to cardiovascular, pulmonary, metabolic, and psychological diseases during adulthood with and without alterations in birth weight. This so called "fetal programming" includes developmental disruption, immediate adaptation, or predictive adaptation and can lead to epigenetic changes affecting a specific organ or overall health.

The intrauterine environment is dramatically impacted by the overall maternal health. Both premature birth or low birth weight can result from a variety of maternal conditions including undernutrition or dysnutrition, metabolic diseases, chronic maternal stresses induced by infections and inflammation, as well as hypercholesterolemia and smoking. Numerous animal studies have supported the importance of both maternal health and maternal environment on the long term outcomes of the offspring. With increasing rates of obesity and diabetes and survival of preterm infants born at early gestational ages, the need to elucidate mechanisms responsible for programming of adult cardiovascular disease is essential for the treatment of upcoming generations.

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Introduction

The "fetal origin of adult disease" hypothesis was introduced by Barker et al. almost 25 years ago and addresses the influence of the intrauterine and early postnatal environment on the development of adult diseases (Barker and Osmond, 1986; Barker, 1997a, 1997b, 2004a, 2004b). Based on epidemiological data, Barker and coworkers described low weight at birth as highly correlated with increased risk for the development of cardiovascular complications (Barker et al., 1989). Numerous retrospective and prospective clinical studies have revealed significant associations between low weight at birth and the development of cardiovascular diseases (CVD) during adulthood (Eriksson et al., 1999; Frankel et al., 1996; Stein et al., 1996). Further

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studies revealed that not only low birth weight, but also low weight at one year of age was associated with cardiovascular death (Osmond et al., 1993). Most recently, studies have indicated correlations between maternal metabolic dysfunction and the intrauterine environment on the development of adult CVD rather than simply low birth weight (Palinski and Napoli, 2008); however, the pathogenic mechanisms of this so called fetal programming remain to be fully elucidated.

A stimulus or an insult occurring during a crucial developmental period can elicit lasting structural or functional effects that lead to adult morbidities; a process termed "programming" (Barker, 2004a, 2004b; Gluckman et al., 2005; Godfrey and Barker, 2001; Hanson and Gluckman, 2005). Programming takes place at a time of developmental plasticity which includes periods of rapid cell division and/or prior to terminal differentiation when normal processes allow a range of phenotypes to develop from a single genotype (Barker, 2004a, 2004b). The fetus or newborn is able to respond and adapt to environmental changes; however, if the adaptation persists beyond the window of plasticity, it becomes permanent.

Programming can take the form of developmental disruption, immediate adaptation, or predictive adaptation (Hanson and Gluckman, 2005). Developmental disruption occurs as a direct response to adversity and results in an alteration of the normal developmental pattern, but is unrelated to any adaptive advantage. Immediate adaptation enables the fetus to respond and adapt to changes in the environment for self preservation, i.e. conserving nutrients for essential organs such as cardiac function at the expense of somatic growth. Predictive adaptation occurs in the developing organism with no obvious immediate value but in expectation of an altered future environment. Ultimately, the accuracy of the predictive information will determine the degree of match or mismatch and risk for disease as a result. All three forms of developmental programming can induce epigenetic changes (Gluckman et al., 2009).

Interestingly, the concept of fetal programming in the context of preterm birth has been controversial and reports have been largely inconclusive (Dalziel et al., 2007; Doyle, 2008; Irving et al., 2000; Kaijser et al., 2008). At the time the first studies were performed, the survival of preterm infants <30 weeks was rare. Therefore, these earlier population-based studies have specified preterm birth as all infants born <36 weeks and by today's criteria modestly preterm infants dominated the composition of this preterm group. Due to new medical therapies over the last 15–20 years, a substantial population of infants born between gestational ages 23 and 28 weeks, have survived, and are classified as extremely preterm (Claas et al., 2010). More recent epidemiologic studies have included these extremely preterm infants and are composed of a very different population than earlier studies. The interventional care provided to these infants in addition to their prematurity is likely to have a profound influence on their overall health later in life. Consequently, the discrepancies in reports on the associations between preterm birth and cardiovascular complications are likely due to changes in the population itself.

Furthermore, maternal health was rarely considered a confounding factor in past epidemiologic studies but more recent investigations imply that maternal wellbeing impacts fetal development in profound ways that were not previously appreciated (Napoli and Palinski, 2001; Ozanne and Constancia, 2007; Palinski and Napoli, 2008). Overall maternal health is tightly linked to the causes and occurrence of preterm birth, thus discerning the distinct associations between maternal health alone and the development of adult cardiovascular disease will be difficult. In spite of these confounding factors, the relationship between maternal health, growth retardation, preterm birth, and low birth weight needs to be explored as we address increased survival rates of extremely preterm infants and a growing population of adults with CVD (Fig. 1).

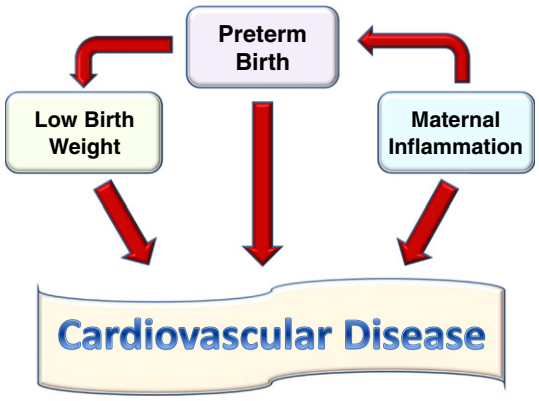

Fig. 1. Preterm birth contributes to low birth weight. Both, preterm birth and low birth weight are directly correlated with the development of adult cardiovascular diseases. Maternal inflammation is associated with preterm birth, subsequently leading to low birth weight. However, the influence of maternal inflammation linked preterm birth on the development of adult cardiovascular disease is likely to be significant but has not been extensively investigated.

Cardiovascular risks and low birth weight; the "Barker hypothesis"

By analyzing birth records from Hertfordshire (England), Barker was first to describe the association between low birth weight and weight at one year of age with an increased risk for cardiac and stroke related death (Lomax and Calder, 2009; Thienprasert et al., 2009). Within this group, CVD related mortality during adulthood doubled from the highest to the lowest birth weight and was similar between men and women (Frankel et al., 1996; Madden et al., 2009). Their theory was that the fetus channeled limited nutritional resources to cardiac function and neurological development at the expense of somatic growth. As a result of this observation, a large number of additional investigations have supported this tight correlation between low weight at birth and the development of cardiovascular diseases during adulthood (Bergvall et al., 2007; Huxley et al., 2004; Koupilova et al., 1999; Leon et al., 1998; Wadhwa et al., 2009).

Low birth weight may result from a broad range of pathogenetically diverse maternal conditions including mechanical obstructions of the uterine artery, severe maternal undernutrition or dysnutrition, corticosteroid treatment, and metabolic diseases (Curhan et al., 1996). In addition, chronic maternal stresses induced by infections and inflammation, as well as hypercholesterolemia and smoking, are likely to be contributors (Gluckman and Hanson, 2004; Palinski and Napoli, 2008; Yang et al., 2004). Cardiac morphometry and function studies on adults born with fetal growth restriction (FGR) have revealed changes in cardiac shape, decreased stroke volume, increased heart rates, and decreased systolic mitral and tricuspid ring displacements (Crispi et al., 2010). Vascular effects have included increased blood pressure and aortic intima-medial thickness. Most of these changes have remained subclinical during childhood but have become significant health issues combined with additional behaviors or stressors during adulthood.

Preterm birth and fetal programming

Premature birth is the leading cause of infant mortality and morbidity in the United States and according to the March of Dimes there were over 500,000 preterm babies born, representing 12.3% of all live births in the United States (2008). Extremely premature infants (<28 weeks gestation) have routinely survived only within the last 15–20 years. Approximately 50% of the deliveries at <30 weeks gestational age are associated with a diagnosed source of maternal inflammation or infection (Gomez et al., 1998; Romero et al., 2006, 2007). In many cases, however, systemic infection or chronic inflammation is not appreciated as etiological to the cause of preterm