Preterm Birth and the Shape of Your Heart

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Preterm birth, i.e., delivery more than 3 weeks before term, affects annually an estimated
13,000,000 newborn infants and rates are increasing\(^1\). Only in the USA, about 500,000 infants
are born preterm each year and of those, 80,000 are delivered very preterm (more than 8 weeks
before the expected date). Without effective care, the number of deaths among very preterm
infants would equal that of major causes of death in adults, such as Alzheimer's disease or
essential hypertension. While mortality after preterm birth was high until a few decades ago,
advances in perinatal medicine have resulted in almost universal survival\(^2\) so that the concept of
prematurity nowadays is shifting from being a pregnancy complication to a common
developmental basis for a whole and new generation of young adults. Although this progress is
very welcome for women delivering preterm, their infants and their families, there is an
increasing concern because preterm birth has been identified as an emerging risk factor for
arterial hypertension\(^3-5\), diabetes\(^6,7\), cardiovascular disease\(^8\) and stroke\(^9\) in later life.

Observational and experimental studies suggest that not only genetic influences but also
exposures in early life change and shape human development, which ultimately may affect later
health and susceptibility for disease\(^10-11\). Previously, most of the "developmental origins" studies
focused on poor fetal growth and low birth weight at term as a perinatal risk factor for later
disease. However, with rapidly increased survival, preterm birth has become the major
determinant of low birth weight in many countries. Considering preterm birth as an event in
which early developmental adaptations may occur, studies of the cardiovascular system in
infants, children and young adults born preterm may help to clarify underlying mechanisms and
effects, as well as any clinical relevance in a life-course perspective.

In this issue of Circulation, Lewandowski et al show for the first time that cardiac
development in humans may be fundamentally altered after very preterm birth\(^12\). Using cardiac
magnetic resonance, the authors studied a cohort of 234 healthy subjects aged 20-39 years. As compared to two reference groups born at term, the authors found that: 1) young adults born very preterm exhibited increased left ventricular mass, shorter left ventricles with smaller internal diameters and with apical displacement - findings which were robust also after adjustments for maternal preeclampsia, fetal growth restriction and current blood pressure; 2) low gestational age at birth correlated in a dose-response fashion to increased left ventricular mass in young adulthood - suggesting causality; and 3) that changes in cardiac geometry were accompanied by reduced systolic and diastolic function of the left ventricle.

In lambs delivered moderately preterm and examined at an age when cardiomyocyte proliferation and maturation had ceased, the myocardium was found to be remodeled and characterized by cellular hypertrophy and increased collagen deposition\(^{13}\). The work by Lewandowski et al is in line with these findings and extends them to encompass also humans born preterm. While their research focus was on long-term cardiac consequences after preterm birth, previous clinical studies have shown that the vascular tree - both at the micro- and macrovascular level - stops growing and becomes smaller after preterm birth\(^{3,14-17}\), and that arterial dynamics can be permanently altered\(^{3,18}\). Young subjects born preterm also exhibit cardiovascular hyperreactivity\(^{19,20}\), higher blood pressures\(^{3-5}\) and higher heart rates - both at rest and during mental stress\(^{21}\) - as well as signs of sympathoadrenal overactivity\(^{21}\). These findings point at multiple, systemic and long-standing effects after preterm birth that all - independent of each other or in interaction - may affect cardiovascular function, aging and disease risk in later in life.

The underlying mechanisms for cardiovascular programming after preterm birth remains to be clarified. A genetic and/or socioeconomic contribution cannot be excluded\(^{22}\). In addition,
exposure to antenatal corticosteroids for accelerated lung maturation, early cord clamping and premature loss of placental circulation with concomitant decrease in aortic blood flow, postnatal transition to a relative high pressure system with increased afterload for the immature heart, drop in IGF-1 levels (an important promotor of cardiovascular growth in fetal life), loss of placental estrogens, neonatal malnutrition, poor postnatal somatic growth, as well as feto-neonatal exposure to inflammation, oxidative and physical stress (pain) have all been suggested as potential driving forces for adverse cardiovascular adaptations after preterm birth. Given that improved neonatal nutrition and growth have been associated with lower risk for high blood pressure at the age of 2½ years\textsuperscript{23} and improved endothelial function in young adults born preterm\textsuperscript{24}, selected perinatal interventions may be one way forward towards effective cardiovascular risk reduction for adults born preterm.

Reassuringly for elderly people, preterm birth was not found to be associated with increased mortality from ischemic heart disease in a historic cohort (collected before the modern era of perinatal medicine and characterized by limited and selective survival)\textsuperscript{25}. However, current data – boosted by the pioneering work by Lewandowski et al\textsuperscript{12} – suggests that the first adult generation surviving very preterm birth are at significant risk for cardiac events. The most obvious clinical implication of this new knowledge is that young people born very preterm needs continued and tailored follow-up, taking the total cardiovascular risk factor burden into account. Coming studies will disclose whether this recommendation is also valid for the 4-5 times larger group of adults born moderately preterm.

**Conflict of Interest Disclosures:** None.
References:


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