Preterm Birth and the Shape of Your Heart

Running title: Norman; Preterm birth and the shape of your heart

Mikael Norman, MD, PhD

Address for Correspondence:
Mikael Norman, MD, PhD
Department of Clinical Science, Intervention and Technology
Department of Neonatal Medicine
Karolinska Institutet & University Hospital, H1:02
SE-17176 Stockholm, Sweden
Phone: 46 700 021 007
Fax: 46 517 730 53
Email: mikael.norman@ki.se


Key words: cardiac dysfunction; cardiac magnetic resonance imaging; cardiac remodeling; preeclampsia; preterm birth
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 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 promoter 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 and improved endothelial function in young adults born preterm, 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). However, current data boosted by the pioneering work by Lewandowski et al 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:


Preterm Birth and the Shape of Your Heart
Mikael Norman

_Circulation_. published online December 5, 2012;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/12/05/CIRCULATIONAHA.112.152827

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/