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Best practice guidelines

Preeclampsia, prematurity and cardiovascular health in adult life

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ABSTRACT

Investigations into how perinatal growth and intrauterine environment may 'programme' risk of later cardiovascular disease have been ongoing for over two decades. One of the more recent outcomes of these studies is the observation that certain pregnancy-related conditions, such as preterm birth, have an unusually large impact on the long-term cardiovascular health of the offspring. In the present paper, we review the current literature of how preterm birth affects the long-term cardiovascular structure and function of the offspring, considering three major areas of investigation: firstly, outlining the long-term cardiovascular phenotypic changes in preterm-born individuals; secondly, investigating factors related to preterm birth that may be modifying cardiovascular phenotype, such as preeclampsia, perinatal interventions, and physiological disturbances; and thirdly, the expected clinical relevance of these cardiovascular changes. This review discusses the importance of continued research focused on the mechanistic understanding of these cardiovascular alterations in order to develop specific primary prevention strategies.

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1. Introduction

Recent improved survival of infants born preterm (<37 weeks of gestation) has led to a growing cohort of very preterm-born individuals now entering adulthood [1]. It is estimated that preterm birth affects 9.6% of births worldwide and is currently the leading cause of perinatal morbidity and mortality in the developed world [2]. Before birth, such adults were often exposed to a suboptimal intrauterine environment,

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and after delivery, key developmental stages that would normally occur in utero during the third trimester had to take place under ex utero physiological conditions [3]. Since such a large proportion of births are preterm, any adverse health impact of this unusual developmental pattern is relevant to a large population of adults.

Recent studies have consistently demonstrated negative alterations in classical cardiovascular risk factors related to preterm birth, as well as long-term impacts on cardiovascular structure and function related to being born preterm [4,5]. This review will focus on the latter, considering three major areas of investigation: firstly, we will define the long-term cardiovascular structural and functional changes in preterm-born individuals; secondly, we will present factors related to preterm birth that may be modifying cardiovascular phenotype, in particular pre-eclampsia, as well as perinatal interventions, and physiological disturbances; and thirdly, we will discuss the expected clinical relevance of these cardiovascular changes.

2. Cardiovascular phenotype in preterm-born individuals

2.1. Cardiac

We have recently demonstrated a long-term impact of preterm birth on cardiac structure and function. Kozák-Bárány et al. found that left ventricular mass in humans born preterm increases 56% in the first month postnatally compared with 35% in those born at term [6]. It is possible that this increase had merely reflected the expected in utero cardiac growth rate for this point in development. However, our data indicate that the rapid increase in neonatal cardiac ventricular mass is a pathological event that persists into adulthood [4,5]. Using cardiovascular magnetic resonance and computational atlases, we demonstrated that preterm birth is associated with an increase in cardiac myocardial mass, inversely related to gestational age and independent of blood pressure variation and other perinatal factors. Preterm-born young adults also have shorter cardiac ventricles, smaller internal ventricular cavity diameters, and a displaced left ventricular apex compared to term-born controls, with distinct reductions in left and right ventricular function.

2.2. Macrovascular

Structural changes in the macrovasculature have also been observed in a number of recent studies, specifically a reduction in aortic size [7,8]. Studies investigating arterial stiffness have been less conclusive; several have shown increased stiffness in preterm born individuals [9–12], while others have shown no difference [13,14]. We have shown in a large-scale follow-up study of preterm-born young adults, using cardiovascular magnetic resonance, that preterm birth per se does not relate to an increase in arterial stiffness [15,16]. However, factors associated with preterm birth, such as perinatal interventions, did lead to alterations. This could explain why studies vary in their results depending on the frequency of these interventions within cohorts. Consistent changes in smaller conduit vessel size are less well described, but endothelial responses in later life have not been found to vary in relation to prematurity, unless other complications, such as preeclampsia, are also present [9,14,17–22].

2.3. Microvascular

Changes in the microvasculature have been observed in the majority of studies. Retinal vascularisation is abnormally reduced in preterm-born individuals with retinopathy of prematurity, and it has now been shown that such reductions are consistently found in other preterm-born individuals [23]. More recently, it has been demonstrated that individuals born preterm also have reductions in dermal capillary density into childhood and adolescence [18].

3. Relevant perinatal factors

Why preterm-born individuals demonstrate this cardiovascular phenotype is of interest. Preeclampsia is recognised as an antecedent for around 20 to 30% of all preterm births and, therefore, the role of this specific condition in 'programming' cardiovascular phenotype may be relevant [2,24]. However, two other key things distinguish the preterm infant. Firstly, they are exposed to relatively large physiological disturbances during the transition from the in utero to ex utero environment when their cardiovascular system is still immature. Secondly, they have a high exposure to perinatal interventions such as antenatal glucocorticoids, postnatal intravenous lipids, and mechanical ventilation, which are potent regulators of growth and development.

3.1. Preeclampsia

Preeclampsia is defined as the new onset of hypertension (brachial systolic blood pressure ≥140 mm Hg and/or brachial diastolic blood pressure ≥90 mm Hg) after 20 weeks of gestation in combination with proteinuria (≥300 mg/day or a spot urine protein/creatinine ratio of ≥30 mg/mmol) [25,26]. Both in experimental models and human epidemiological studies it is now clear that the offspring of pregnancies complicated by preeclampsia have an increased risk of developing high blood pressure and double the risk of stroke in later life [26]. The risk is greatest in early onset preeclampsia, diagnosed before 34 weeks of gestation, which is strongly linked with preterm birth [17]. However, although preeclampsia often occurs in combination with in utero growth restriction and preterm birth, the later cardiovascular risks associated with preeclampsia appear to be independent of these factors.

Through a series of investigations based around preterm infants whose mothers did, or did not, have a hypertensive disorder of pregnancy, our group has demonstrated that preeclampsia has an impact on the cardiovascular system independent of preterm birth. Specifically, as young adults, they exhibit endothelial dysfunction and increased carotid intima media thickness, a subclinical marker of atherosclerosis [9]. In addition, they have reductions in cardiac function that cannot be accounted for by prematurity alone, without additional cardiac structural changes [4]. Our hypothesis is that the associations between pre-eclampsia and later cardiovascular function relate to the abnormal placental development in preeclampsia [26]. This leads to the release of reactive oxygen species that trigger a systemic oxidative and inflammatory state [27]. As such, offspring of preeclamptic pregnancies develop in an environment of placental insufficiency, restricted oxygen supply [28] and abnormal levels of circulating antiangiogenic factors in the mother [29]. Animal studies indicate exposure to hypoxia related to abnormal placental development results in elevated myocardial collagen [30]. This is consistent with findings in newborn pigs, whereby short-term exposure to hypoxemia led to sustained reductions in longitudinal peak systolic strain [31]. This is potentially mediated through subendocardial and subepicardial fibres, which are susceptible to ischaemia [32].

3.2. Development and physiological disturbances

The most dynamic change in circulation in humans occurs during the transition from foetal to neonatal life as the low resistance placental circulation transforms into a high resistance arterial system [33]. This haemodynamic shift may be of particular relevance in preterm birth as it occurs during a period of development that would normally take place in utero and the immature cardiovascular system has to develop in an ex utero circulation.

During this period, cardiac size increases primarily via an increase in the number of mononucleated myocardial cells [34]. At birth, there is a switch in cardiomyocyte phenotype from a foetal hyperplastic pattern to neonatal hypertrophic response. While hyperplasia continues to an