Cardiovascular Medicine

Review article | Published 11 June 2020 | doi:10.4414/cvm.2020.02113
Cite this as: Cardiovasc Med. 2020;23:w02113

Fetal programming as the cause of all the evils in adult humans: atherosclerosis and coronary heart disease included

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The theory of David Barker on "the fetal origin of adult diseases" is revolutionising the pathophysiology and aetiopathogenesis of adult human diseases such as atherosclerosis. Atherosclerosis and related coronary heart diseases (CHDs) appear to be the result of fetal programming, with the cardiovascular system, and particularly the endothelium component, being the principal target of this process. This suggests that cardiovascular diseases can take place during fetal development. This life period is crucial for developmentally programming body systems (such as the cardiovascular system), their ageing and disease. A sophisticated interplay of exogenous-gestational environmental factors with the fetal genome induces epigenetic changes (microRNA, DNA methylation patterns and histone structure alterations) and expression of altered phenotypes of developing systems. A poor maternal diet rich in cholesterol, diabetes, obesity, smoking and exposure to various environmental pollutants represent the major factors related to an increased risk and progression of atherosclerosis in postnatal life. The fetal cardiovascular system is susceptible to these factors, and developmental programming events cause endothelial dysfunction, small coronary arteries, stiffer vascular tree, fewer cardiomyocytes, coagulopathies and atherogenic blood lipid profiles in the fetus. Consequently, preventive interventions are recommended for both parents who want to have children, for counteracting the onset of atherosclerosis and CHDs in new generations.

***Keywords**: developmental programming, fetal cardiovascular development, endothelial dysfunction*

Introduction

For many decades, researchers have focussed their interest and efforts on identifying the mechanisms involved in the complex pathophysiology of atherosclerosis and its common complications, such as coronary heart diseases (CHDs). Thanks to modern treatments, such as new thrombolysis and percutaneous coronary intervention procedures, CHDs show a significant reduction in incidence [1]. In addition, the intense experimental investigation in both animal models and humans has allowed the discovery of mechanisms and pathways involved in the pathophysiology of atherosclerosis and, thereby, to attribute it to diverse processes [2]. Accordingly, the first process was cholesterol storage, since accumulation of cholesterol and thrombotic debris in the artery wall, and more precisely in the intima, has been shown to be a crucial mechanism. Subsequently (during the time between the 1960s and 1970s), a typical mechanism in arterial pathology was found to be the proliferation of smooth-muscle cells in atherosclerotic plaques [2]. Today, it is considered to be a multistep chronic inflammatory disease, because inflammation represents the primary mechanism [2]. Well-established evidence supports this, indicating the inflammatory molecular and cellular pathways involved [3, 4]. These last release into the vascular microenvironment mediators able to alter arterial structure and function, and promote atherothrombotic events at a systemic level [5]. The best-studied innate inflammatory pathways are the Toll-like receptors (TLRs), particularly the TLR-4 and TLR-2, which have been and are an object of research in atherosclerosis investigations [6, 7]. Accordingly, their crucial role has been demonstrated, particularly of the TLR-4, in driving the pathway networks involved in the complex pathophysiology of both atherosclerosis and CHDs [6, 7], as well as in myocardial infarction as demonstrated by our group [8, 9].

The crucial relevance of inflammation in the onset of atherosclerosis also derives from its role as an independent mechanism in the condition of allograft arteriosclerosis (widely quoted in [2]). These data emphasise that inflammation *per se,* without traditional risk factors, can determine arterial hyperplasia. Today, in the era of the modern medicine, including precision and regenerative medicine and the biotechnologies of the last generation, the modulation of inflammatory pathways, for example via TLR-4, can influence the onset of atherosclerosis in experimental models [10, 11]. Validation of these results in humans and their clinical application is ongoing. In addition, these concepts reduce the importance of risk factors as causal factors. This leads to the consideration that inflammation is a "tool" that mechanistically connects alterations induced by traditional risk factors with changes in the vascular (artery)

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wall related to onset of atherosclerosis and its complications, such CHDs

Evidence on the central role of inflammation in the pathophysiology of atherosclerosis is leading to a search for its primordial origins in the early stages of the life of an individual, since Dr Barker proposed the theory "of the fetal origin of adult diseases*"* [12]. Recent findings suggest that atherosclerosis is the result of the "fetal programming process", which governs the development of body systems and sets their ageing and disease (such as atherosclerosis) in adult life. Here, a concise overview of recent evidence in this field is reported and discussed, with the hope to provide additional knowledge on the mechanisms and pathways involved, and to confirm their inflammatory basis in order to suggest potential interventions.

Does atherosclerosis origin from fetal developmental programming?

Based on Dr Barker's theory on the fetal origin of adult diseases [12], today the origin of the major age-related disorders (ARDs) of new progeny may be attributed to developmental processes occurring during embryonic, fetal and early postnatal life. This supports the view that the clinical problems of both parents and the exposures to external influences during the intrauterine/perinatal life of each Eutherian mammal, humans included, can permanently modulate the structure and functionality of specific body systems, such as the cardiovascular system, predisposing them to ARDs such as atherosclerosis and CHD. Established evidence supports these concepts. It has been reported that new progenies born after intrauterine growth restriction (IUGR) show an augmented risk of perinatal morbidity/mortality, and those who survive have long-term consequences, specifically a high susceptibility to developing systemic hypertension, atherosclerosis, CHD and chronic kidney disease [13]. Hyperactivity of the hypothalamic-pituitary-adrenal axis, systemic inflammation, and early alterations in vascular structure and function have, indeed, been detected in IUGR new-borns [14]. Furthermore, maternal hypercholesterolaemia during pregnancy has been associated with augmented fatty streak formation in human fetal arteries and accelerated progression of atherosclerosis during childhood. Consistent with this, data from recent investigations in genetically more homogeneous rabbits subjected to temporary diet-induced maternal hypercholesterolaemia provide evidence that this condition induces in the offspring postnatal atherogenesis in response to the hypercholesterolaemia. Maternal treatments with cholesterol-lowering agents or antioxidants have been demonstrated to decrease fetal and postnatal atherogenesis [15]. Another study, using an apoE mouse model, demonstrated a strong effect of fetal programming on the development of atherosclerosis [16]. Other studies report that fetal exposure to high cholesterol, diabetes and maternal obesity is significantly associated with increased risk and progression of atherosclerosis in new-borns (amply quoted in [17, 18]) In addition, some studies have shown a relevant role of epigenomic mechanisms in the transgenerational transmission of programmed obesity and metabolic syndrome, as recently reviewed by Desai and colleagues [18].

The endothelium as the key target of fetal programming

Evidence has demonstrated that endothelium is the major target of fetal programming. Its modifications leading to dysfunction have been shown to primarily derive from adverse parental and fetal environmental conditions. In support of this evidence, it has been found that levels of the crucial molecules involved in the physiological maturation and differentiation of fetal endothelium (vascular endothelial derived growth factor [VEDGF], its receptors and transcription factors) are affected by several adverse conditions, such as chronic hypoxia, maternal food restriction, altered levels of glucocorticoids and microRNA [19]. In addition, other studies have shown how chronic hypoxia and altered maternal clinical conditions impact the maturation and differentiation of endothelium and the vasculature of all the tissues, ranging from feto-placental arteries, carotid arteries and myocardium, to the cerebrovascular system and renal, liver and pulmonary arteries [20–22]. Another study also reported that the IUGR condition in rats affects the function of both endothelium cells and their progenitors [23, 24]. The relevance of this evidence is particularly stressed by Musa and co-workers [25]. They have recently reviewed the data, from about 230 studies, on the key role of maternal and intrauterine conditions on endothelium structure and function in the offspring, by reporting all the related alterations mechanisms and pathways involved.

Furthermore, an investigation published in 2018 and conducted in equine embryos has shown that maternal obesity induces long-term effects in offspring, predisposing them to obesity and metabolic syndrome [26]. Similar data have been obtained from a study conducted in the transgenic apoE*3 Leiden mouse [27]. Specifically, the impact of maternal consumption of dietary partially hydrogenated vegetable oil (PHVO; P), and ruminant milk fat (R) on the development of atherosclerosis in their offspring has been investigated [27]. Data obtained demonstrated that there is a significant effect of maternal diet during pregnancy on the development of atherosclerosis in the offspring, and particularly in new-borns born from mothers fed R or P diet during pregnancy [27]. In addition, the group of Dr Martino reported that epigenetic factors have a key role in determining these effects in offspring and may be used as biomarkers for early detection of children at risk and as targets for developing new therapies [17].

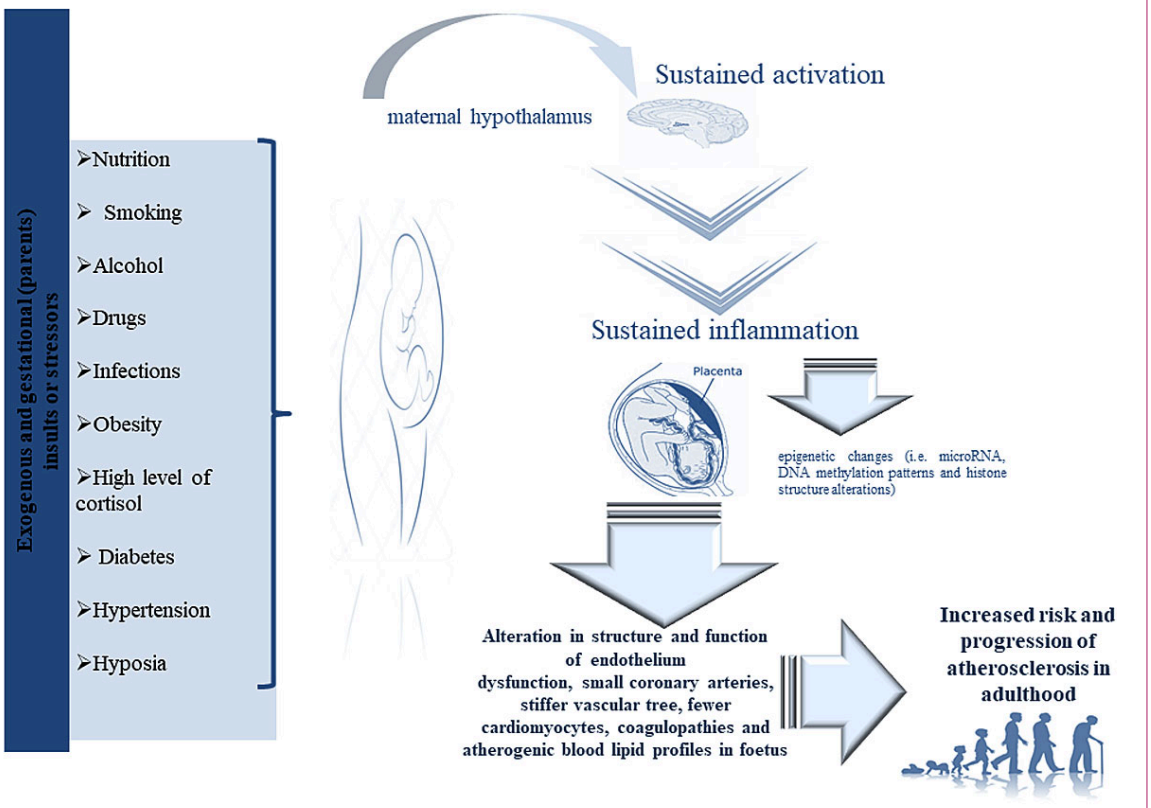
Based on this evidence, endothelium appears to be the key target of fetal programming, and this determines its susceptibility to develop dysfunction, conditions related to many human pathologies, not only of the cardiovascular system such as ARDs and, indeed, essentially linked to the ageing process [28–31].

Furthermore, the key role of inflammation as key determinant of programmed atherosclerosis in new-borns is emerging, as reported in next section.

Inflammation as key determinant of programmed atherosclerosis in newborns

Given the well-recognised role of inflammation in the onset of CVDs such as atherosclerosis and CHDs, its importance in offspring that have experienced prenatal in-

Figure 1: All the factors recognised to modulate foetal programming that determines an increased activation of hypothalamic-pituitary-adrenal axis and consequently sustained inflammation. These mechanisms both impact through epigenetic factors the expression of cardiovascular phenotypes that lead to long-term alterations in structure and function of endothelium, modulating its subsequent functioning in neonatal and adulthood periods provoking dysfunction, contributing to small coronary arteries, stiffer vascular tree, fewer cardiomyocytes, coagulopathies and atherogenic blood lipid profiles. All these adverse conditions significantly will increase the susceptibility to onset of atherosclerosis and coronary heart diseases.

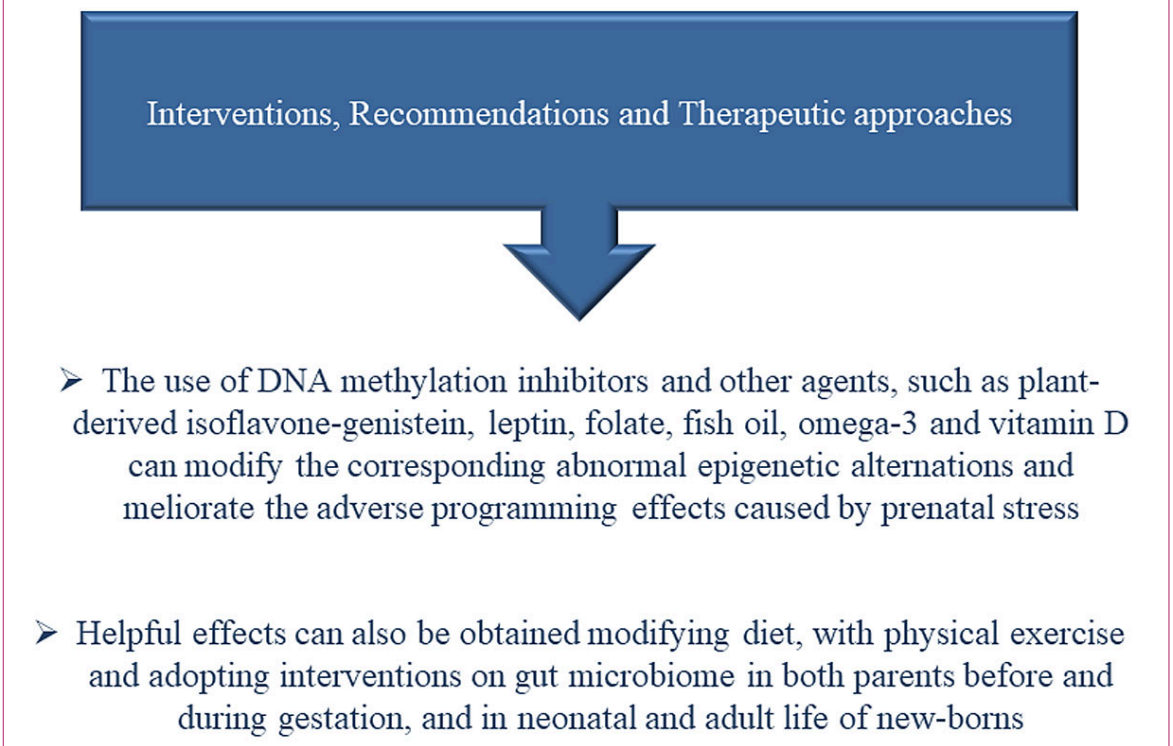


flammation exposure (PIE) has also been investigated. Specifically, it has been demonstrated that maternal influenza exposure and febrile genitourinary infections affect fetal cardiovascular development, predisposing the progeny to CVDs such as atherosclerosis [32–36]. Similar data have been obtained by investigating maternal pre-pregnancy obesity and diabetes, and excessive gestational weight gain. Specifically, under these maternal conditions an increased activation of inflammatory pathways and a sustained macrophage infiltration in the placenta has been detected [37–40]. Furthermore, early onset of maternal higher blood pressure or preeclampsia during pregnancy have been associated with a sustained response of inflammatory $CD4^+$ T cell subsets, accompanied by higher plasma levels of interleukin-6 (IL-6), IL-17 and tumour necrosis factor (TNF)-α in mothers [41]. In addition, it has been demonstrated that maternal hypertension can affect early childhood blood pressures and cardiovascular health in the offspring [42, 43]. Maternal smoking has been also demonstrated to cause a proinflammatory state, including elevated maternal serum levels of TNF-α and IL-1β, that is recognised as an independent risk factor for CVDs [44–46]. This sustained inflammation has been also demonstrated to be the result of the crosstalk among inflammatory pathways (such as TLR-4), oxidative stress, over-activation of the renin-angiotensin system (RAS), NF-κB (nuclear factor "kappa-light-chain-enhancer" of activated B cells) deregulated homeostasis, epigenetic reprograming, and dysregulation of the immune system and the hypothalamic-pituitary-adrenal axis [47]. This evidence has been recently stressed by Deng and co-workers in a well-structured review [47]. Moreover, oral administration with pyrrolidine dithio-carbamate (PDTC), a potent antioxidant, in the second pregnancy trimester has been shown to effectively prevent PIE-programmed hypertension, vascular damage [48] and myocardial remodelling [49] in rats. In addition, early postnatal treatment with PDTC, N-acetyl-l-cysteine (NAC), a glutathione precursor, or Tempol, a superoxide dismutase-mimetic drug, has been found to prevent PIE-programmed CVDs in animal models [48]. Consequently, treatments against inflammation, oxidative stress, etc. in prenatal and early postnatal life might be appropriate therapeutic methods for the prevention of PIE-CVDs.

Conclusions and perspectives

Mounting evidence from epidemiological, clinical and experimental studies has clearly shown a close association between developmental adversity *in utero* and an augmented risk of diverse diseases, such as atherosclerosis, in later life [12]. Fetal stressors such as hypoxia, infections, malnutrition, obesity and fetal exposure to nicotine, alcohol, cocaine and glucocorticoids may directly or indirectly impact cardiovascular programming, by inducing a sustained

Figure 2: Some interventions and therapeutic approaches that might reduce the inflammatory status responsible for the altered programming of the cardiovascular system, and recommendations for modifying the diet, performing physical exercise and adopting interventions on the gut microbiome in both parents before and during gestation, and in neonatal and adult life of new-borns, are also suggested.



inflammation and activation of hypothalamic-pituitary-adrenal axis, alterations to cellular and molecular levels of cardiovascular system, with the result of programming the endothelium and the susceptibility to onset of diverse pathologies, such as atherosclerosis [8] (figure 1). The fundamental mechanisms and pathways are not completely recognised. However, the role of inflammation and epigenetic mechanisms on developing endothelium appears to be very relevant [9]. Consequently, pharmacological manipulations of both inflammation and epigenetic mechanisms in the second pregnancy trimester might represent promising interventional strategies. Accordingly, several experimental studies in animals show promising data based on the use of DNA methylation inhibitors and other agents, such as plant-derived isoflavone-genistein, leptin, folate, fish oil, omega-3 and vitamin D (figure 2). These treatments can modify the corresponding abnormal epigenetic alternations and ameliorate the adverse programming effects caused by prenatal stress [50]. Helpful effects have been also obtained modifying diet, physical exercise and performing interventions on the gut microbiome [51, 52]. Scrupulous studies are essential to advance our knowledge in this field and to develop appropriate treatments, such as prenatal or postnatal supplementations.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article were reported.

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