Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease

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Adapt yourself to the environment in which your lot has been cast, and show true love to the fellow-mortals with whom destiny has surrounded you. —Marcus Aurelius, Meditations VI, 39

Fetal Programming of Adult Cardiovascular Disease

It is now accepted that the risk of cardiovascular disease (CVD), which is a leading cause of death in the twenty-first century, is influenced by the interaction between our genes and environment.

In the modern world, cardiovascular disease is a leading cause of death for both men and women. Epidemiologic studies consistently have suggested an association between low birthweight and/or fetal growth restriction and increased cardiovascular mortality rate in adulthood. Furthermore, experimental and clinical studies have demonstrated that sustained nutrient and oxygen restriction that are associated with fetal growth restriction activate adaptive cardiovascular changes that might explain this association. Fetal growth restriction results in metabolic programming that may increase the risk of metabolic syndrome and, consequently, of cardiovascular morbidity in the adult. In addition, fetal growth restriction is strongly associated with fetal cardiac and arterial remodeling and a subclinical state of cardiovascular dysfunction. The cardiovascular effects occurring in fetal life, includes cardiac morphology changes, subclinical myocardial dysfunction, arterial remodeling, and impaired endothelial function, persist into childhood and adolescence. Importantly, these changes have been described in all clinical presentations of fetal growth restriction, from severe early- to milder late-onset forms. In this review we summarize the current evidence on the cardiovascular effects of fetal growth restriction, from subcellular to organ structure and function as well as from fetal to early postnatal life. Future research needs to elucidate whether and how early life cardiovascular remodeling persists into adulthood and determines the increased cardiovascular mortality rate described in epidemiologic studies.

Key words: cardiovascular disease, echocardiography, epigenetics, fetal growth restriction and fetal programming

Subclinical CVD begins to evolve early in life, long before the clinical symptoms appear decades later and strong evidence supports that it may start before birth.1-3 The best characterized prenatal risk factor for CVD is fetal growth restriction (FGR). Epidemiologic studies that have been published in the past four decades, first demonstrated that low birthweight was associated with an increased risk of death from coronary heart disease,4-12 stroke,5,10 hypertension,13-16 impaired glucose tolerance, and non–insulin-dependent diabetes mellitus.15,17,18 These associations have been described beyond disparities in life expectancy or healthcare system.10,19 The phenomenon to explain this relationship was denominated fetal programming.20,21 Structural, functional, and metabolic changes that occur in the fetus as an adaptive response to an adverse or suboptimal environment persist into postnatal life, which leads to a greater risk of disease in adulthood.20,22 In relation with CVDs, fetal programming is thought to occur through two main pathways: metabolic programming and cardiovascular remodeling.

Metabolic programming was the first hypothesis to explain the association of CVDs with low birthweight.23-25 Nutrient restriction during a period of intense epigenetic programming, such as fetal life, would promote developmental pathways that best suit this environment, through the selection of “thrifty genes” (or molecular pathways).1,2,16,25-27 Because in postnatal life nutrient availability will be normal, this programming will facilitate a higher incidence of metabolic disease, which includes obesity, diabetes mellitus, and metabolic syndrome, which secondarily may lead
Compelling experimental evidence supports the effects of nutrient restriction on epigenetic metabolic pathways in the offspring after FGR. Likewise, postnatal follow-up studies of children with FGR have reported the influence of postnatal nutrition and catch-up in the risk of metabolic syndrome and obesity. However, postnatal obesity, diabetes mellitus, or metabolic syndrome affect, in a highly heterogeneous manner, subjects who were born with a low birthweight and these conditions are actually uncommon in some reported cohorts. Consequently, although metabolic programming must be a contributing factor, it cannot explain per se the epidemiologic association between FGR and CVDs. Over the last 10 years, a second important line of evidence has shown that FGR is also associated with direct changes in the cardiovascular system. Because these changes persist into childhood and early adulthood, primary cardiovascular programming and remodeling can also be an important link to explain the association between FGR and adult CVDs. However, cardiovascular remodeling leads to subclinical changes in cardiac and vascular structure and function. Therefore, as with metabolic programming, it remains to be established how these changes combine with other prenatal or postnatal factors to lead to clinical CVD in adulthood.

Table 1 is a glossary containing terms used in this review that might be new or uncommon for obstetricians and gynecologists.

### Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>2-Dimensional speckle tracking echocardiography</td>
<td>Imaging technique that analyzes the magnitude of myocardial deformation in different directions by the use of the naturally occurring speckle pattern in the myocardium.</td>
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<tr>
<td>Cardiomyocyte</td>
<td>Columnar-shaped cells 20 μm in diameter and 60–140 μm in length that make up the cardiac muscle.</td>
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<tr>
<td>Epigenetics</td>
<td>The study of the chemical modification of specific genes or gene-associated proteins of an organism.</td>
</tr>
<tr>
<td>Epigenome</td>
<td>Record of the chemical changes to the DNA and histone proteins of an organism.</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>The enlargement or overgrowth of an organ or part because of an increase in size of its constituent cells.</td>
</tr>
<tr>
<td>Intima-media thickness</td>
<td>Measurement of the thickness of tunica intima and tunica media, the innermost 2 layers of the wall of an artery.</td>
</tr>
<tr>
<td>M-mode echocardiography</td>
<td>One-dimensional analysis of the heart in motion. It provides both high spatial and temporal resolution and usually is used to measure the thickness of the ventricular walls and the volumes of the cardiac chambers.</td>
</tr>
<tr>
<td>Myocardial performance index (Tei index)</td>
<td>Doppler-derived index of combined systolic and diastolic function. Defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time.</td>
</tr>
<tr>
<td>Myocardial strain</td>
<td>Percentage of change in the length of a myocardial segment during a given period of time.</td>
</tr>
<tr>
<td>Sarcomere</td>
<td>Fundamental contractile unit within the cardiomyocyte, defined as the segment between 2 neighboring Z-lines (or Z-discs, or Z bodies).</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td>Echocardiographic technique that uses Doppler effect principles to quantify the myocardial tissue motion.</td>
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### Cardiovascular Remodeling and Dysfunction in FGR

Fetal cardiovascular adaptations to FGR

FGR, defined as a failure to achieve the genetic growth potential, affects 7–10% of pregnancies. In the majority of cases, fetal smallness is the consequence of placental insufficiency. FGR has two main clinical presentations according to the gestational age of appearance, early and late onset, which are discussed in detail elsewhere. By arbitrary convention, late-onset small fetuses are usually subclassified into late-onset FGR (birthweight <3rd percentile or abnormal fetoplacental and uterine Doppler findings) or small for gestational age (SGA; birthweight 3rd - 9th percentile and normal Doppler findings). Although they differ in severity, clinical features, and perinatal outcomes, all the aforementioned clinical forms (early or late
FGR or SGA) have been reported to be associated with cardiovascular programming and remodeling.55-58 Placental insufficiency has two direct effects on fetal cardiovascular development. First, reduced oxygen and nutrients supply may disrupt cardiomyocyte growth and fiber architecture; and second, villous hypoplasia/thrombosis leads to increased placental resistance and chronic cardiac afterload. Consequently, the developing myocardium develops a variety of changes in cardiac macro and microstructure and function, which is defined as cardiac remodeling, to maintain ventricular output (Figure 1).59 Initially, the heart develops a more spherical shape that allows maintaining stroke volume with less contraction force, while also reducing wall stress to better tolerate pressure overload.60 This may happen in one ventricle ("elongated" phenotype, where a globular right ventricle pushes the septum and elongates the left ventricle) or both ventricles ("globular" phenotype). In more severe and/or prolonged cases, increased sphericity may not be enough, then hypertrophy develops to increase contractility and decrease local wall stress. Thus, cardiomegaly is a characteristic change, with three different phenotypes (elongated, globular, and hypertrophic) suggesting a progression of severity.60 Early-onset FGR is more associated with a hypertrophic response, whereas cardiac phenotypes late-onset FGR usually develops globular or elongated.60 Evaluation of cardiac morphometric parameters, such as the sphericity index, might be more stable and reproducible compared with functional parameters (eg, more susceptible of being affected by heart rate or fetal movements).

Sustained restriction of nutrients and oxygen is associated with cardiovascular remodeling at organ, tissue, and subcellular levels (right upper panel) and with epigenetic changes (mid left panel). Different fetal cardiac phenotypes—elongated, globular and hypertrophic (lower panel)—may be observed by cardiac imaging, depending on the severity/duration of the insult. Other abnormalities not included in this Figure (such as hypertension, endothelial dysfunction, and insulin resistance) can operate simultaneously.

miRNA, microRNA.
Alterations in cardiac shape are accompanied by subclinical cardiac dysfunction. \(^{29}\) Both can be demonstrated with fetal echocardiography. \(^{51,62}\) M-mode and tissue Doppler imaging show reduced longitudinal myocardial motion (reduced tricuspid and mitral annular excursion [tricuspid annular plane systolic excursion/mitral annular plane systolic excursion] and annular peak velocities), which reflects subclinical systolic dysfunction. \(^{38,60}\) Likewise, diastolic dysfunction appears from early stages \(^{63-67}\) as increased pulsatility in diastolic relaxation time), and systolic function (reduced contractility and cardiac output). \(^{69-71}\) Likewise, other studies reported impaired global longitudinal strain and regional asynchrony at 2–5 days of life, \(^{76}\) systolic and diastolic cardiac dysfunction \(^{1}\), and increased cord blood serum concentrations of B-type natriuretic peptide. \(^{77}\) Regarding vascular changes, FGR neonates have increased blood pressure, \(^{79}\) arterial stiffness, \(^{79-81}\) and aortic intima–media thickness (IMT), which is a marker of preclinical atherosclerosis. \(^{82,83}\)

Cardiovascular changes associated to FGR persist also into childhood (Figure 2). Remarkably, both early- and late-onset forms of FGR and SGA are associated with cardiac remodeling. Children with both, early and late-onset FGR, have more globular hearts, reduced longitudinal motion, and impaired relaxation in early and late childhood. \(^{57}\) Children with milder late-onset FGR show reduced longitudinal motion, apparently compensated by increased radial function, although early-severe FGR cases fail to show the compensatory increase in radial motion, which leads to reduced stroke volume accompanied by a compensatory increase in heart rate to maintain cardiac output. \(^{56,57}\) Significant vascular changes have also been reported that include microvascular endothelial dysfunction and increased blood pressure and IMT. \(^{56,57,84}\) Furthermore, autopsy studies of children 1–13 years old demonstrated atherosclerotic lesions in the aorta, which is associated inversely with birthweight. \(^{85}\)

A recent study reported persistence of FGR-associated cardiac remodeling until preadolescence (8–12 years old), with more spherical ventricles, reduced longitudinal motion, and impaired relaxation. \(^{86}\) Literature on vascular structure and function in adolescents and young adults with FGR is controversial. A Swedish cohort showed smaller aortic dimensions in young adults born with severe FGR. \(^{57,86}\) Two large cohorts recently have found no association with arterial wall thickening (IMT) at 11–19 years old. \(^{89,90}\) Large population studies seem to confirm a significant inverse correlation between low birthweight and blood pressure in people of all ages. \(^{91}\) However, this association is of little magnitude (an increase of 1–4 mm Hg), which could explain the absence of significant differences in small sample sizes.

**CVD in adults born with FGR**

Aside from retrospective epidemiologic evidence, there are very few prospective studies in former low birthweight adults. The Cardiovascular Risk in Young Finns study was initiated in 1980 and enrolled 3596 children and adolescents aged 3–18 years. \(^{92}\) At an average of 31 years old, those children born SGA (<10th percentile) had markedly greater triglycerides, low density lipoprotein cholesterol, systolic blood pressure, and IMT compared with controls. \(^{93}\) In the most recent follow-up evaluation (34–49 years), there were subtle differences in heart size and lower ventricular stroke volume, with normal ventricular sphericity indices, diastolic function, and blood pressure in SGA at term. \(^{94}\) The Enigma study, a long-term follow-up study of 882 young individuals from the United Kingdom, reported a small increase in systolic blood pressure and central pulse pressure in young adults (mean age, 21 years) born SGA (<9th percentile). \(^{95}\) However, this association disappeared after adjustment for body size. \(^{95}\) Similar findings have been reported in a longitudinal follow-up study from the United States that described 20-year-old young adults born with very low birthweight (<1500 g) between 1977 and 1979. \(^{96}\)

Interpretation of these studies is challenging, taking into account the multiple influences that occur during the life of these individuals and the inherent limitations in the accuracy of obstetric information. In any event, available data suggest that, as life progresses, multiple factors seem to intervene, which as a whole attenuate the differences observed in FGR both in utero and during early life. Whether there are specific subgroups where cardiovascular differences persist or worsen remain open questions for future research, as briefly discussed later on this review.
Other factors that influence the developmental origins of CVD

Besides FGR, prematurity is a common cause of low birthweight. Preterm birth is also linked to cardiac remodeling (shorter and smaller ventricles with increased mass),\(^\text{97}\) higher blood pressure later in life\(^\text{98}\) and insulin resistance.\(^\text{99,100}\) Furthermore, in a nationwide Swedish cohort study that included >2.6 million live births, Carr et al\(^\text{101}\) have provided the first evidence that preterm birth increases the risk of clinical heart failure during childhood and adolescence. A relevant finding of The Cardiovascular Risk in Young Finns study is the discrimination between birthweight and prematurity in the susceptibility to CVDs.\(^\text{92}\) Reduced fetal growth and preterm birth increased independently the severity of subclinical carotid atherosclerosis and reduced arterial endothelial function in early adulthood.\(^\text{93}\) However, this association was most pronounced in those born preterm with FGR; for those born preterm without FGR, vascular markers did not differ from controls, which indicated that impaired fetal growth drives the association of preterm birth with poor vascular health, as opposed to prematurity per se.\(^\text{93}\) In addition, a recent study that included only preterm gestations (delivered at 30 weeks gestation) has shown that, 10 days after birth, infants with FGR have higher systolic blood pressure and maximum aorta intima-media thickness compared with preterm AGA infants.\(^\text{102}\) These studies suggest that the mechanisms that program increased cardiovascular risk after preterm birth differ from those that contribute to increased risk in those born low birthweight but at full term.

Preeclampsia is often associated to FGR and prematurity. Interestingly,
offspring of preeclamptic pregnancies have increased blood pressure during childhood and higher risk of stroke later in life. A 20-year follow-up study found that preterm offspring of hypertensive pregnancies have evidence of endothelial dysfunction and greater subclinical atherosclerosis. The authors postulated that abnormal vascular development in the fetus in response to the same placenta-related factors that affect the mother might represent the underlying mechanism.

Other factors such as maternal obesity and diabetes mellitus have also been postulated as potential factors that influence fetal metabolic programming and cardiovascular remodeling. However, the experimental evidence that supports its role in CVD programming is limited compared with that with FGR, and long-term follow-up studies have discredited the role of some such as maternal diabetes mellitus. The extent of the influence of these other perinatal factors in the individual susceptibility to CVD may be established in response to the intrauterine milieu or because of genetic variation that determines both general and vascular development of the fetus.

**Biologic Basis for Fetal Cardiovascular Programming**

**FGR and cardiac remodeling at organ, cellular, and subcellular level**

The biologic basis for fetal programming derives from copious evidence from animal experimentation, with the use of animal models of ligature of the uteroplacental vessels, maternal hypoxia, reduction in maternal food intake or protein restriction, and finally, glucocorticoid exposure. Adult offspring of pregnant rats that were subjected to undernutrition develop obesity, hyperinsulinemia, and hyperleptinemia, specifically in the presence of inactivity and a high-fat diet. Animal models of maternal nutrient deprivation reported reduced number of cardiomyocytes at birth, increased myocardial interstitial fibrosis, expression changes of profibrotic genes and structural cardiovascular abnormalities, and, importantly, impairment of recovery after myocardial ischemia in the offspring. Cardiac hypertrophy and coronary artery vascular reactivity is also evident in lambs born to ewes undernourished during early gestation. Maternal food restriction also induces reduced glomerular number and structural changes (remodeling) in smooth muscle content of small and large vessels in neonatal and young adult rat offspring. Studies that mimic placcental insufficiency by reduction of uteroplacental vasculature have reproduced biometric and cardiovascular changes of human FGR, such as increased ductus venous pulsatility, more spherical ventricles, reduced longitudinal motion, and presence of postsystolic shortening.

Experimental FGR models have shown the extensive variety of cellular and subcellular changes induced by this condition, which include reduced number of cardiomyocytes, increased cardiomyocyte volume, reduction in myocardium microvascularization, shorter sarcomeres, mitochondrial rearrangement, and altered gene expression related to energy and oxygen homeostasis. Reduced sarcomere length have also been reported in human fetuses. Other studies that focused on chronic hypoxia showed changes in fetal cardiac structure and function, increased collagen content, changes in cardiomyocyte proliferation and apoptosis, postnatal changes in the isoforms of proteins that are important for the sarcomeric structure, including titin and myosin, and increased cardiac susceptibility to ischemia reperfusion.

**Molecular mechanisms of fetal programming: epigenetics**

Epigenetic changes have been postulated as the most important mechanism driving fetal programming. Individuals prenatally exposed to the Dutch famine of 1944–45 had, six decades later, less DNA methylation of the imprinting insulin growth factor-2 gene compared with their unexposed, same-sex siblings. Clinical studies have reported that the DNA methylation pattern in cells from cord blood and placenta between FGR human pregnancies and controls is different, affecting genes involved in metabolism and adipose tissue differentiation. Importantly, the phenotypic effects of epigenetic modifications during development may not manifest until later in life, especially if they affect pathways of genes that modulate responses to environmental challenges, such as a high-fat diet.

The influence of the prenatal environment in the epigenome has also been shown in experimental studies. A caloric-dense maternal diet has the ability to generate epigenetic effects on the offspring, altering fetal chromatin structure in primates. Moreover, maternal undernutrition leads to long-term cholesterol dysregulation in the offspring via epigenetic mechanisms, modifies gene expression of fetal renal transcription and growth factors, and can alter permanently the expression of miRNAs in the aortas of newborn and aging rat offspring. These epigenetic marks may also be transmitted to future generations. This effect has also been demonstrated in animal models, showing that fetal adaptations such as endothelial dysfunction, hypertension, and insulin resistance are passed to the second and third generation of undernourished pregnant rats.

The relevance of epigenetics in the adaptation to chronic cardiac failure has been highlighted in human adults, with distinct reported signatures of DNA methylation in cardiac tissue. A recent analysis of the DNA methylome from cardiomyocytes of neonatal healthy, adult, and adult with failing heart revealed a dominant role for DNA methylation as a highly dynamic and reversible process during cardiomyocyte development, postnatal maturation, and disease. In fetal life, treatment of pregnant rats with hypoxia leads to DNA hypermethylation that has been associated with early transition from mono- to binucleate cardiomyocyte, which reduces the number of cardiomyocytes in the developing heart, and an increase in the susceptibility to ischemic injury in the offspring. These considerations point to epigenetic processes.
that play a key role in the developmental origins of CVD.

**Clinical Implications, Open Questions, and Opportunities for Research**

The evidence summarized herein supports that FGR induces cardiovascular programming and remodeling, and that it is plausible that these changes pose an increased risk for CVD later in life. However, whether and how other factors that appear later in life interact with this predisposition to evolve to clinical CVD remains a subject of research. The “second hit” hypothesis, which is well accepted in fields such as human oncology, postulates that a genetic/epigenetic predisposition requires a second insult to manifest as clinical disease. Therefore, it is not unreasonable to postulate that cardiovascular subclinical remodeling in growth-restricted fetuses entails a higher predisposition, which needs to be combined with other factors to evolve to clinically relevant disease. And hence, some of the structural and functional changes that result from fetal programming could be corrected or further deviated, depending on other events or exposures during life.

In combination with this idea, a second important aspect that needs to be addressed by future research is the existence of windows of opportunity (Figure 2). As shown in animal models, changes in metabolism or epigenetic patterns that are determined by prenatal exposure are correctable if the intervention is introduced very early in life, but not later.\(^\text{130-133}\) Regardless of whether there is a well-defined period, a “window of opportunity” that “closes” later in life, or just a steady decline of the opportunity for correction as the individual matures, evidence suggests that early life interventions can have strong effects on the cardiovascular changes that are associated with FGR. Key putative early life intervention strategies that may improve or restore vascular and cardiac health in a childhood that was affected by FGR include maintenance of healthy weight, promotion of breastfeeding,\(^\text{144}\) and dietary interventions.\(^\text{155,156}\) Observational and in-vivo studies indicate that breastfeeding and consumption of a diet with a high polyunsaturated:saturated fat ratio in early childhood improves cardiovascular remodeling in individuals born with FGR.\(^\text{7,154}\) Similarly, dietary consumption of either marine (eicosapentaenoic acid) and docosahexaenoic acid or plant-derived (α-linolenic acid) omega-3 fatty acids appear to have specific hemodynamic and vascular benefits in children and adolescents who were born SGA, but not in children who were born with normal birthweight.\(^\text{90,156,157}\)

Therefore, important challenges for future research are to ascertain the mechanistic pathways whereby fetal cardiovascular programming might lead to CVD in adulthood. Although it is likely that, as a whole, the effects of FGR on adult cardiovascular mortality rate are not huge, the identification of specific subgroups at higher risk, and especially the characterization of lifestyle factors that promote accelerated progression to CVD disease in subjects who experienced FGR, could have a strong influence on their quality of life. Considering that FGR affects a large share of the population, the possibility of reducing morbidity in only a fraction of these patients could be remarkable.

In summary, FGR has a strong influence in cardiovascular health, opening opportunities to improve public health by the identification of perinatal factors that can determine strongly the individual’s health and potentially accelerate the implementation of preventive strategies starting from fetal or early postnatal life.

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