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Review article

In utero programming and early detection of cardiovascular disease in the offspring of mothers with obesity

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ABSTRACT

The offspring of women with obesity during their pregnancy are exposed to an altered intra-uterine environment. A subsequent influence on the cardiovascular development during fetal life is assumed. In the present thematic review, we report on the current knowledge about this early development of cardiovascular disease from fetal life until adolescence. Based on animal studies, different contributing mechanisms have been hypothesized that still need confirmation in human subjects. Insulin resistance, increased levels of leptin, chronic inflammatory state, perturbation of sympathetic tone and epigenetic modifications contribute to a suboptimal nutrient environment and changed hemodynamics. The ensuing aberrant cardiomyocyte development, impaired endothelial cell relaxation and atherogenic lipid profile put these children at risk for the development of endothelial cell dysfunction. Increasing possibilities for early detection of this preliminary stage of atherosclerotic disease offer new insights into future prevention and treatment strategies. Future research should focus on further unraveling the effect of moderate intense, aerobic exercise. Since it is used to treat the condition in children and adolescents with good results, it might be a contributor to tackling endothelial cell dysfunction at its cradle when applied in early pregnancy.

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1. Introduction

Ischemic cardiovascular events remain the global leading cause of death and an important contributor to premature deaths [1–3]. Strategies for the improvement of these figures focus on the identification and treatment of cardiovascular diseases and associated risk factors in its early stages [4]. Childhood obesity is a known risk factor and one of the major global public health challenges of this century [5]. A specific population of children at risk for the development of (childhood) obesity and/or cardiovascular diseases is the offspring of pregnant women with obesity. There is a growing body of literature that recognizes adverse outcomes of obesity during pregnancy in short- and long-term. Short-term complications include an increased risk of delivery by caesarean section, macrosomia or large-for-gestational-age infants at birth, admission to a neonatal care unit and stillbirth [6,7]. Long-term complications induce an unfavorable metabolic profile in later life with a tendency to insulin resistance, adverse body composition and lipid profile and chronic state of low-grade inflammation [8–13]. The adverse metabolic consequences put these children at risk for the early development of atherosclerosis and cardiovascular disease. Epidemiological studies link maternal obesity to cardiovascular disease and premature death in later life in the offspring [14,15]. This review sheds light on the *in utero* programming of cardiovascular disease in the offspring of women with obesity, the subsequent clinical implications of its detection in the earliest stages and valuable perspectives on prevention strategies.

2. Maternal obesity and *in utero* programming of cardiovascular disease

A higher (pre)pregnancy maternal weight is associated with altered cardiovascular development in the offspring causing a greater risk for congenital heart defects and myocardial hypertrophy, hypertension, an atherogenic lipid profile and higher

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circulating levels of vascular and cellular adhesion molecules [9,16–20]. An abnormal *in utero* environment and placental development, resulting in a suboptimal nutritional climate and changed hemodynamics play a central role (see Fig. 1). One of the pioneers in this research field was David Barker with the development of the hypothesis of *fetal programming*, following studies in malnourished pregnant women over 30 years ago. [21] This relationship between a poor nutritional intra-uterine environment in malnourished women during pregnancy and cardiovascular disease in the offspring at adult age, has been suggested in the offspring of mothers with obesity during pregnancy as well [14]. The still ongoing follow-up studies of the Dutch Hunger Winter (1944–1945) families' cohort provide valuable additional information on these correlations [22,23].Most of the evidence regarding the underlying programming mechanisms arises from animal studies.

2.1. Data from animal studies

To assess the consequences of a poor intra-uterine nutritional climate, animal studies with maternal high-fat diet (HFD) during pregnancy in rodents, sheep and nonhuman primates are used (Table 1). The offspring of HFD fed animals demonstrates an impaired endothelial cell relaxation in combination with a raised intimal wall thickness and increased expression of vascular inflammatory markers [24,25]. Underlying insulin resistance and higher levels of leptin are thought to contribute. Raised leptin levels, secreted by the adipose tissue, inhibit the *in vitro* proliferation of smooth muscle cells and could impede the angiogenesis process *in vivo*, but this assumption needs scientific validation in humans [26]. The high circulating levels of lipids induce a pro-inflammatory cascade which can up- or down regulate the placental nutrient transporters and influence placental (vascular) development and function [16].

Chronic inflammation in mothers with obesity causes a combination of vasoconstriction, platelet aggregation and lipid storage in the placenta. This contributes to a suboptimal trophoblast invasion and aberrant vascular development with hypoxia and decreased blood flow [27,28]. A decreased foetal:placental weight ratio is observed in combination with the development of atherosclerosis–like plaques in the placental arterioles and occurrence of infarcts [16,19,29]. These placental abnormalities cause hemodynamic changes leading to a shift in fetal blood supply which most affects, for reasons yet unknown, the blood vessels, kidneys and heart ([17]).

The fetal cardiomyocytes are influenced through different pathways. Insulin-like growth factor-1 (IGF-1) stimulates the proliferation of cardiomyocytes and is suppressed when placental insufficiency is present, leading to less proliferation and maturation of the cardiomyocytes [17,30,31]. The observed ventricular hypertrophy and myocardial fibrosis are possibly caused by the activation of protein kinase B, sympathetic dominance, lipotoxicity and/or increased mechanical systolic load to the fetal heart [32–34]. The combination of the aforementioned hypertrophy and immaturity predispose the offspring to cardiac dysfunction and premature cardiac failure at adult age [16].

2.2. Data from human studies

Human data on long-term cardiovascular effects of maternal obesity mostly arise from epidemiological studies and are based on associations. Therefore, they cannot be used to confirm or contradict the aforementioned programming hypotheses. A Finnish study by Forsen et al. from 1997 [35] is repeatedly referred to as a pioneering study. It links an increased death from cardiovascular disease in adult men with their mothers suffering from obesity during pregnancy. Other contributory studies link gestational weight gain and maternal obesity during pregnancy to an elevated blood pressure at childhood, adolescent and adult age and even demonstrate increased incidence of adverse cardiovascular outcomes and premature death [36–38]. So far only the aberrant pro-inflammatory and lipotoxic state of pregnant women with obesity has been confirmed in humans [24,39]. But since it is known that maternal hyperlipidemia during pregnancy is associated with increased formation of fetal atherosclerotic lesions and their progression in childhood, indications for the underlying mechanisms might be closer than we think [40,41].

Some issues remain when translating animal findings based on HFD to humans, since the used HFD are not standardized (as illustrated in Table 1) and diverse animal phenotypes are obtained. In order to overcome these issues, a new promising animal diet has been developed by Bortolin et al., in 2017 based on the human Western diet [42]. Further research should be undertaken to investigate the accuracy of the formulated programming mechanisms, extrapolated from animal studies and eventual adaptations based on new animal diets.

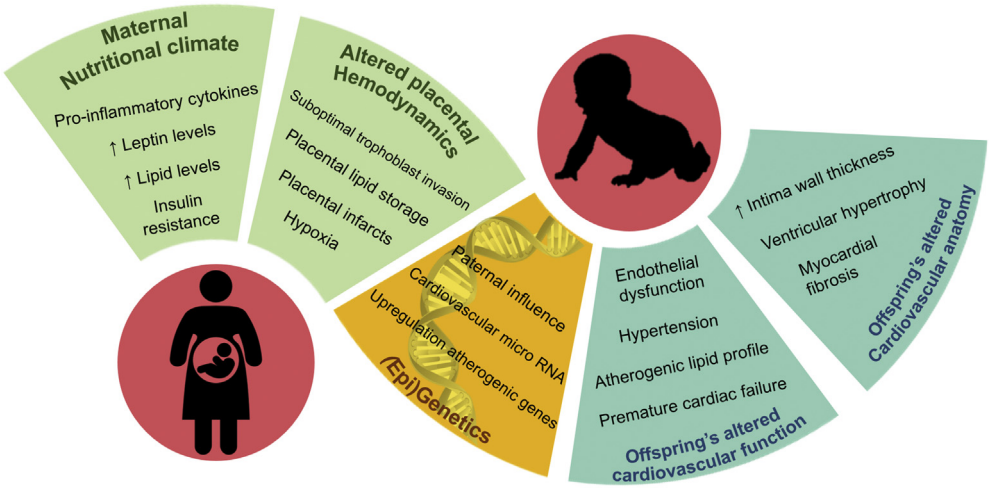

Fig. 1. This figure provides an overview of the major contributors in the programming process putting the offspring at risk for the development of cardiovascular disease.

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