Long-Term Follow-Up of Intrauterine Growth Restriction: Cardiovascular Disorders

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Key Words

Intrauterine growth restriction · Cardiovascular disease · Fetal programming · Long-term consequences

Abstract

In the modern world, cardiovascular disorders are the leading cause of mortality in developed countries, which in most cases undergo a long subclinical phase that can last decades before the first clinical symptoms appear. Aside from the well-known risk factors related to lifestyle and genetics, there is growing evidence that in a proportion of cases, the predisposition to cardiovascular disease lies in prenatal life. Moreover, numerous historical cohort studies and animal models have shown a clear association between low birth weight and increased cardiovascular mortality in adulthood, including increased risk of hypertension, diabetes, dyslipidemia and coagulation disorders in children and adults. Besides premature birth, low birth weight in the majority of the cases is caused by intrauterine growth restriction (IUGR), which affects up to 10% of all births. Several clinical and experimental studies showed that IUGR fetuses present signs of cardiac dysfunction in utero that persist postnatally and may condition higher cardiovascular risk later in life. The present review discusses the importance of the long-term cardiovascular follow-up of the patients who suffered early

or late IUGR in utero, particularly with regard to the long-term epidemiological studies in adults, prospective studies in children and the possible mechanisms that trigger IUGR and cardiovascular programming. Considering the high prevalence of IUGR and the progressing availability of intervention strategies, it is of the highest clinical relevance to detect cardiovascular risks as early as possible, to introduce timely preventive interventions and to adapt the lifestyle, in order to improve the long-term cardiovascular health outcome of IUGR cases.

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Introduction

Fetal Programming of Adult Cardiovascular Disease

In the modern world, cardiovascular disorders are the leading cause of mortality in developed countries, with an estimated 23% of all disease burdens and over 4 million deaths each year in Europe [1]. For many years the cardiovascular condition was thought to be determined by the genetic factors and lifestyle, defined by the amount of physical activity and quality of nutrition in early adulthood. In most cases, cardiovascular diseases (CVDs) undergo a long subclinical phase that can last decades before the first clinical symptoms appear [2]. However, already

in 1989, David Barker's group [3] in Southampton, UK, established a direct correlation between low birth weight and CVD in adulthood, including hypertension and cardiovascular mortality. This discovery was confirmed and widely explored in the last few decades of intensive research in both humans [4] and animals [5]. Taken together, the collective data obtained suggests that the complex interaction between genetic constitution and the prenatal and early postnatal environment determines the growth and development of the fetus and defines the susceptibility to certain disorders in adult life, like hypertension, diabetes, dyslipidemia and coagulation disorders [6]. This phenomenon is known as 'fetal programming', when an insult in utero leads to functional changes in key organs remaining in postnatal life and leading to a greater risk of various diseases in adulthood [5, 7–9]. The rapid cell proliferation and differentiation during fetal growth are very sensitive to any of the even smallest changes damaging to the environment that can lead to permanent alterations in structural and functional constitution, which then may persist into the adult life [6].

Definition and Classification of IUGR

Besides premature birth, low birth weight in the majority of the cases is caused by intrauterine growth restriction (IUGR) [10]. According to the 2001 classification of the American College of Obstetricians and Gynecologists, IUGR is diagnosed when a fetus does not reach its growth potential, characterized by the birth weight and body mass lower than normal with respect to the number of gestational weeks below the tenth percentile [11]. IUGR is a major cause of perinatal morbidity and mortality [12] and may complicate 7–10% of all pregnancies, depending on the population, geographical location and the standard growth curves used as reference in different countries.

Most IUGR causes are associated with placental insufficiency. The gestational age at which the IUGR develops is of major significance for the outcome of pregnancy [13]. Therefore, IUGR is also classified by early and late onset. Early IUGR is diagnosed by the classical Doppler flow measurements before 34 weeks of gestation, recognized as an increase in impedance to blood flow at the umbilical artery and subsequent fetal vasodilation mechanism to maintain cerebral oxygen supply [14]. The severity of placental dysfunction and its impact on the fetal cardiovascular status is then determined by the grade and the progression rate of Doppler abnormalities. Late-onset IUGR after 34 weeks differs by clinical manifestations, patterns of deterioration, and severity of placental dys-

function, which normally is milder and with normal umbilical artery blood flow [15, 16]. Unfortunately, the lack of information in the literature makes it very difficult to differentiate between early and late IUGR, and most of the studies fail to identify the origins of IUGR in order to select the correct patient cohorts accordingly.

IUGR and Cardiovascular Remodeling

Assessing cardiovascular conditions in utero, multiple studies revealed that fetuses which have been diagnosed with IUGR have cardiac systolic and diastolic dysfunction [17], with increased E/A ratios and myocardial performance index [18] and reduced myocardial tissue velocities [19]. Moreover, it has been postulated that IUGR fetuses experience hypertension and hypervolemia due to hemodynamic redistribution and adaptation to hypoxia and insufficient nutrition [20]. Further follow-up evaluation of these children and experimental evidence have demonstrated that cardiovascular remodeling, triggered in response to the stress conditions in utero, persist as a permanent feature in postnatal life [5] including dilated cardiomyopathy-like heart remodeling and vascular dysfunction, increased blood pressure and carotid intima-media thickness. These findings are similar to those of cardiac remodeling associated with sustained pressure and volume overload. The closer analysis revealed that molecular changes in the cardiac myocyte contractile machinery in IUGR fetuses are similar to those described in dilated cardiomyopathy and diastolic heart failure [21]. At the same time, sarcomere length is decreased, which results in a less efficient contraction. In addition, gene expression of the sarcomere regulatory proteins is altered and these alterations persist in adulthood as well [21]. Again, these molecular changes are in line with alterations described in other models of cardiac disease driven by high pressure and/or volume [22].

In addition to the obvious importance of the intrauterine environment during critical developmental stages, the conditions of early childhood are likewise of great significance. The accelerated postnatal growth, so-called 'catch-up' growth, is one of the most important triggers of hypertension in small for gestational age children who are more likely to suffer cardiovascular complications in adult life [23].

Importance of Early Diagnosis and Prevention of CVD

Fetal developmental programming, besides determining a cardiovascular health condition in adult life, also provides an exclusive and potent approach of intervention to prevent CVD and improve the health condition in

adulthood. The current 'European guidelines on CVD prevention in clinical practice' highly support the clinical follow-up of patients with a high risk of CVD, although IUGR patients are unfortunately still not included in this group [24]. The importance of early diagnosis and consequent monitoring of IUGR has been stressed by recent studies showing an improved cardiovascular outcome in children due to the timely applied preventive measures like dietary ω -3 supplementation [25, 26].

In this review we will discuss the importance of long-term cardiovascular follow-up of patients who suffered early or late IUGR in utero, particularly with regard to the long-term epidemiological studies in adults, prospective studies in children and the possible mechanisms that trigger IUGR and cardiovascular programming.

Epidemiological Studies Supporting the Link between IUGR and Adult CVD

After Barker and colleagues discovered in 1989 the apparent link between low birth weight and increased risk of death from CVD and stroke, the increasing number of subsequent studies confirmed these observations. Moreover, the correlation between low birth weight and hypertension was reported already in 1988 in a Swedish study analyzing a cohort of male army recruits who had been small at birth [27]. The described association was also confirmed later in men and women in several larger studies [28–31].

One of the main disadvantages of early epidemiological studies was a lack of a correct and complete follow-up for several decades [32]. These requirements, however, were achieved in the following study that included almost 15,000 Swedish men and women, with a 97% follow-up over a period of more than 50 years [33]. This study showed a strong correlation between lower birth weight and death rate from ischemic heart disease. A further large cohort study performed by the group of Rich-Edwards et al. [34] in 1997 in more than 120,000 American women revealed strong negative trends of recorded birth weight and incidents of non-fatal coronary heart disease and stroke.

The awareness of environmental influences that impair fetal and infant growth was increased after the report that men with the lowest birth weights and at 1 year of age had the highest death rates from ischemic heart disease [35]. An interesting observation was that despite the similar increase in general death rate in men and women inversely related to their lower birth weight, only men developed CVD in adult life [36].

Following the described observations, a hypothesis was proposed that the promotion of growth during prenatal and early postnatal life could improve cardiovascular conditions in adulthood, especially in boys who weighed <3.5 kg [3]. Later, however, it was proven to be wrong, as in the cohort study in Finnish men the cardiovascular mortality was also increased as a result of the rapid weight gain in the first 3 years of life [37]. The increased mortality rate was also confirmed in obese men who had a BMI above average between 7 and 15 years of age [38]; moreover, this effect was greater in males born to obese mothers [39].

A study in women born short in length showed that an increase in height later in life was associated with the higher risk of mortality from coronary heart disease [40]. Since most of these women had tall mothers, it was suggested that their prenatal growth was constrained. Taken together, these data confirm that men and women with a lower birth weight and subsequent obesity in adulthood have the highest CVD risk [37].

Despite the certainty of the observations described above, one also needs to take into consideration the environmental factors that can have a great influence on the cardiovascular development. For example, a cohort study in South Africa showed the link between low birth weight and adult glucose intolerance and blood pressure elevation that occurs in young adults despite the lack of full catch-up growth as a consequence of a high-risk, disadvantaged environment of the population [41].

Taken together, the epidemiological evidence described above confirms the critical correlation between the early life environment and the major risk factors for CVD. Moreover, the collected data supports the great importance to identify early origins of the disease and to perform a thorough long-term follow-up of the high-risk patients (fig. 1).

Prospective Cohort Studies in IUGR Children and Adolescents

Further studies investigating the link between fetal growth restriction and development of CVD in postnatal life, particularly in children and adolescents, have confirmed a strong inverse correlation between birth weight and cardiovascular disorders.

The association between elevated blood pressure in children and low birth weight has been known for a decade following the collective strong evidence in the literature [42]. Already in 1997, one of the largest cohort stud-

Fig. 1. Cardiovascular programming in IUGR. Cardiovascular programming is triggered by an insult in utero, which can lead to functional changes in key organs persisting in postnatal life and leading to a greater risk of various diseases in adulthood. Therefore, it is critical to intervene as early as possible in order to prevent CVD in adult life.

ies of almost 150,000 adolescents in Sweden showed that systolic blood pressure was significantly higher in young men who had the lowest birth weight, thus supporting the notion of a programming effect of fetal growth retardation in utero on hemodynamic regulation in early adult life [43].

The well-known Generation R study has showed that fetal hemodynamic patterns already change in the presence of reduced fetal growth while the fetus is still within the normal estimated fetal weight range. The condition of decreased fetal growth triggers cardiac remodeling and cardiac output that are consistent with a gradual increase in afterload and compromised arterial compliance [44].

Furthermore, our group has obtained consequent conclusive data in a prospective cohort study in children 3–6 years of age, suggesting that fetal cardiovascular programming is not exclusive for premature and severe forms of growth restriction, but it also occurs mildly in late-onset IUGR [45, 46], which often is referred to as small for gestational age [47, 48]. In both early- and late-onset IUGR children, more globular hearts, reduced longitudinal motion and impaired relaxation were observed. Late-onset IUGR could compensate by increased radial function, while the more severe early-onset cases showed decreased radial function leading to lower stroke volume and increased heart rate in order to maintain cardiac output [49]. Additionally, both groups showed signs of vascular remodeling including increased blood pressure, as well as carotid intima-media thickness [49]. The significantly progressive increased aortic intima-media thickness and elevated blood pressure were also observed in another recent study in IUGR fetuses and infants at

18 months of age compared to control, suggesting predisposition of the infants to hypertension early in life and cardiovascular risk in adulthood [50].

Proposed Mechanistic Pathways of IUGR

Despite the many studies performed investigating different aspects of IUGR in human pregnancies, the pathophysiological processes underlying this disorder remain very complex and not completely understood. Various animal models have been developed and employed in order to clarify processes regulating fetal growth in normal conditions and IUGR, and to develop potential strategies of intervention.

Several possible risk factors have been proposed and evaluated in animal models as possible triggers of IUGR – maternal nutrition, impairment of uteroplacental function and early exposure to harmful exogenous factors.

Maternal Nutrition

Fetal nutrition is the most critical factor that determines pregnancy outcome, and the strong correlation between maternal nutritional diet and fetal development was described already decades ago [51]. Since then, many animal studies have confirmed that the limitation of general food intake to pregnant animals to 30, 50 or 70% of the regular free intake ad libitum, besides significantly lower birth weight, also programs increased blood pressure, decreased angiogenesis, and increased risk of endothelial dysfunction in the adult undernourished offspring compared to the offspring of the control dams [52–54].

The programming of these symptoms, however, depends on the severity and on the gestational period of the restriction [55, 56]. Interestingly, birth weight is significantly decreased in rodents only if the general caloric restriction is carried out late in pregnancy from days 7 or 15 to 21 [57], but not during gestational days 7–14.

Compared to the balanced reduction in maternal nutrient intake, the specific restriction of maternal protein in rat programs more consistent rise of blood pressure in adult life [58–60]. Since the early 1990s, many studies have shown that a maternal low-protein diet during the gestational period leads among other symptoms to lower birth weight, hypertension, vascular dysfunction, increased angiotensin-converting enzyme activity, decreased nephron number and increased oxidative stress in adulthood [56, 61, 62]. Endothelial dysfunction has also been shown to be associated with maternal low-protein diet in a non-litter-bearing species [63]. Moreover, recent studies have also shown that maternal protein restriction also affects the lifespan of the offspring. Similar to general caloric restriction, duration and timing of the maternal low-protein diet are also very important. If dams are fed the low-protein diet only for single weeks, the magnitude of the diet's effect on postnatal blood pressure is greatest when the low-protein diet is consumed during the last week of gestation [64].

Impairment of Uteroplacental Function

Induction of IUGR by maternal nutritional manipulation provides easy and reproducible tools to study fetal programming, but they fail to reproduce the restriction of oxygen supply [65], which is considered to be among most critical factors in fetal development. As an alternative, one of the most frequently used methods to study mechanisms of IUGR is to induce placental insufficiency by the direct restriction of vascular perfusion.

The permanent ligation of both uterine arteries leads to hypoxia, decreased growth factor availability and hypoglycemia [66]. The high degree of blood flow obstruction results in a significantly lower birth weight and programs reduced nephron numbers, hypertension, type 2 diabetes and proteinuria in the adult offspring [55]. The mortality rate of this model is, however, much higher compared with nutrition manipulation models. A permanent ligation of one uterine artery performed at mid-gestation in guinea pig causes alterations of the placenta, heart, aorta and kidneys in the offspring [67]. Moreover, growth-restricted fetuses and neonates are chronically hypoxic [68], hyperglycemic [69] and have an altered brain development [70]. A selective ligation of 30–50% of

uteroplacental vessels late in gestation programs pronounced cardiovascular Doppler changes in fetuses, particularly in the ductus venosus, which partially reproduces the hemodynamic features of the IUGR condition in human fetuses [71]. Other interventions mimicking placental insufficiency, such as uteroplacental embolization, carunclectomy or maternal hyperthermia [72], result in a similar phenotype and cardiovascular dysfunction as that in rodent surgical models [73], suggesting a common underlying mechanism of cardiovascular programming.

Prenatal Exposure to Exogenous Factors

Studying the possible mechanisms of fetal cardiovascular programming, the group of Langley-Evans [74] has discovered that hypertension induced by fetal exposure to a maternal low-protein diet in the rat can be prevented by treatment with metyrapone – an inhibitor of maternal glucocorticoid synthesis. It is also known that maternal exposure to glucocorticoids has been associated with reduced birth weight and adult disease in humans [75, 76]. Consequently, it has been shown that treatment of pregnant rats with the synthetic glucocorticoid dexamethasone results in a lower birth weight and persistent elevation of arterial blood pressure in the adult offspring [77, 78]. Identical results were obtained after treatment of pregnant rats with carbenoxolone – an inhibitor of placental enzyme, 11 β -hydroxysteroid dehydrogenase-2 (11 β -HSD2), which metabolizes corticosterone to the inert 11-dehydrocorticosterone [79]. Interestingly, the model of low-protein diet treatment of pregnant rats has also been associated with a decreased activity of 11 β -HSD2 in placenta, which would in turn increase access of endogenous maternal glucocorticoids to the fetus [80]. Moreover, a 40–50% reduction in food intake of pregnant animals results in an increase in maternal and neonatal glucocorticoids in rats [81] and in guinea pigs [82]. Taken together, the collective data points towards the pivotal role of the placental 11 β -HSD2 in the programming of hypertension and that excessive exposure of the fetus to the glucocorticoids would inevitably lead to the reduction in birth weight and elevated blood pressure which persists into adult life [83].

It was also found that exogenous environmental factors like high altitude can act independently from other factors to reduce birth weight. Increased maternal ventilation and ventilator response to hypoxia during pregnancy raises arterial oxygen saturation and correlates with the offspring's birth weight [84]. Similarly, the exposure of pregnant rats to chronic hypoxia (10.5% O₂) between days 15 and 21 of gestation leads to an increase in the percentage and size of binucleated myocytes, an in-

crease in apoptotic cells in the fetal heart [85] and in an increased susceptibility of the adult heart to ischemic-reperfusion injury [86]. The increased cell death in fetal heart could lead to cardiac hypertrophy, resulting in asymmetric enlargement of the heart's chambers and an increased cardiovascular risk in adulthood.

It has also been known for many years that maternal smoking is one of the factors that has a strong association with fetal growth restriction, dramatically affecting the placental vessels due to nicotine and hypoxia [87–89]. Moreover, fetal exposure to maternal smoking might also lead to adverse cardiovascular effects, like hypertension, that persists into adulthood [90, 91]. Accordingly, it has been shown in the animal experimental model that daily inhalation of tobacco throughout gestation causes a significantly reduced birth weight in rat offspring [92, 93]. Similar adverse effects of growth restriction are observed after fetal exposure to alcohol [94] or harmful drugs like cocaine [95]. The adverse effects of fetal alcohol exposure are clearly demonstrated in various animal models, including inhalation of ethanol vapor, direct intraperitoneal injection and oral exposure by gavage, diet or drinking water [96].

These conclusive data indicate that cardiac overload due to the changes in placental function or maternal nutrition may result in a change in the developmental profile of cardiomyocytes and cardiac function in adult life.

Possible Mechanisms and Therapeutic Targets

Various interlinking mechanisms have been proposed to explain the effect of early insults on cardiovascular health condition in adult life. After investigating structural and physiological changes in different tissues, the most promising field currently is epigenetic regulation of organ development and molecular processes in pre- and early postnatal life [97–100]. The fetal environment can trigger various epigenetic modifications, changes in gene expression pattern without alterations of DNA sequence, and thus lead to different phenotypes of the offspring [97, 99, 100]. Three main processes are identified that can silence, activate or regulate the level and timing of the gene expression: DNA methylation, histone modifications (acetylation, methylation, ubiquitination, phosphorylation or ADP-ribosylation), and microRNAs (miRNAs). These mechanisms appear to work together in a complex interconnected network to accurately regulate gene expression, since DNA methylation and/or histone modifications can alter the miRNAs expression and vice versa. It has been shown that specific nutrients can affect methyl group supply. For example, folate, vitamin B₁₂ and methionine can increase the availability of the methyl groups

when their restriction can lead to obesity, insulin resistance and hypertension in the offspring [101, 102]. Similarly, in rats fed a low-protein diet, gene expression of various pulmonary and cardiac genes was significantly altered in the placentas and offspring. Additionally, the genes coding several enzymes involved in various epigenetic processes have been found to be affected in organs like the lungs, heart, kidney and liver, and the severity was inversely correlated with the onset of organ function [103]. These complex epigenetic modifications could explain the low birth weight, kidney maldevelopment and hypertension, as well as increased angiotensin-converting enzyme activity [59, 104].

Apart from epigenetic changes during early development, modifications in metabolism and in the morphology and physiology of the cardiovascular and renal systems are the main mechanisms of fetal programming that leads to the adverse long-term effects discussed in this review. In particular, enhanced vasoconstrictor responses, related to increased angiotensin receptor 1 (AT1) expression and superoxide production, have been reported to be involved in the cardiovascular programming pathway [61, 105]. This might be the consequence of an increased reactive oxygen species production, a decreased expression of endothelial NO synthase or soluble guanylate cyclase, resulting in decreased availability of NO.

In parallel to cardiovascular alterations, a decreased number of nephrons and different stages of kidney maldevelopment have been observed in several models studying fetal programming [106, 107]. These modifications in renal development, as well as alterations in the activity of the renin-angiotensin system, renal nerves and tubular transporters [108], have been proposed as the most potential mechanisms to program hypertension in postnatal life.

Quite a few studies have already shown that targeting the described pathways by administering beneficial substances during the perinatal period can counteract the effects of programming, prevent or reduce the abnormal development and, therefore, reduce the risk of CVD in adult life. Different nutritional interventions in perinatal and early postnatal life can revert or alleviate the cardiovascular consequences of IUGR programming. For example, supplementation with vitamin C, vitamin E and NO has been shown to reduce blood pressure and prevent proteinuria in rats [109]. On the other hand, inhibition of certain factors can also improve cardiovascular health as well, as shown for NF- κ B inhibitor pyrrolidine dithiocarbamate and soluble epoxide hydrolase inhibitor 12-(3-adamantan-1-yl-ureido)dodecanoic acid, which significantly reduce blood pressure in perinatal treated off-

spring of spontaneously hypertensive rats [110, 111]. It has also been shown that IUGR fetal programming induced by a low-protein diet in rats can be reversed or even prevented by co-treatments with urea, which normalized body weight, or with glycine, which prevented an increase in blood pressure [112]. These findings support the importance of nitrogen for healthy development and growth of the fetus. Similar results have been obtained in rats fed a low-protein diet by various other treatments, like perinatal administration of folate [113], metyrapone (11 β -hydroxylase inhibitor) [114] or lazaroide (an inhibitor of lipid peroxidation) [115], as well as postnatal treatment with fish oil (ω -3 polyunsaturated fatty acids) [116] or atorvastatin (cholesterol-lowering and anti-atherosclerotic drug) [117].

It is clear that further intensive research is still needed to fully understand the mechanisms of fetal programming and its precise timing. The progress that has been made so far, however, seems very promising for successful development of early intervention therapies to prevent and maybe even reverse CVD later in life.

Clinical Implications

The conclusion that can be drawn from the known data is that IUGR has a very strong association not only with metabolic, but also with primary cardiovascular programming, that lead to the long-term adverse consequences in later life (fig. 2). Therefore, it is of utmost importance not only to identify the onset of IUGR as early as possible, but also to follow up patients in adulthood in order to manage and improve their cardiovascular health condition.

Although current clinical guidelines still do not include IUGR as a risk factor for CVD, it is recommended to perform thorough screening for hypertension in children in order to provide strategies to improve and maintain cardiovascular health [118]. Hypertension and prehypertension in the child has been associated with substantial long-term health risks and considered an indication for lifestyle modifications. Close monitoring together with lifestyle (promoting physical activity and lack of exposure to secondary smoking or obesity) and dietary interventions have demonstrated to improve cardiovascular health in hypertensive children [118]. In particular, a high intake of dietary long-chain ω -3 fatty acids is associated with lower blood pressure and may prevent progression of subclinical atherosclerosis in children born with low birth weight [119, 120]. A recent randomized trial in a large cohort of children suggests that the

Fig. 2. Long-term cardiovascular consequences of IUGR. The complex interconnection of cardiovascular and metabolic programming in IUGR can lead to adverse outcomes in postnatal life, including CVD and mortality. A thorough follow-up of the patients is highly important to prevent long-term consequences of IUGR.

inverse association of fetal growth with arterial wall thickness in childhood can be prevented by dietary ω -3 fatty acid supplementation over the first 5 years of life [121].

However, it is critical to adequately select the high-risk population that may benefit from these therapeutic strategies. The severity of IUGR is currently defined mainly by gestational age and birth centile, which are inversely related to perinatal and neurodevelopmental outcomes [122–125]. For further antepartum surveillance of the IUGR-viable fetus, umbilical artery Doppler has been proposed to be used, thus significantly decreasing the necessity of labor induction, delivery via cesarean section, and perinatal death [126]. However, as mentioned earlier, cardiovascular programming occurs not only in premature and severe IUGR cases, but also in mild late-onset IUGR cases with normal umbilical artery parameters [18, 45, 49, 127]. Therefore, standard perinatal parameters such as gestational age, birth weight centile or umbilical Doppler show a poor performance for predicting long-term cardiovascular outcome. A recent prospective study has pointed out fetal echocardiography as a promising tool for the early identification of those IUGR cases with postnatal hypertension and arterial remodeling [128, 129].

Taken together, there is accumulating and highly significant evidence that supports the importance to follow-up IUGR patients into their adulthood. Considering the strong prevalence of IUGR, it is of utmost clinical relevance to detect cardiovascular risks as early as possible, to introduce timely preventive interventions and to adapt the lifestyle in order to improve the long-term cardiovascular health outcome and the quality of life of IUGR patients.

Conclusions

IUGR is a very complex and multifactorial disorder affecting the fetal development rate that often results in multiple adverse peri- and postnatal complications in-

cluding death. The strong evidence discussed in this review proves the consistent long-term persistence of CVD in patients who suffered IUGR early in life. Considering the high prevalence of IUGR and the progressing availability of intervention strategies, it is critical to detect cardiovascular risks as early as possible, to introduce timely preventive interventions and to adapt the lifestyle in order to improve the long-term cardiovascular health outcome of IUGR cases. Although there are still no general pediatric guidelines used in clinical practice, the implementation of correct follow-up and management could help high-risk patients who suffered from IUGR tremendously. Therefore, based on the collective research data known today, such guidelines ideally should be developed and introduced into clinical practice as soon as possible.

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