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,
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 preeclampsia, 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 preeclampsia 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
extent following birth, there is little evidence of continued hyperplasia beyond three weeks postnatally. In lambs, the early transition of preterm birth leads to cardiac remodelling, with increases in myocardial collagen content, cell volume and cell ploidy, suggestive of accelerated maturation [3]. These findings are in line with the cardiac changes we have demonstrated in young adults born preterm [4,5].

The vascular system is also exposed to these premature changes in cardiovascular physiology. Vascular development in the embryo occurs through a combination of vasculogenesis and angiogenesis regulated by specific circulating molecules, with newly formed vessels undergoing vascular remodelling through formation and growth of new vessels and regression of others [35]. Preterm birth occurs during a key phase of arterial growth, characterised by rapid expansion of the capillary network to support rapid foetal growth and organ development [7]. It is possible that the interruption of this process and stress related to preterm birth, occurring during key developmental phases, might explain the observed capillary rarefaction in preterm-born individuals [18].

3.3. Perinatal interventions

A range of perinatal interventions were introduced in the late 1970s and early 1980s that increased preterm neonatal survival [36]. However, some of these interventions, such as intravenous lipid infusions, antenatal glucocorticoids, and mechanical ventilation, are known to be relevant to growth and development. Therefore, the possibility that these have long-term cardiovascular effects is worth considering.

3.3.1. Intravenous lipid infusions

Intravenous lipids, such as Intralipid, are widely used in parenteral nutrition of preterm-born individuals as a source of energy and essential fatty acids and have proven to be beneficial for neonatal brain and central nervous system development [37]. However, Intralipid consists of triglycerides in the form of soybean oil emulsified by egg phospholipid and glycerol, and results in a secondary hypercholesterolemia in preterm-born neonates [38]. Hypercholesterolemia is an important mediator of atherogenesis, which begins with lipid rich fatty streaks [39]. Fatty streaks first emerge in the abdominal aorta during foetal life [40], and exposure to abnormal circulating cholesterol levels of the mother during pregnancy has been shown to increase aortic fatty streaks in the offspring [41]. As such, we designed a nested case–control study of preterm-born young adults to determine the impact of exogenous lipids during early postnatal life on later cardiovascular function [15]. We found intravenous lipid infusions during the first nine weeks of life correlated strongly with a rise in total cholesterol levels at this time. Interestingly, this rise in total cholesterol also strongly related to increased aortic stiffness in young adulthood, most notably in the abdominal aorta. Furthermore, the postnatal rise in total cholesterol also related to reduced left ventricular systolic function.

3.3.2. Antenatal glucocorticoids

Antenatal glucocorticoids, such as betamethasone and dexamethasone, are commonly given to women who show evidence of preterm labour as they are beneficial for the prevention of neonatal respiratory distress syndrome in preterm-born infants, and substantially reduce neonatal morbidity and mortality [42]. However, glucocorticoids are potent regulators of growth and development [43]. While a single course of antenatal glucocorticoid treatment is beneficial for lung maturation and reduces complications such as neonatal respiratory distress syndrome [44], concerns have increased as to whether multiple doses have a greater influence on foetal development and later risk of adverse health [45]. A consistent finding from animal studies is that even transient exposure to glucocorticoids during specific windows of foetal life has lasting effects on later vascular function [46]. However, in the only double-blind, placebo controlled, randomised trial of antenatal betamethasone investigating vascular and metabolic changes in humans, there was no evidence of any differences in brachial blood pressure parameters in the offspring [47]. Nevertheless, we found that antenatal glucocorticoid exposure is associated with a localised increase in aortic arch stiffness in preterm-born young adults, similar in magnitude to term-born individuals a decade older [16]. This is in line with findings in animal models, which have demonstrated a specific effect of antenatal glucocorticoid exposure on connective tissue accumulation and arrangement within the aortic wall in late gestation [48].

3.3.3. Mechanical ventilation

Respiratory disease and the need for ventilation are major complications of preterm birth [49,50]. While respiratory distress or infection may lead to changes in the pulmonary vasculature sufficient to have a haemodynamic impact on the heart, mechanical ventilation may in itself negatively affect cardiac remodelling. The use of mechanical ventilation in neonates is known to increase survival and is considered as an essential clinical intervention for managing neonates born preterm with respiratory distress syndrome [49]. Despite these advantages, it is recognised that changes in pulmonary physiology induced by mechanical ventilation may have negative influences on normal cardiac function and lead to distinct changes in cardiac remodelling [50]. We explored this possibility in young adults born preterm, and were able to demonstrate that postnatal mechanical ventilation was an independent predictor of increased right ventricular mass in preterm-born young adults [5].

4. Clinical relevance

Data on the relevance of cardiovascular structural and functional changes in the general population are sparse for young populations. Nevertheless, the cardiac changes we have observed would be expected to relate to significantly increased risk of later life cardiovascular clinical events, based on longitudinal studies in older populations.

For instance, increased left ventricular mass index is an independent predictor for cardiovascular morbidity and mortality [51]. The average 19.8 g higher left ventricular mass in young adults born preterm is equivalent to that associated with a 9 kg/m² increase in body mass index [52] and in longitudinal studies, would equate to a >50% increased risk of cardiovascular clinical events in later adult life [53,54]. Furthermore, it was found in the Multi-Ethnic Study of Atherosclerosis that clinical cardiovascular disease-free participants with increased right ventricular mass have a significantly greater risk of heart failure and cardiovascular death, independently of left ventricular mass [55]. How the pattern of right ventricular remodelling we observed in those born preterm compares with remodelling observed in different disease states will be of future interest, and may also give further insight into the clinical significance of our findings in the longer term. Right ventricular systolic function is of independent and additive prognostic value in chronic heart failure and is one of the most powerful predictors of mortality in left heart failure [56]. Therefore, changes in the right ventricular structure and function may not only serve as a sensitive marker of subclinical pulmonary or left ventricular disease, but may also directly contribute to the onset of clinical heart failure [55]. As such, our finding that nearly 6% of young adults born preterm in our study had systolic function below the clinically accepted lower limit of normal and that 21% had ejection fractions below the lower limit observed in adults born at term is of particular concern.

It might be expected that the vascular changes related to hypertension would be of particular relevance to hypertensive risk. Recent follow-up studies in adolescents and young adults have shown magnitudes of increase in brachial systolic blood pressure ranging from 3 to 15 mm Hg between individuals born preterm and term [4,36,57,58]. These differences in blood pressure are clinically significant as blood pressure is known to track into later life [59] and it has been demonstrated on a population level that a 5 mm Hg increase in brachial systolic blood pressure corresponds to a 2% increase in cardiovascular death and a 34% increased incidence of stroke [60]. The reductions in capillary...
density seen throughout the course of development in preterm-born individuals may be of particular relevance, as microvascular rarefaction is a major determinant of increased vascular resistance and associated with the development of hypertension [61,62]. In 2011, Crump et al. showed in a cohort of over 630,000 individuals followed to age 25 to 37 years that young adults born preterm have an increased relative rate of antihypertensive medication prescription, which increased monotonically with the degree of prematurity and was independent of foetal growth restriction [13].

Whether the macrovascular changes in aortic size are also of relevance is unclear [7,8]. We, like others, demonstrated no particular difference in aortic stiffness between preterm-born individuals and term-born controls [15,16]. However, our investigations revealed a particular influence of antenatal glucocorticoids on aortic arch stiffness and postnatal intravenous lipids on the abdominal aorta in preterm-born young adults, both showing around a 1 m/s increase in pulse wave velocity. Outcome data in relation to pulse wave velocity are not yet available based on measures performed in young adulthood. Nonetheless, if this magnitude of difference is maintained into later life, we know from other studies that a 1 m/s increase in aortic pulse wave velocity relates to a 14% age- and sex-adjusted increase in total cardiovascular events in middle-aged and elderly individuals [63]. Nevertheless, reassuringly, preterm-born individuals exposed to the perinatal interventions showed no signs of increased blood pressure. However, to understand the true impact, interactions with age and disease development may need to be considered [64], and further investigations to understand how these changes might modify cardiovascular risk will need to be considered.

5. Conclusions

In summary, studies to date have provided a holistic and well-defined understanding of cardiovascular structural and functional in young adults born preterm. Through sophisticated imaging techniques and other non-invasive surrogate measures, it has been possible to isolate different components of the cardiovascular system and determine which perinatal events related to preterm birth are important determinants of long-term microvascular, macrovascular, and cardiac changes. As 10% of births are preterm, any adverse health impact of this unusual development pattern on cardiovascular development is relevant to a large population of adults. While this review has provided an insight into some of the key cardiovascular structural and functional changes, it is the first to present the progression of cardiovascular disease in this growing subgroup of individuals, further research is required to better understand the underlying mechanisms driving the observed changes in cardiovascular structure and function. In addition, follow-up of these individuals into later life will allow for the quantification of cardiovascular disease progression over time, providing direction for developing primary prevention strategies.

Conflict of interest

There are no conflicts of interest.

References
