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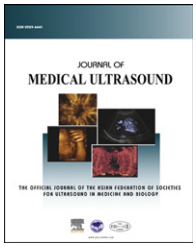

REVIEW ARTICLE

Sequelae of Fetal Growth Restriction

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Intrauterine growth restriction (IUGR) is a unique and important issue for obstetricians. The acute neonatal consequences of IUGR are perinatal asphyxia and neonatal adaptive problems. However, the long-term outcomes of such neonates are less discussed because obstetricians usually only care for pregnant woman until delivery. The aim of this article is to review the sequelae, especially the long-term effects including the neurological, cardiovascular, renal, and metabolic effects of the growth restriction in an obstetrician's view.

Introduction

An individual whose mother was exposed to a stimulus that led to adverse intrauterine milieu during pregnancy would be more susceptible to the development of adult diseases [1—7]. A minor event that would cause minimal or no damage in a healthy person could result in significant unwanted health events in a susceptible individual [8,9]. Worse still, the effects do not stop at the exposed individual but could be perpetuated across generations leading to transgenerational impacts [10—15].

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Genes and imprinted genes transferred from mother to offspring determine the genotype. The expression of genes is time-specific and tissue-specific. Any events at a specific time and on specific tissue can have significant effects on the expression. There is growing evidence on the role of epigenetic factors in intrauterine growth restriction (IUGR)-related adult diseases [16—19].

In utero perturbations lead to fetal organ and functional adaptations, a process known as fetal programming [20]. The adaptations lead to a ''thrifty'' phenotype, which is advantageous if poor diet is to be maintained postnatally. When exposed to abundant postnatal supplies, the functions of the programmed organs lead to the development of adult diseases [3,21,22]. Growth patterns during infancy or childhood contribute further to cardiovascular disease and type 2 diabetes mellitus [23,24].

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With improved detection methods, antenatal surveillance and management, and better neonatal care, there will be increased perinatal and neonatal survival, and the long-term effects of IUGR will have significant implications on the world population. Globally, metabolic disorders such as obesity, diabetes, and hypertension are on the rise. Hence, the health surveillance of these children would be a burden to healthcare systems.

The aim of this article is to review the sequelae of growth restriction and to give an insight into what is new in the issue of fetal programming. Our literature searches include PubMed, Medline (OVID), the current contents and references of initially identified relevant articles.

The keywords for the literature search were: IUGR, fetal growth restriction (FGR), fetal programming, fetal origin of adult disease (FOAD), developmental origin of adult disease (DOAD), nutrition, cardiovascular, neurodevelopmental, catch-up growth, kidney disorder, and metabolic disorder. We only selected articles in the English language, and these included both animal and human studies.

We found that studies have not been consistent in defining the population sample and there was no standard categorization of the severity of IUGR, partly because the use of ultrasound Doppler imaging is a more recent advance. Therefore, comparison of data was difficult.

Definition of IUGR

The terms IUGR or FGR suggest diminished growth velocity in the fetus as documented by at least two intrauterine growth assessments. The term "small for gestational age" (SGA) refers to the size of the infant at birth. SGA and IUGR are not synonymous. IUGR indicates the presence of a pathophysiologic process occurring *in utero* that inhibits fetal growth. A child who is born SGA has not necessarily suffered from IUGR, and infants who are born after a short period of IUGR are not necessarily SGA [25].

The art of standard antenatal assessment remains important for one to suspect IUGR. Ultrasound is also an important tool, not only for accurate dating, but also to identify growth restriction due to placental diseases. It is essential to exclude constitutionally small fetuses, aneuploidy, and nonaneuploid syndromes where outcomes are unlikely to be improved by intervention.

Manifestations of diagnostic value of growth restriction as a result of placenta diseases were elaborated by Miller et al [26]. Of late, we observe more usage of venous and arterial Doppler imaging for further categorization of IUGR, for timing of delivery of the premature IUGR, or for prognostic information [27]. Doppler is also capable of detecting changes that precede biophysical parameters of IUGR [28—30].

The staging system for IUGR may be valuable in determining more timely delivery of IUGR fetuses, especially premature IUGR fetuses. Using nonstress testing and umbilical artery (UA) Doppler velocimetry categorizing IUGR, Pardi et al grouped fetuses into three groups: Group I, normal nonstress test and UA Doppler, there was no fetal acidosis or hypoxemia; Group II, normal nonstress with abnormal UA Doppler, 5% rate of hypoxia or acidemia; Group III, abnormal nonstress test and abnormal UA Doppler, 60% rate of hypoxia or acidemia [31].

Mari et al proposed a staging using fetal biometry, Doppler cardiovascular changes, amniotic fluid, and clinical parameters: Stage I, an abnormal UA pulsatility index (UA-PI) and middle cerebral artery pulsatility index (MCA-PI); Stage II, an abnormal UA absent/reversed diastolic flow (UA-A/REDF), MCA peak systolic velocity (MCA-PSV), UV pulsation and an abnormal ductus venosus pulsatility index (DV-PI); Stage III, reversed flow at the umbilical vein (UV-RF) or reversed flow at the ductus venosus (DV-RF) or an abnormal tricuspid E wave (early ventricular filling)/A wave (late ventricular filling) ratio, and tricuspid regurgitation (TR). Each stage was divided into A (amniotic fluid index [AFI] $<$ 5 cm) and B (AFI $>$ 5 cm). The presence of maternal abnormalities was also reported [28,32].

A defined diagnosis and standardized staging system may also allow comparison of long-term outcome data for IUGR fetuses.

Causes of IUGRs

IUGR has heterogeneous causes, from fetal causes, such as aneuploidy, syndromes, and infection, to a long list of maternal causes that lead to uteroplacental insufficiency. Among the maternal causes are hypertensive disorders, pregestational diabetes, cyanotic cardiac disease, toxic exposure (smoking, alcohol, drugs, cocaine), malnutrition, infection, low socioeconomic status, racial background, smoking, and many others [33—36].

The above conditions lead to adverse or suboptimal intrauterine milieu that expose the fetus to hormones, growth factors, cytokines, or adipocytokines that alter metabolic or immune systems, vascular hemodynamics, brain and renal functions and growth parameters. In later life, the risks to the individuals are insulin resistance, type 2 diabetes, hypertension, cardiovascular disease, obesity, and heart disease. The risks were further enhanced by postnatal over-nutrition or lifestyle [37].

Animal studies have helped to clarify pathogenetic and pathophysiologic (fetal programming) aspects of IUGR that enable us to understand and associate it to the DOAD in humans [21]. Various methods of inducing placenta insufficiency in animal studies include manipulation of nutrients (global food restriction, caloric restriction, low protein diet, salt diet, glucocorticoid administration), manipulation of uteroplacental circulations (uterine horn ligation, bilateral uterine ligation, umbilical—placental embolization), and soluble fms-like tyrosine kinase-1 (sFLt-1)-induced preeclampsia, which was used to induce chronic anemia, hypoxemia, and acidemia [38—41].

Catch-up growth of IUGR fetus

After a period of intrauterine growth deficit, upon delivery, the SGA infant returns to its genetic trajectory. The intrauterine growth deficit is made up very early in postnatal life, especially during the first 3 months of life [42]. The catch-up growth is a growth velocity (centimeters per year) that is greater than the median for chronological age and gender. It may occur at any stage of growth, but is most commonly observed in the first 1 or 2 years of life, and

pronounced catch-up growth postnatally is often seen after severe intrauterine growth restraint.

Reduced fetal growth has been shown to be associated with an increased risk of insulin resistance, obesity, cardiovascular disease, and type 2 diabetes mellitus. The majority of the pathology is seen in adults who show spontaneous catch-up growth as children. At 5 years of age, children with postnatal catch-up growth were fatter and had more central fat distribution [43]. Rapid weight gain during the first 3 months of life was inversely associated with several determinants of cardiovascular disease and type 2 diabetes in adults aged 18—24 years [24].

Nutritional intervention could alter the catch-up growth during the first months of postnatal life, and the effects of the intervention persisted for at least 9 months beyond the period of intervention [44].

The response of IUGR fetuses towards intrauterine insult

Perturbations in the maternal environment increase placental vascular resistance causing structural and functional abnormalities of the placenta. There is a decrease in insulin growth factor-1 (IGF-1), a significant increase in IGF binding protein-1 (IGFBP-1) mRNA, and overexpression of the IGFBP-1 receptor leading to poor fetal growth [17,45]. The activity of the placental type 2 isoform of 11-beta-hydroxysteroid dehydrogenase (11-βHSD) is decreased leading to an increase fetal exposure to maternal cortisol, which programs the fetus for later adult diseases [16,46]. Perturbations in the maternal compartment may affect the methylation status of placental genes and increase placental oxidative/nitrative stress, resulting in changes in placental function [18,47].

The increased placenta vascular resistance subjects the fetal heart to increased work load that leads to cardiovascular responses in the fetus. Following uteroplacental insufficiency, redistribution of blood flow has been reported even before biometry or hemodynamic evidence of IUGR. Rizzo et al found profound reduction in the placenta/combined cardiac output (P/CCO) fraction and reduced umbilical vein (UV) flow as early as 20—24 weeks at the stage of normal fetal size and arterial and venous PI index values [30].

In fetuses who already have biometric and hemodynamic signs of IUGR, the reduction in both UV flow and placenta/CCO fraction suggest that the volume of fetal blood flow towards the placenta is reduced, and a more extensive recirculation of umbilical blood in the fetal body develops in an attempt to achieve more efficient extraction of oxygen and nutrients [48,49].

As a result of the blood redistribution, there is an increase in blood flow to major organs like the heart and brain, accompanied by a reduction in the supply to the kidneys, liver, gastrointestinal system, and muscular skeletal system [50,51].

Programming of the IUGR fetus

In IUGR fetuses, the organs and their functions adapt to the adverse intrauterine milieu. The adaptations or programming are very much dependent on the severity, the duration, the gestational age, and the gender of the fetus. Severe short-term umbilical—placental embolization has resulted in minor morphologic changes in placenta without significant tissue damage, growth restriction with reduced fetal weight, and morphologic changes in the liver, but the fetal membranes and kidneys were normal [52].

Early gestational hypoxia causes the epicardium (source of growth factors for the myocardium) to detach from the myocardium leading to thin myocardium and reduced heart size [53]. Late gestational hypoxia (at the critical period of cardiovascular maturation) results in lower cardiomyocyte binucleation, suggestive of retarded cardiomyocyte maturation, and has enhanced reactivity and mechanical properties of coronary arteries towards vasoconstrictors, angiotensin II, and thromboxane analogue [39]. Prolonged hypoxia in late gestation also increases the heart-to-body weight ratio in fetuses, neonates, and adults.

Although vascular changes are evident in both genders, only males show overt functional changes that could contribute to increased peripheral vascular resistance and cardiovascular disease [54].

The effects of fetal programming

Mortality and survival of the IUGR

In order to survive, the IUGR fetus goes through a series of adaptations that seem to benefit it in the short term, that is immediate survival during fetal and neonatal life. The mortality rate of IUGR babies should be largely influenced by gestational age of delivery; delivery at lower gestational age would cause more mortality [56,57]. Most mortality in babies happened within 2 years of delivery; after that, mortality was seldom seen. There is also more illness in infancy [55] and more sudden unexplained infant deaths.

In the Growth Restriction Intervention Trial (GRIT), brain development was compared between early deliveries (to pre-empt intrauterine hypoxia) and delayed deliveries for as long as possible (to gain maturity). At 2 years after delivery, the overall rate of death was 11.5%. There were more deaths when IUGR babies were delivered at 24—30 weeks as compared to 31—36 weeks gestation (24% vs. 6.6%) [58]. The overall rate of disability at 2 years was 5.6%; if dividing into gestational age of delivery, it was 9.5% in babies born between 24 weeks and 30 weeks, and 5.1% in babies born between 31 weeks and 36 weeks [58].

The survival of IUGR fetuses is increasing with improved prenatal diagnosis, the use of steroids, and improved neonatal backup, and this has led to increasing long-term sequelae of IUGR issues.

IUGR/SGA fetus who adapts and survives (the long-term effects)

Fetal programming leads to durable physiological effects on multiple biological systems. Diseases that have been found associated with IUGR include: cardiovascular disease, type-2 diabetes, abnormal lipid metabolism, hypertension, end-stage renal disease, obesity, and even psychiatric disorders [24,59,60]. Clinical manifestations of the diseases usually

occur in early childhood or later in life. Subclinical manifestations have been observed during fetal life, at birth, and in childhood [20,30].

The "brain sparing effects" to fetuses of IUGR

Fetal circulatory redistribution occurs so that the brain is preferentially perfused, however it does not completely protect IUGR individuals from cerebral palsy (CP), neurodevelopmental disorders, or behavioral and psychiatric disorders.

CP rate of IUGR fetuses

An association between CP and IUGR has been suspected for some time but is difficult to prove because information about antenatal growth is usually not available in cohort studies large enough to assess CP as an outcome [61]. The risk of CP appears to be highest in preterm small children whose gestational age at birth was greater than 33 weeks [62,63]. In the Western Australia Study, the risk of spastic CP associated with poor intrauterine growth appeared to depend on gestational age, with infants delivered at 34—37 weeks of gestation being at the highest risk (odds ratio of CP for children 34—37 weeks of gestation and third percentile at birth: 19.6, 95% CI 8.1—47), followed by those at term. There was no association between FGR and CP at lower gestations [62].

The risk of CP appears to be highest in preterm small children whose gestation at birth was greater than 33 weeks [62,63]. In babies who were delivered at 34—37 weeks of gestation, the problem of prematurity is less important than those delivered below 34 weeks. Generally, it was considered that the effect of very preterm birth with its greatly increased risk of CP from perinatally acquired brain injuries may overwhelm the lesser association between IUGR and CP [64].

However, recently, Petersen et al focused on the severe growth restriction fetus where the estimated fetal weight (EFW) was less than 501 g and with umbilical artery-absent or reversed end diastolic flow (UA-A/REDF). They found a low overall perinatal survival rate for pregnancies complicated by early onset, severe growth restriction. When delivery occurred due to fetal indications, the majority of these women required classical cesarean sections. The short-term neonatal morbidity was high although none of the survivors had CP [65].

It is tempting to hypothesize that a prolonged period of reduced intrauterine nutrition will put the baby at increased risk of developing CP. This notion would be consistent with evidence from magnetic resonance imaging studies, which suggest that approximately 75% of brain lesions associated with CP occur in the early or middle part of the third trimester. While early delivery may lead to neonatal and delayed complications associated with prematurity, including CP, spontaneous preterm labor following IUGR could, in many instances, be a fetal adaptive response, an ''escape'' from an unfavorable intrauterine environment [61].

The low CP rates in extreme premature IUGR fetuses seemingly cannot be fully explained by previous explanations. Term singletons with severely SGA birth weights had a five- to sevenfold risk of developing CP compared to gestational age-matched infants with birth weights within normal limits. For children born preterm, SGA was not more likely to be present in cases than in controls [61]. The risk of developing CP is linked to the severity of restricted growth status at birth and that this is only the case if the pregnancy had reached term. In babies born preterm, there was no difference between cases and controls [61].

Neurodevelopmental function of IUGR fetuses

Children with IUGR were observed to have a small tendency to catch up in weight at 3 years of age, but at preschool age (6—7 years old), they are not only lagging behind in somatic growth but also in neurodevelopmental performance and cognitive function, when compared to appropriate for gestational age (AGA) control children [66]. They had been reported to be associated with lower intelligence, poor academic performance, and demonstrated a specific profile of neurocognitive difficulties at school age, accounting for lower school achievements after 10 years follow-up [65]. Difficulties in executive functioning, inflexibility—creativity, and language, indicative of frontal lobe dysfunction, were typically affected by IUGR [67].

The earlier in gestation that the slowing of intrauterine head growth was identified the poorer was the neurodevelopmental outcome [64]. Adolescents who were born SGA were more likely to experience learning difficulties than the AGA counterparts (>10th percentile), with a higher prevalence in those of birth weight less than the third percentile [68]. The preterm IUGR babies whose median gestational age of delivery was 32 weeks scored lower in the Hammersmith Infant Neurological Examination but median global score was within the optimal range at 18 months after delivery follow-up [69]. Regardless of socioeconomic background, full term IUGR babies have increased risk of neurodevelopmental difficulties at 8 months and at 4 years of age [70].

IUGR with abnormal fetal blood flow is associated with impaired executive cognitive functions in young adults [71]. umbilical artery- absent end diastolic flow (UA-AEDF) is well recognized as a marker of fetal compromise, which is associated with acute perinatal sequelae but it is not associated with adverse neurodevelopmental outcome. However, UA-REDF was found to be associated with a wide range of problems at school age, suggesting that UA-REDF represents intrauterine decompensation, which may have adverse effects on the developing brain [72]. UA-AEDF is not severe enough to be an indicator of association with poor neurodevelopmental outcome but UA-REDF is severe enough to be associated with neurodevelopmental outcome.

Baschat et al, in his prospective studies of 2-year neurodevelopment in IUGR secondary to placental dysfunction, further confirm that UA-REDF are at risk of abnormal neurodevelopment. CP, hearing deficit, and global delay were related to UA-REDF. Contrary to their hypothesis, elevation of DV Doppler and umbilical vein pulsations did not increase the likelihood of

developmental abnormalities. Neither brain sparing (middle cerebral artery PI $>$ 2.0 standard deviation (SD)) nor deterioration of biophysical profile (BPP) was statistically associated with an increased likelihood of abnormal developmental outcome. They conclude that mild deterioration of venous Doppler parameters and BPP does not appear to have a negative impact on neurodevelopment [73].

Cardiovascular (atherosclerosis, hypertension, coronary heart disease) effects of fetuses of IUGR

Postnatal physiological adaptation and maturation of IUGR infants is slower than normal, therefore they remain in a physiologically immature state for a longer period. The higher heart rates and greater cortisol excretion in such infants may be precursors to the hypertension and cardiovascular disease seen in adults [74]. IUGR fetuses with abnormal aortic flow *in utero* have smaller aortic dimensions and higher resting heart rate at 18 years of age. This indicates that IUGR with abnormalities in fetal blood flow caused by placental insufficiency is associated with a general effect on vascular growth that persists into young adulthood in both male and female persons [75].

The clinical complications of atherosclerosis (ischemic heart disease, stroke) occur in adult life, but the process of atherogenesis begins in childhood. Intima thickening appears as changes in atherosclerotic lesions. It was found that the intima thickening of abdominal aorta (aIMT) results in the first atherosclerotic lesions. It is now possible to visualize the abdominal aorta and measuring aIMT might provide a better index of preclinical atherosclerosis in high risk children than the intima thickness of carotid artery (cIMT) and the intima thickness of coronary artery that has not been affected in IUGR children [76—78]. IUGR neonates have significant aIMT and lumen diameter with decreased serum IGF-1 and leptin levels. Mean aIMT was negatively correlated with serum IGF-1 and was positively correlated with gestational age in the neonates with IUGR [79].

Disruption of the aortic internal elastic laminal (IEL) is an early feature of atherosclerotic pathology [41]. Elastic properties of arteries largely depend on the presence of elastin. The rate of elastin synthesis is highest *in utero* and during infancy and falls rapidly thereafter with a half-life of approximately 40 years. At birth, investigation of the umbilical artery of IUGR and elevated resistance in feto-placental circulation, Bukhart [80] found umbilical arteries that are thinner and stiffer, lower plasma levels of IGF-1 (a known regulator of elastin synthesis), increased arterial stiffness correlated inversely with IGF-1 plasma levels, and umbilical artery walls containing less elastin [81].

In term IUGR of mothers who were exposed to substance use during pregnancy, 24% of the children developed hypertension by the age of 6 years [59]. In a prospective follow-up study of adults born in 1925—1949 at four major delivery units in Sweden, FGR constitutes a strong perinatal risk factor for ischemic heart disease, whereas neither low birth weight nor short gestational duration *per se* increases risk [5].

Prenatal stress *per se* does not dramatically change a given structure or function, but it affects resilience and renders individuals more susceptible to pathophysiological outcomes when further insults occur during adulthood [8]. Postnatal nutrition and catch-up growth increased cardiovascular risk. It was found that there was reduced insulin sensitivity, serum low HDL cholesterol levels, and increased waist circumference in early adulthood of IUGR individuals who had rapid catch-up growth [24].

The generation R study by Verburg et al [20] is a large population-based prospective cohort study from fetal life to young adulthood that found that cardiovascular performance in reduced fetal growth is consistent with increased afterload and increased end-diastolic ventricular filling pressure. The adaptive hemodynamic changes were observed even before the stage of clinically apparent growth restriction. The children are currently being followed up to determine whether the hemodynamic changes persist into childhood and whether they are related to cardiac function and blood pressure development in postnatal life.

Renal function of IUGR fetuses

Sixty percent of nephrogenesis occur during the third trimester and ends on the 36th week of gestation. In premature infants, nephrogenesis continues after birth for another 40 days, but not beyond. Nephrogenesis is further compromised by renal failure that commonly occurs in severely premature births. Both prematurity and IUGR can impair nephrogenesis.

Late impairment of fetal growth during the third trimester has been shown to inhibit nephrogenesis and decrease glomerular number. Consequent to reduced nephrogenesis, there is increased mean glomerular volume due to compensatory glomerular enlargement. There is also increased apoptosis and plasma sodium concentration, and suppression of renin and angiotensinogen [82,83]. However, these adaptations or hyperfiltration cause proteinuria, glomerular hypertension, glomerular sclerosis, and arterial hypertension in the long term [84].

In the Generation R study, Verburg et al [85] found decreased kidney volume (indirect index of nephrons) in late fetal life of IUGR fetuses with signs of raised placental resistance and fetal blood flow redistribution. Rakow et al [86] found no significant changes in kidney volume (indirect index of nephrons) and function in school-aged children of premature, term SGA, or term AGA. The long-term renal outcome of children in the Generation R study would be an interesting finding.

Postnatal overfeeding to obtain early catch-up growth with high energy and protein intake is usually recommended; however, there is a risk of enhanced fetal programming that causes glomerular hyperfiltration from increased solute load.

Diabetes associated with IUGR fetuses

Both intrauterine and postnatal environments contribute to an increased diabetes risk [87,88]. Animal research has provided an insight into the mechanisms responsible; the

pancreas was shown to have decreased cell mass, proliferation, islet number and size, insulin content, insulin response to glucose and amino acids, and blood flow that lead to diabetes [40,89—91]. The IGF-1 and peroxisome proliferator-activated receptor (PPAR) genes play an important role in the regulation of glucose, lipid, and metabolism.

Pdx1, a pancreatic and duodenal homeobox 1 transcription factor, is required for prenatal pancreas development and β cell differentiation as well as postnatal maintenance of insulin production and the glucose-sensing system in beta cells. Pdx1 was found absent or silent in IUGR fetuses [40,92] .

Park et al [92], in an animal study, demonstrate how intrauterine stress can initiate a disturbing epigenetic cascade of progressive transcriptional repression linked to beta cell failure. The author found reduced beta cell mass (−70%), absent first phase insulin secretion, and nearly absent Pdx1 expression. Their results demonstrate that IUGR induces a self-propagating epigenetic cycle. The corepressor/histone deacytelase (mSin3A/HDAC) complex is first recruited to the Pdx1 promoter, histone tails are subjected to deacetylation, and Pdx1 transcription is repressed. At the neonatal stage, this epigenetic process is reversible. However, histone 3 lysine 9 (H3K9me2) accumulates, DNA methyltransferase 3A (DNMT3A) is recruited to the promoter and initiates *de novo* DNA methylation (which locks in the silenced state in the IUGR adult pancreas), and the result is diabetes.

Obesity associated with IUGR fetuses

Following uteroplacental insufficiency, the decrease in substrate availability causes a decrease in IGF-1 that leads to poor fetal growth. In response, for survival, the IUGR fetus increases its adipocyte sensitivity to insulin, and this is accompanied by increased levels of insulin receptors in adipocytes. These expose the IUGR fetus to a high risk of developing metabolic disorders such as impaired glucose tolerance and hyperinsulinemia and adiposity [93].

IUGR newborns are prone to central redistribution of adipose tissue. The fat-sparing may occur because it confers a survival advantage in the neonatal period. Postnatally, the excess of fat may persist and lead to increased insulin resistance. Abdominal obesity plays a key role in the development of insulin resistance because of the high lipolytic rate of visceral adipose tissue and its secretion of adipocytokines.

Adipocytokines are hormones secreted by adipose tissues, which are important in modulating metabolism and intrauterine growth [94]. They are classified according to their putative physiological role into two groups: (1) 'insulin resistance-inducing factors' such as resistin, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), PAI-1, ghrelin, angiotensinogen, adipsin, acylation-stimulating protein (ASP), and retinol binding protein-4 (RBP-4); and (2) 'insulin-sensitizing factors' such as adiponectin, leptin, and visfatin. Leptin, the adipocyte-derived protein encoded by the *Ob* gene, is important for neuroendocrine regulation of body fat, feeding behavior, energy homeostasis, reproduction, puberty, and pregnancy [95].

Lower leptin, normal or lower adiponectin, and higher ghrelin, as well as visfatin fetal/neonatal concentrations in the IUGR state, probably holds implications for susceptibility to long-term development of obesity and insulin resistance [9]. Leptin administration to protein-restricted dams inhibits suppression of 11-βHSD [96], which could be one intervention pathway.

Excessively rapid weight gain in the first 16 postnatal weeks after FGR increases body mass index (BMI) [97]. Some studies showed no association between IUGR and obesity; IUGR children gain weight at a much faster rate but do not fully catch up by the age of 9 years [98].

Windows for intervention

Minimizing the long-term adverse effects of IUGR could be done at different stages: to prevent IUGR, to halt the fetal programming when IUGR already occurred, and to prevent enhancement of fetal programming during the catch-up period. However, interventions may jeopardize the short-term advantages for fetal intrauterine adaptations. Many potential interventions are observed in the growing number of animal studies.

Identification and assessment of child-bearing age women with ''prior risk'' of developing IUGR is important for early preventive measures: prepregnancy nutritional advice and supplementations, adequate prepregnancy management of maternal disorders or behavior, especially cessation of smoking [99—101]. There is growing evidence that maternal nutritional status can alter the epigenetic state of the fetal genome. Promoting optimal nutrition will not only ensure optimal fetal development, but will also reduce the risk of chronic diseases. Improvement in primary healthcare systems, targeted nutrition and education of child-bearing age women, and political measures in reducing poverty and inequalities affect overall fetal growth [102].

In the high-risk pregnancy

(a) Identification of the subclinical stage of the IUGR fetus by Doppler imaging of a decreased placenta/CCOP fraction could offer a window for interventions. Promising interventions that are ongoing such as altering placental growth and nutrient transport by administration of IGF, altering maternal levels of methyl donors, and leptin during pregnancy could prevent or alleviate fetal programming [96].
(b) Timely delivery of the IUGR fetus with clinical ultrasound manifestations.

Timing of delivery is important, not only to prevent perinatal mortality but also to prevent or halt the programming process. In IUGR fetuses between 28 weeks and 31 weeks of gestation, the best predictor for intact survival and neonatal mortality is A/REDF in ductus venosus and delivery is always immediate. In severely preterm IUGR fetuses between 25 weeks and 29 weeks of gestation, A/REDF in the DV, Picconi et al proposed the S-wave/isovolumetric A-wave (SIA) index to distinguish fetuses likely to survive after delivery (SIA index < 2) from fetuses that would not benefit from aggressive management [103].

After delivery

Identification of the IUGR newborn, in order to give special appropriate neonatal management, is crucial to prevent mortality and reduced morbidity, while at the same time targeting the minimization of long-term effects [104].

Nutrition

Optimal nutritional management to minimize hyperinsulinemia and insulin resistance may potentially improve neurodevelopment and facilitate catch-up growth with normal body composition [105]. However, what is the optimum?

(i) Leptin

The administration of leptin to protein-restricted dams during pregnancy and lactation produces offspring that have an increased metabolic rate. When the offspring are fed on a high-fat diet, they do not become obese or insulin resistant. In pregnancy with high levels of glucocorticoids, leptin inhibits suppression of 11-βHSD type 2, which could be one of the preventive mechanisms of metabolic diseases [96,106].

(ii) Long-chain polyunsaturated fatty acids (LCPUFAs)

LCPUFAs are low in IUGR newborns, diabetes, hypertension, and coronary heart disease (CHD). LCPUFAs enhance endothelial nitric oxide synthesis, suppress the production of the pro-inflammatory cytokines TNF and IL-6, attenuate insulin resistance, and have anti-atherosclerotic properties. LCPUFAs improve fetal and postnatal growth and are useful in the management of hyperlipidemia. If given during critical periods of growth, especially from the second trimester of pregnancy to age 5 years, they prevent CHD in adult life [80].

Growth hormone

Children of IUGR fetuses who do not display catch-up growth would be shorter in height than the average child [107]. They are usually treated with growth hormone. There are many studies that showed that administration of growth hormone does not worsen metabolic diseases [108,109].

Exercise

Sedentary conditions predispose IUGR offspring to the development of obesity. Moderate daily exercise activates enhanced metabolic flexibility in the muscle that effectively prevents prenatal-induced obesity of fetal programming [110,111]. These highlight the importance of tailoring obesity prevention strategies that improve long-term health.

Adipocytes

Interventions aimed at normalizing fat partitioning in childhood could prevent insulin resistance and metabolic syndrome in subjects born small for gestational age [95].

Epigenetic factor

The epigenetic process during the neonatal stage of development is reversible. This would be another potential window of intervention [92].

Health surveillance plan for IUGR children

With many data supporting the DOAD, it is wise to have a further health surveillance monitoring plan, especially in IUGR infants with rapid postnatal catch-up growth. Growth monitoring during the early postnatal period provides useful information, and different growth patterns may be identified in infants as young as 3 months of age [112]. The rapid catch-up growth might be a window for intervention and prevention of associated adult diseases [22].

Conclusions and recommendations

The identification of mothers with ''*priori* risk'' could lead to earlier diagnosis of IUGR. Intensive maternal and fetal monitoring of such patients could avoid severe fetal deterioration and allow the optimal time for delivery. Identification at preclinical manifestations of adult disease at birth, childhood, and adulthood, with an individualized health surveillance plan of susceptible individuals, would prevent or halt the programming of organs (and their functions) towards the progression of disease.

Continuous improvement in the Doppler technique, the standardized definition of IUGR, and the standardized staging of IUGR should be incorporated into future studies of DOAD. These would lead to better understanding or better identification of the stage of the IUGR fetus that is likely to progress into specific fetal programming sequelae. We would like to emphasize the recommendation made by Mari and Picconi [32] to differentiate IUGR fetuses with and without placenta insufficiency, and to divide different types of IUGR with placenta insufficiency based on fetal and maternal pathology, which can be categorized according to severity and etiology in future clinical trials.

In the future, we may observe institutions for treatment at preclinical or clinical stages of IUGR (fetal therapy), further improvement in neonatal care especially identification of optimal nutrients or micronutrients, and the best environment for the IUGR newborn. Future fetal programming issues should account more for epigenetic factors, especially in explaining the causative role, and open new windows for intervention.

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