Preterm Birth and the Shape of the Heart

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Preterm birth, that is, delivery $\geq$3 weeks before term, affects an estimated 13 000 000 newborn infants annually, and rates are increasing. In only the United States, $\approx$500 000 infants are born preterm each year, and of these, 80 000 are delivered very preterm ($\geq$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 disease or essential hypertension. Although mortality after preterm birth was high until a few decades ago, advances in perinatal medicine have resulted in almost universal survival, so the concept of prematurity nowadays is shifting from a pregnancy complication to a common developmental basis for a whole 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, diabetes mellitus, cardiovascular disease, and stroke in later life.

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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. 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 the underlying mechanisms and effects, as well as any clinical relevance in a life-course perspective.

In this issue of Circulation, Lewandowski et al12 show for the first time that cardiac development in humans may be fundamentally altered after very preterm birth. Using cardiac magnetic resonance, the authors studied a cohort of 234 healthy subjects 20 to 39 years of age. Compared with 2 reference groups born at term, the authors found that (1) young adults born very preterm exhibited increased left ventricular mass and shorter left ventricles with smaller internal diameters and with apical displacement—findings that were also robust after adjustment 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) 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. The work by Lewandowski et al is in line with these findings and extends them to encompass humans born preterm. Although their research focus was on long-term cardiovascular consequences after preterm birth, previous clinical studies have shown that the vascular tree—at both the microvascular and macrovascular levels—stops growing and becomes smaller after preterm birth, and that arterial dynamics can be permanently altered. Young subjects born preterm also exhibit cardiovascular hyperreactivity, higher blood pressures, and higher heart rates both at rest and during mental stress, as well as signs of sympathoadrenal overactivity. These findings point at multiple, systemic, and longstanding effects after preterm birth that all, independently of each other or in interaction, may affect cardiovascular function, aging, and disease risk in later life.

The underlying mechanisms for cardiovascular programming after preterm birth remain to be clarified. A genetic or socioeconomic contribution cannot be excluded. 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 relatively high-pressure system with increased afterload for the immature heart, drop in insulin-like growth factor-1 levels (an important promoter of cardiovascular growth in fetal life), loss of placental estrogens, neonatal malnutrition, poor postnatal somatic growth, and feto-neonatal exposure to inflammation and 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 2.5 years and improved endothelial function in young adults born preterm, selected perinatal interventions may be one way toward 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). However, current data, boosted...
by the pioneering work by Lewadowski et al,\textsuperscript{12} suggests that the first adult generation surviving very preterm birth is at significant risk for cardiac events. The most obvious clinical implication of this new knowledge is that young people born very preterm need continued and tailored follow-up, taking the total cardiovascular risk factor burden into account. Future studies will disclose whether this recommendation is also valid for the 4- to 5-times-larger group of adults born moderately preterm.

**Disclosures**

None.

**References**


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