

# Human fetal growth restriction: a cardiovascular journey through to adolescence

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Intrauterine growth restriction has been noted to adversely impact morbidity and mortality in the neonatal period as well as cardiovascular well-being in adolescence and adulthood. Recent data based on a wide range of ultrasound parameters during fetal and neonatal life has noted early and persistent involvement of the cardiovascular system. Some of these measures are predictive of long-term morbidities. Assessment of vascular mechanics is a new and novel concept in this population, and opens up avenues for diagnosis, monitoring and evaluation of the likely effectiveness of interventions. Prevention of these adverse vascular and cardiac outcomes secondary to fetal growth restriction may be feasible and of clinical relevance. This review focuses on growth restriction in humans with respect to cardiovascular remodeling and dysfunction during fetal life, persistence of functional cardiac impairment during early childhood and adolescence, and possible preventive strategies.

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## Introduction

Intrauterine growth restriction (IUGR) complicates 5–10% of pregnancies and constitutes a major cause of perinatal morbidity and mortality.<sup>1,2</sup> Fetal programming in the subjects may result in permanent structural, metabolic and functional changes.<sup>3,4</sup> Fetal programming is a process whereby permanent alterations in physiology and metabolism result from insult or stimuli during critical early periods of development. IUGR may be described as maladaptation with deleterious effects on the developing cardiovascular system. Lower birth weight has been associated with higher blood pressure (BP) at 7 and 10 years of age.<sup>5,6</sup> A close relation between differences in adult cardiovascular mortality and differences in infant mortality 60 and more years ago between different parts of the United Kingdom, led to the proposal of fetal origins of adult diseases.<sup>7,8</sup>

Circulatory adaptations, which in time may manifest as cardiac dysfunction, have been noted on fetal ultrasound in the form of impaired relaxation and increased globularity. These may predict postnatal vascular remodeling and hypertension in childhood.<sup>9</sup> Recent data noted impaired cardiac and vascular mechanics in the early neonatal period.<sup>10–12</sup> As an adaptive response to the IUGR state, fetal ultrasound evidence of increased globularity and impaired relaxation of the heart has been noted. These circulatory adaptations may in time, affect systolic function and contractility.

An example of vascular adaptation to IUGR state is the thickening of arterial vessel walls. Increased arterial thickness has also been noted in children and young adults born small-for-gestational age (SGA).<sup>13,14</sup> These are sensitive markers of hypertension in young children and of atherosclerosis risk in adults, supporting the epidemiologic link between IUGR and later cardiovascular disease (Barker's hypothesis).<sup>7,8</sup> Given the significant long-term impact on cardiovascular health and the overall public health importance of the issue, preventive strategies are being proposed. Hence, earlier identification of this high-risk population in the fetal and/or neonatal period is vital for long-term monitoring and/or early interventions. In this review, we provide an overview of the fetal, neonatal and pediatric evidence of the cardiovascular impact of IUGR using echocardiography as the primary modality of assessment. The possibility of dietary interventions reducing cardiovascular disease is also discussed.

The objectives were:

- (1) Appraisal of the cardiovascular manifestations in fetal IUGR setting.
- (2) Discuss cardiac dysfunction and vascular mechanics in the early neonatal period.
- (3) Discuss ongoing impairments in school age and pre-adolescent children and explore preventive options.

## Cardiovascular manifestations in fetal IUGR setting

IUGR is defined as a failure of a fetus to achieve its growth potential and is characterized by a birth weight lower than expected for gestational age (GA) (below the 10th centile).<sup>1,15</sup>

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Once genetic disorders, perinatal infections and toxics are ruled out, constitutional SGA fetuses, with a near-normal perinatal outcome, should be distinguished from 'true' IUGR, the latter being associated with abnormal fetoplacental Doppler<sup>1</sup> and poorer perinatal outcome. IUGR is usually described under two different phenotypes according to the onset of the restriction.<sup>1</sup>

Early-onset IUGR (before 34 weeks' gestation) affects <1% of deliveries and constitutes a major cause of perinatal and long-term mortality and morbidity.<sup>2</sup> It is usually associated with pre-eclampsia and severe placental insufficiency leading to abnormal umbilical artery Doppler, quick and progressive hemodynamic deterioration and preterm delivery of the fetus in order to preserve its life.<sup>1,16</sup>

Late-onset IUGR fetuses usually have a milder degree of placental insufficiency (not reflected by umbilical artery Doppler abnormalities), and are delivered near or at term.<sup>1,13,17</sup> About two third of late-onset small fetuses present severe forms of smallness, that is estimated fetal weight <3rd centile, or as abnormal cerebro-placental ratio or uterine artery Doppler.<sup>1</sup> This group has poorer perinatal outcomes and abnormal placental histological signs.<sup>18</sup> The remaining third of fetuses do not present any of the above features and usually have near-normal perinatal outcomes. By arbitrary convention, the first group is thought to represent a subset of 'true IUGR' within small fetuses, while the second is often defined as 'constitutionally' SGA.<sup>1</sup>

### ***Fetal cardiovascular manifestations of IUGR***

The heart is a key organ in the fetal adaptive response to IUGR. Placental insufficiency leads to fetal undernutrition, hypoxia and pressure/volume overload. In order to adapt to this adverse environment, the fetal heart remodels; changing to a more globular shape and thereby becoming less efficient.<sup>9,19</sup> Recent advances in fetal echocardiography have facilitated additional analysis in IUGR fetuses; spherical ventricles with decreased longitudinal motion [decreased annular displacement by M-mode and peak velocities by tissue Doppler imaging (TDI)] has been noted.<sup>9,20,21</sup> These fetuses also had impaired relaxation [prolonged isovolumetric relaxation time (IVRT)] with maintained cardiac output.<sup>9,19</sup> These changes are more prominent in the early-onset IUGR, but also present in late-onset IUGR and SGA state.<sup>19,22</sup>

### ***Cardiovascular remodeling and dysfunction in early IUGR***

Early-onset IUGR usually results from severe placental insufficiency which is reflected in abnormal umbilical artery Doppler profile.<sup>1</sup> These are very severe cases that usually show cardiomegaly, hypertrophied and globular hearts, and mild pericardial effusion.<sup>23</sup> The pathophysiology underlying these cardiac shape changes is complex and most probably includes pressure and volume load to the fetal heart due to a chronic state of hypoxia, undernutrition and increased placental resistance. Probably, the inadequate provision of nutrients and

oxygen has a direct effect on the myocardial contractility. In addition, the heart responds to pressure and volume overload by reducing the radius of curvature (toward a more spherical heart) and thickened myocardial walls (toward cardiac hypertrophy). Finally, volume overload would explain the cardiomegaly and mild pericardial effusion.<sup>23</sup>

Cardiac remodeling is regularly associated with cardiac dysfunction. While ejection fraction is generally preserved in IUGR, stroke volume is frequently reduced and compensated by an increase in heart rate in order to maintain cardiac output and perfusion to organs.<sup>9</sup> Early IUGR fetuses also show decreased longitudinal motion (reduced displacement). This can be assessed using M-mode echocardiography by measuring tricuspid annular peak systolic excursion (TAPSE)/mitral annular peak systolic excursion and annular peak velocities.<sup>20,24</sup> This is complemented by signs of diastolic dysfunction from the early stages of deterioration<sup>19,24</sup> (increased pulsatility in ductus venosus<sup>16,25</sup> trans-mitral E/A ratios<sup>16,19,26</sup> and IVRT,<sup>19,27</sup> and decreased diastolic annular peak velocities).<sup>20,24,28</sup> Very recently, data from two-dimensional (2D) speckle tracking echocardiography (STE) has demonstrated the presence of post-systolic shortening in the basal septal part of almost half of the early-onset IUGR cases.<sup>29</sup> This indicates abnormal regional myocardial deformation possibly due to chronic pressure overload in these cases. Cardiovascular biomarkers in cord blood of early-onset IUGR also illustrate the cardiac dysfunction of these fetuses; higher fetal concentrations of B-type natriuretic peptide have been noted.<sup>19,26</sup> This is considered the gold standard marker of heart failure and is usually increased in response to hypoxia and volume overload. The most severe early-onset IUGR cases also present signs of myocardial involvement as measured by increased concentrations of plasmonic troponin and heart-fatty acids-binding protein.<sup>19</sup>

### ***Cardiovascular remodeling and dysfunction in late IUGR***

The initial reports of cardiac function in IUGR were focused on the most severe (early) cases. However, recent advances in fetal echocardiography have facilitated demonstration of signs of cardiac dysfunction in milder cases using more sensitive techniques such as TDI.<sup>21</sup> Late-onset IUGR fetuses are characterized by non-hypertrophic, more globular hearts, most probably reflecting a milder degree of placental insufficiency.<sup>23,30</sup> In addition, late-onset IUGR fetuses show increased values of myocardial performance index (MPI)<sup>30,31</sup> and decreased longitudinal motion.<sup>21,30</sup> These changes have been reported in late-onset IUGR cases but also in SGA fetuses without signs of severity.<sup>30</sup> Moreover, increased cord blood levels of troponins have been detected in some late-SGA newborns alluding to a degree of myocardial involvement.<sup>32</sup>

### ***Postnatal persistence of cardiac remodeling in IUGR***

Recently, it has been demonstrated that cardiovascular changes in IUGR persist postnatally, suggesting primary fetal cardiovascular programming with implications for adult disease.<sup>22</sup>

In both, early- and late-onset IUGR children, more globular and less efficient hearts with reduced longitudinal motion and impaired relaxation have been demonstrated.<sup>22</sup> The more severe early-onset cases have decreased radial function leading to lower stroke volume and increased heart rate in order to maintain cardiac output while the late-onset IUGR demonstrate increased radial function.<sup>6</sup> In addition, both groups of IUGR show signs of vascular programming including increased BP and intima-media thickness.<sup>13,22,33</sup>

### Cardiac and vascular dysfunction in the early neonatal period

#### Cardiac dysfunction in infants with IUGR

While there is pre-existing data indicating abnormal cardiac function (systolic as well as diastolic) in fetuses with IUGR and children who were born growth restricted, the lack of information in the early postnatal period stands out as a knowledge gap. A range of cardiac and vascular mechanics parameters have been studied using trans-thoracic echocardiography (Table 1). These can give comprehensive information about cardiac and vascular adaptation and dysfunction. Recent data noted early cardiac changes in clinically asymptomatic growth restricted infants.<sup>10,11</sup> In a prospective observational echocardiographic study, cardiac performance was compared between SGA infants (<3rd centile for GA) and appropriate for gestational age (AGA) infants in the first few days of postnatal life. Conventional echocardiography noted diastolic dysfunction (poor relaxation and compliance) which was echocardiographically apparent as higher trans-mitral E/A ratio and prolonged IVRT in addition to impaired systolic function (contractility and cardiac output).<sup>10</sup> TDI imaging is a relatively recent addition to imaging techniques; persistently raised MPI on TDI assessment suggests combined systolic/diastolic dysfunction.<sup>12</sup> Other measures such as reduced S' and E' myocardial velocities (reflecting impaired contractility), higher E/E' ratios (impaired relaxation and an important prognostic marker of diastolic dysfunction) have been noted when compared with AGA infants.<sup>12</sup> The echocardiographic assessment from the left ventricle (LV MPI) also correlates well with elevated  $\beta$ -natriuretic peptide ( $r^2 = 0.69$ ;  $P < 0.001$ ). The higher LV mass (bigger, globular hearts) in turn influences coronary flow as coronary evaluations inform about myocardial oxygen delivery and cardiac performance.<sup>34,35</sup> Coronary and ductus venosus flow abnormalities predict poor fetal and neonatal outcomes in fetuses with IUGR.<sup>34</sup> The physiological explanation is that the cardiac hypertrophy (related to chronic cardiovascular stress in fetal life) leads to increased myocardial oxygen consumption, which is almost exclusively met by the augmentation of coronary blood flow.<sup>36,37</sup>

STE is a non-Doppler method considered much more sensitive than conventional echocardiography. Alterations in the speckle patterns in time create regional strain vectors depicting global and segmental deformations (segmental wall motion).

Strain (deformation from the original state) and strain rate (rate of deformation) has informed that different parts of the heart adapt differently to chronically raised afterload state. We studied the SGA population using STE and noted a significantly lower global deformation compared with the AGA peers. In addition, a significant basal to apical segment gradient was noted.<sup>38</sup> This has important physiological correlations as the heart adapts to chronically elevated afterload by hypertrophy; functionally, the basal segments are the most affected (Fig. 1). This regional asynchrony reflects the orientation of muscle fibers and its interaction with local wall stress and LV pressure. In other words, it is the basal part of the myocardium which is the first to get affected.

#### Vascular mechanics in infants with IUGR

Arterial vascular mechanics in infants with IUGR have been noted in the early neonatal period,<sup>10</sup> which may contribute toward raised afterload overtime. Arterial vascular mechanics and morphometry have been the focus of recent work, which could potentially provide prognostic information. Aortic wall thickness can be measured with high frequency ultrasound probes. Skilton *et al.* first noted maximum aortic intima-media thickening (aIMT) to be significantly higher in the term infants with IUGR compared with controls.<sup>33</sup> These findings were replicated recently; the aortic vasculature was noted to be significantly thicker in SGA infants compared with the AGA cohort.<sup>10</sup> Increased carotid intima-media thickness has been reported in infants, children and young adults born SGA.<sup>13,39</sup> The aIMT is a good non-invasive marker of pre-clinical atherosclerosis<sup>40</sup> and may serve as a sensitive marker of hypertension in young SGA children and of atherosclerosis risk in adults.<sup>41,42</sup> Along with the vascular architecture, the arterial vascular mechanics have been recently assessed. In a recent study on term infants, the stiffness index and impedance were found to be significantly elevated in growth restricted infants compared with well-grown controls in the early postnatal days.<sup>10</sup> Stiffness index measures the relationship between pulsatile changes in arterial diameter and pressure while impedance measures afterload.<sup>43</sup> The abdominal aortic wall distensibility coefficient (DC) and whole-body arterial compliance (WBAC) have also been proposed as useful measures. These may provide indices of early vascular changes that predispose to further vascular disease.<sup>44</sup> Very low birth weight infants are characterized as early as the 5th day of life by high arterial stiffness (significantly lower WBAC and DC).<sup>44</sup> These early alterations in arterial elastic properties may pave the way for long-term elevation of arterial pressure and may reflect impaired elastin synthesis and decreased endothelial function.<sup>45,46</sup> Early endothelial dysfunction, increased sympathetic tone, raised concentrations of apolipoprotein B and reduced concentrations of insulin-like growth factor I may all contribute to vascular abnormalities and arterial thickening.

Along with their contribution to afterload and BP, vascular mechanical impairments may also have deleterious

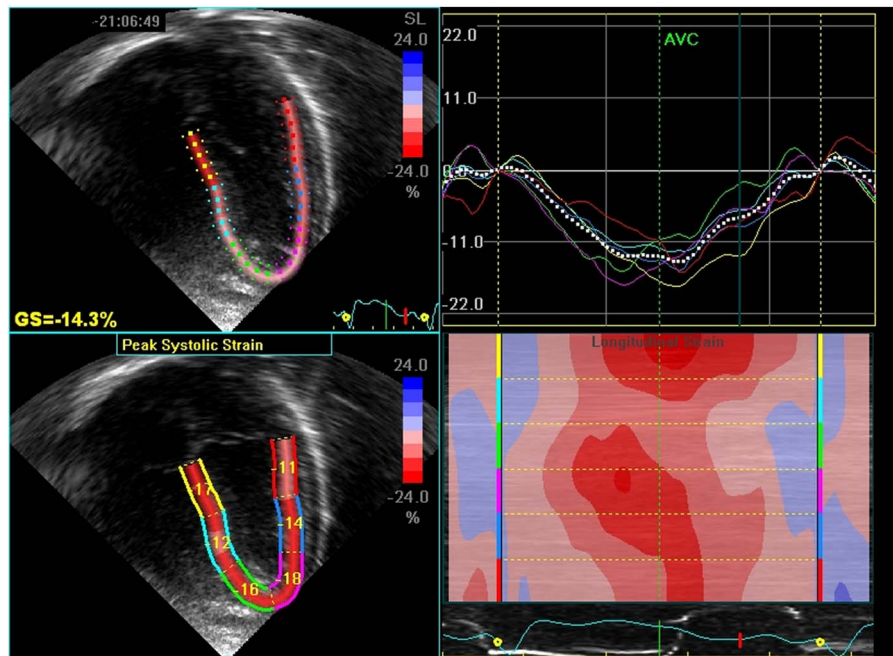
**Table 1.** Range of cardiac and arterial mechanical parameters for assessment in intrauterine growth restriction

Component of function	Technique	View	Cursor position	Comments
<i>Cardiac systole</i>				
1 LVO	PWD	Apical five chamber	Aligned with the flow, sample just beyond aortic valve	Angle and cursor position dependant
2 FS	M-mode	Parasternal long axis	Just distal to mitral valve leaflet tips at end diastole	$\frac{LVEDD - LVESD}{LVEDD}$
3 Myocardial performance index	PWD	Apical four and five chamber	Trans-mitral and apical five chamber	$\frac{IVCT + IVRT}{LVET}$
4 mVCFc	2D/M-mode	Combination of 1 and 2	Combination of above two	FS/LVET
5 Fractional area change	2D	Apical four chamber	Include full view of the left ventricle (base to apex)	$[(LV \text{ four-chamber area at end diastole} - LV \text{ four-chamber area at end systole}) / LV \text{ four-chamber area at end diastole}] \times 100\%$
6 Tricuspid annular plane systolic excursion	M-mode	Apical four chamber	Lateral aspect of tricuspid annulus	Maintain vertical alignment with the apex
7 Mitral annular plane systolic excursion	M-mode	Apical four chamber	Lateral aspect of mitral annulus	Maintain vertical alignment with the apex
<i>Cardiac-diastolic</i>				
8 Tissue Doppler	TDI PWD	Apical four chamber	Sample just below the lateral annulus (mitral and tricuspid)	Peak systolic (S'), early diastolic (E'), late diastolic (A') and peak isovolumic contraction velocities
9 E/A ratio, EDT	PWD	Apical four chamber	Aligned with the flow, sample at tips of mitral leaflets	E wave-early passive filling A wave-late active filling
10 IVRT	PWD/CWD	Apical five chamber	PW – sample volume placed within LVOT (in proximity to the anterior mitral leaflet to record both inflow and outflow signals) CW – Doppler beam at an intermediate position (between inflow and outflow) to record both velocities	From closure of the aortic valve to the opening of mitral valve
<i>Vascular mechanics</i>				
11 LAD coronary artery flow	PWD	Parasternal short-axis view, moving the transducer down one or two intercostal spaces, rotating it clockwise and angling superiorly	Placed over the LAD distal to the bifurcation	Identify using color Doppler, set to a low Nyquist limit (15–30 cm/s) Internal dimensions measured at end diastole on 2D
12 Stiffness index	M-mode	Longitudinal abdominal	Straight, non-branched 1 cm segment of the abdominal aorta	$\ln \text{ (systolic BP/diastolic BP) } / [(AAOs - AAOd) / AAOd]$
13 Input impedance	PWD	Apical five chamber	Aligned with the flow, sample just beyond aortic valve	Pulse pressure/peak flow

Table 1. (Continued)

Component of function	Technique	View	Cursor position	Comments
14 Systemic vascular resistance	PWD	Apical five chamber	Aligned with the flow, sample just beyond aortic valve	(Mean BP – right atrial pressure)/LVO * estimated right atrial pressure 5 mmHg
15 Distensibility coefficient	2D	Transverse subcostal view	Abdominal aorta in the supra-celiac region	[(A syst – A diast)/A diast]/pulse pressure
16 Whole-body arterial compliance	2D and PWD	Parasternal long axis and apical five chamber	Aortic valve cusps for aortic cross section and aligned with the flow, sample just beyond aortic valve for stroke volume	Stroke volume/pulse pressure
<i>Morphometry</i>				
17 Sphericity index	2D	Apical four chamber	End-diastolic 2D view	(Base to apex length)/basal diameter
18 LA:Ao	M-mode	Parasternal long axis	Aortic valve cusps	Measured at end systole
19 LVMI	M-mode	Parasternal long axis	Just distal to mitral valve leaflet tips at end diastole	0.8 [1.04 (diastolic LV internal diameter + diastolic LV septal thickness + diastolic LV posterior wall thickness) 3 – (diastolic LV internal diameter) 3] + 0.6.
20 Interventricular septal hypertrophy	M-mode	Parasternal long axis	Just distal to mitral valve leaflet tips at end diastole	Septal thickness indexed to LV posterior wall thickness in diastole
21 Relative left ventricular dilatation	M-mode	Parasternal long axis	Just distal to mitral valve leaflet tips at end diastole	Wall thickness relative to end-diastolic LV cavity dimension
22 aIMT	M-mode	Longitudinal abdominal	Straight, non-branched 1 cm segment of the abdominal aorta	Focused on the dorsal arterial wall using high resolution; measured at end diastole

LVO, left ventricular output; PWD, pulsed-wave Doppler; CWD, continuous wave doppler; CW, continuous wave; FS, fractional shortening; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; LVET, left ventricular ejection time; mVCFc, mean velocity of circumferential fiber shortening; 2D, two dimension; LV, left ventricle; TDI, tissue Doppler imaging; EDT, E wave deceleration time; LVOT, left ventricular outflow tract; LAD, left anterior descending artery; BP, blood pressure; AAOs, abdominal aorta dimension at end systole; AAOd, abdominal aorta dimension at end diastole; A syst, abdominal aorta cross-sectional area at end systole; A diast, abdominal aorta cross-sectional area at end diastole; LA:Ao, left atria aortic ratio; LVMI, left ventricular mass index; aIMT, aortic intima media thickness.



**Fig. 1.** Top left: mapping of the region of interest in the left ventricle myocardium. Bottom left: peak segmental longitudinal strain values depicting basal to apical gradient. Top right: Segmental peak systolic strain curves. Bottom right: curved anatomical M-mode of longitudinal deformation (*with permission*). GS, global strain; AVC, aortic valve closure.

end-organ effects. Zanardo *et al.* studied the relationship between IUGR, fetal aortic thickening and glomerular function during infancy. Urinary micro-albumin and albumin–creatinine ratio were significantly higher in the IUGR cohort and was associated with persistently increased aIMT.<sup>40</sup> In addition, the increased arterial wall stress may, by itself, induce a cardiac remodeling response.<sup>47,48</sup> Histologically, decreased myosin heavy chain in cardiac sarcomeres, decreased cardiac myocytes, increased apoptosis and glycogen deposition result in globular ventricles with different/less efficient architecture. Increased afterload may affect cardiac function in the longer term and be associated with early onset and chronically high BP.<sup>49–51</sup>

These changes appear to be long lasting. Similar alterations in BP and carotid intima media have also been noted at age 3–6 years too.<sup>13</sup> Bradley *et al.*<sup>14</sup> noted similar changes in arterial mechanics in pre-adolescent children born growth restricted, indicating ongoing effect. Miles *et al.* studied the impact of birth weight on BP and arterial stiffness in young adults (mean age, 21 years) and noted that it reflected in higher central pulse pressure and peripheral vascular resistance.<sup>52</sup> Identification of these alterations are in conformity with the long-standing epidemiologic association between IUGR and associated morbidity in later life.

### Persistence into later childhood and adolescence

While there is strong evidence that IUGR is associated with increased arterial wall thickness and cardiac remodeling, evidence that these alterations persist into later childhood is less clear. Two large cohorts have recently found no association of

SGA with arterial wall thickening in children and adolescents aged 11 and 19 years of age,<sup>53,54</sup> while in 8-year-old children recruited antenatally into a clinical trial, fetal growth was inversely associated with carotid intima-media thickness in those randomized into the dietary control group.<sup>55</sup> The dietary control group aimed to replicate the omega-3:omega-6 fatty acid ratio of the general population.<sup>55</sup> This is consistent with evidence from adults, which is also mixed.<sup>56,57</sup> However, perhaps the best direct evidence that IUGR is associated with greater atherosclerosis in childhood comes from autopsy studies of children aged 1–13 years at the time of their death, demonstrating that the extent of atherosclerotic lesions in the aorta is inversely associated with birth weight.<sup>58</sup>

For cardiac structure and function, the evidence from the STRIP study indicates that while birth weight is directly associated with LV mass in adolescents aged 15 years, those born SGA may also have increased LV mass.<sup>59</sup> Whether this would be more pronounced in people born with more severe forms of IUGR has not been determined.

### Intervention strategies

These alterations in vascular and cardiac structure and function in childhood and adolescence are consistent with the well-described association of lower birth weight with higher risk of adult cardiovascular disease events, such as heart attack and stroke. Prevention of these adverse clinical outcomes in adulthood, may be feasible and of clinical relevance.<sup>60</sup> As clinical cardiovascular disease manifests almost exclusively during adulthood, the theoretical window for the initiation of

prevention strategies spans almost the entire life-course, from infancy through adulthood. Nonetheless, others have proposed that prevention strategies aimed at reducing the burden of adult chronic disease will have a more marked benefit if implemented in early life, than if commenced in adulthood after sub-clinical disease is well established, or after the first clinical evidence of disease is detected.<sup>61</sup> The time frame during which early life interventions may need to be initiated is short. The number of currently living adults who were affected by IUGR and the inherent difficulty of demonstrating a reduction in hard cardiovascular outcomes due to an early life intervention, the development of age-appropriate prevention strategies across the entire life-course spectrum is likely warranted.

Markers of vascular and cardiac health in childhood and adolescence may be useful surrogates of cardiovascular disease for testing and monitoring the efficacy of early life interventions. Key putative early life intervention strategies that may improve or restore vascular and cardiac health in childhood affected by fetal growth restriction include maintenance of healthy weight, promotion of breastfeeding and dietary interventions including consumption of a diet rich in healthy fats, or maternal antioxidant supplementation.

On average, children born SGA have lower body mass index (BMI) than those born with healthy birth weight, from infancy through late adolescence<sup>54</sup> with minimal shift in this anthropometric profile in adulthood.<sup>62</sup> Are people who were born with IUGR more susceptible to the cardio-metabolic risks associated with obesity? Or conversely, are they spared the cardiovascular risk of being born with IUGR if they can maintain a healthy weight? Evidence from young children suggests that current BMI is more strongly associated with intima-media thickness in children born with IUGR, than for those born with healthy birth weight<sup>63</sup> while in adults, it would appear that the association of SGA with adult carotid intima-media thickness is independent of adult BMI, and importantly, that there is no interaction between adult BMI and birth weight status with regards to the association with carotid intima-media thickness.<sup>57</sup> This finding in adults suggests that the long-term vascular benefits of obesity prevention and maintenance of healthy weight are no different between those born SGA and those with a healthy birth weight profile, and would argue against the introduction of obesity prevention programs that specifically target those born SGA. That said, there may be a portion of those born with true IUGR who are prone to excessive early life weight gain, also known as catch-up growth. Such excessive weight gain during infancy and early childhood is a risk factor for later childhood obesity,<sup>64</sup> and an independent risk factor for elevated intima-media thickness in later childhood.<sup>65</sup> Obesity prevention programs that target this age group have produced only marginal improvements in BMI, which may not translate to meaningful improvements in prevalence of overweight and obesity<sup>66</sup> although in theory they may be more efficacious in those at risk of catch-up growth. A key component of such early life obesity prevention programs includes the promotion of healthy newborn feeding practices to achieve the World Health Organization goals of at least 6 months

exclusive breastfeeding, yet, such programs achieve only a small absolute increase, of about 10%, in the rate of breastfeeding at any given postnatal time-point.<sup>67</sup> Nonetheless, observational studies indicate that children who are breastfed, particularly those breastfed for at least 6 months, have lower weight gain during early childhood and improved cardiac structural properties,<sup>63–65</sup> although evidence for vascular health benefits is mixed. It is worth noting that these putative benefits of breastfeeding do not appear to be specific to children born with IUGR, but rather appear to be applicable across the spectrum of birth weight.

Consumption of a diet rich in healthy fats, particularly polyunsaturated fatty acids, has recently emerged as a potential postnatal lifestyle prevention strategy. In young children, consumption of a diet with a high polyunsaturated:saturated fat ratio improves cardiac remodeling, including in children who were born with IUGR.<sup>63</sup> In contrast, dietary consumption of either marine (eicosapentaenoic acid) and docosahexaenoic acid or plant-derived ( $\alpha$ -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 birth weight. These include lower BP in childhood and adolescence,<sup>54,68</sup> and lower carotid and aortic intima-media thickness in late adolescence.<sup>54</sup> These findings of benefits specific to those born SGA are independent of dietary fiber, salt and total energy intake, and are supported by a *post-hoc* analysis of a randomized trial of fish oil supplementation in children from birth to 5 years of age,<sup>55</sup> consistent with a direct effect of omega-3 fatty acids themselves. There are plausible general mechanisms through which omega-3 fatty acids may improve cardiac and vascular health,<sup>69</sup> and also mechanisms that are specific to people born with IUGR, who have lower circulating levels of omega-3 fatty acids putatively due to reduced enzyme activity.<sup>70,71</sup>

Other health-some foods and dietary patterns, such as the Mediterranean diet and plant-based diets, have been demonstrated to have cardiovascular benefits in the general population.<sup>72,73</sup> Being a group considered at higher risk of cardiovascular diseases, those born with IUGR may theoretically obtain greater absolute benefits from such healthy diets than people who were born with a normal birth weight profile, although there is limited direct evidence as yet to support this hypothesis.

There is evidence from animal studies for other strategies to prevent the adverse cardiovascular sequelae of fetal growth restriction, most notably maternal antioxidant supplementation which reverses the hemodynamic, vascular, cardiac and autonomic effects of a diverse set of adverse intrauterine stressors mechanistically linked with fetal growth restriction. For example maternal vitamin C supplementation during pregnancy prevents chronic prenatal hypoxia-induced aortic wall thickening, improves autonomic activity and increases birth weight.<sup>74–76</sup> Similarly, a lipid peroxidation inhibitor prevents the increases in BP due to maternal protein restriction, and restores vascular reactivity.<sup>77</sup> Importantly, similar findings from animal models have recently been reported for melatonin, an antioxidant that may be appropriate for use during pregnancy in

humans, and thus a better candidate for translation.<sup>78,79</sup> While fetal growth restriction has diverse etiology in humans, this evidence from animal studies that different antioxidants prevent the cardiovascular outcomes of a diverse set of intrauterine stimuli, suggests that oxidative stress may be a key underlying common pathophysiological mechanism driving the programming of cardiovascular disease in fetal growth restriction, and thus a good target for prevention strategies.

Accordingly, lifestyle interventions show promise for preventing or reversing cardiac and vascular remodeling in children born with IUGR, although *a priori* evidence from randomized controlled trials is missing.

### Future directions

Understanding the cardiovascular changes that occur in IUGR might be useful in the monitoring and risk stratification. Several cardiac parameters have been identified as main predictors of acidemia and adverse perinatal outcome in early IUGR. Particularly, ductus venosus Doppler has a high predictive value for perinatal mortality ( $P < 0.001$ ,  $r^2 = 0.34$ ), principally useful in monitoring early IUGR among 26–28 weeks of gestation.<sup>16</sup> Specifically, the Doppler parameters included elevated ductus venosus index and ductus venosus absent or reversal of atrial velocities. In addition, fetal echocardiography including LV sphericity index, TAPSE and IVRT show a strong correlation with hypertension in childhood. It may be useful in the detection of those IUGR cases at higher cardiovascular risk that might benefit from early therapeutic strategies.<sup>9</sup> Lifestyle interventions such as high intake of dietary long-chain omega-3 fatty acids, breastfeeding promotion and avoiding becoming overweight may prevent the progression of subclinical cardiovascular remodeling in children born with IUGR.<sup>55,63,80</sup> Considering the high prevalence of IUGR and the increasing availability of intervention strategies, the implementation of cardiovascular follow-up and management could improve the future health of IUGR cases with a remarkable effect on public health. Therefore, based on the collective research data known today, IUGR is a recognized cardiovascular risk factor and implementing a specific cardiovascular follow-up and management program could be beneficial.

### Conclusions

IUGR influences or induces cardiovascular adaptation during fetal life affecting both cardiac and arterial mechanical function. Sonographic parameters may assist in detection during a sub-clinical state as pre-clinical markers of disease and may be a useful tool for long-term monitoring. The effects of fetal programming persist well into childhood, adolescence and adulthood; possibly contributing to morbidity and mortality related to circulatory causes. Timely, relatively modest interventions in early life can have a large effect on disease risk later. This requires a long-term investment in terms of public health policy and resources. Implementation of cardiovascular

follow-up and management from early stages could improve the future health in those affected by IUGR, making it an important public health issue.

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### Conflicts of Interest

None.

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