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REVIEW

Endothelial dysfunction in individuals born after fetal growth restriction: cardiovascular and renal consequences and preventive approaches

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Individuals born after intrauterine growth restriction (IUGR) have an increased risk of perinatal morbidity/mortality, and those who survive face long-term consequences such as cardiovascular-related diseases, including systemic hypertension, atherosclerosis, coronary heart disease and chronic kidney disease. In addition to the demonstrated long-term effects of decreased nephron endowment and hyperactivity of the hypothalamic–pituitary–adrenal axis, individuals born after IUGR also exhibit early alterations in vascular structure and function, which have been identified as key factors of the development of cardiovascular-related diseases. The endothelium plays a major role in maintaining vascular function and homeostasis. Therefore, it is not surprising that impaired endothelial function can lead to the long-term development of vascular-related diseases. Endothelial dysfunction, particularly impaired endothelium-dependent vasodilation and vascular remodeling, involves decreased nitric oxide (NO) bioavailability, impaired endothelial NO synthase functionality, increased oxidative stress, endothelial progenitor cells dysfunction and accelerated vascular senescence. Preventive approaches such as breastfeeding, supplementation with folate, vitamins, antioxidants, L-citrulline, L-arginine and treatment with NO modulators represent promising strategies for improving endothelial function, mitigating long-term outcomes and possibly preventing IUGR of vascular origin. Moreover, the identification of early biomarkers of endothelial dysfunction, especially epigenetic biomarkers, could allow early screening and follow-up of individuals at risk of developing cardiovascular and renal diseases, thus contributing to the development of preventive and therapeutic strategies to avert the long-term effects of endothelial dysfunction in infants born after IUGR.

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We performed an extensive and critical review of the literature in order to explore the manifestations of endothelial dysfunction in individuals born after intrauterine growth restriction (IUGR) and examined which mechanisms may be incriminated and which preventive strategies could represent promising approaches. We used the following terms in the Pubmed library (MESH terms and free text), without time or language limits: (Prenatal Exposure Delayed Effects OR Late Effect, Prenatal Exposure OR Nutrition Disorders/Physiopathology OR Fetal Growth restriction) AND (Cardiovascular Diseases/Etiology OR Hypertension/Etiology) AND (Impaired Endothelial Function OR Oxidative Stress/Senescence). We included the most significant human and animal studies. From the references of the retrieved papers, additional articles were selected for this review. One author (C.Y.) read the titles and abstracts and selected the articles to be included.

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IUGR: definition and risk factors

Definition

IUGR is defined as the inability of the fetus to reach its genetically determined potential size.[1,2] IUGR affects ~5–15% of all pregnancies in the United States and Europe, but its incidence varies widely and appears to be higher in low-income countries (it affects 30–55% of infants born in South Central Asia, 15–25% in Africa and 10–20% in Latin America).[3] Using the ReCoDe classification system, IUGR has been considered the most commonly identified factor in stillborn infants.[4] Therefore, the management of growth-restricted fetuses in

terms of choosing the optimal delivery time is important to decrease perinatal mortality/morbidity. Fetal growth restriction is difficult to detect because of the lack of international consensus on the definition and diagnostic criteria for IUGR. In clinical practice, growth-restricted fetuses are usually identified based on birth weight (<10th percentile). However, some propose that using <3rd or <5th percentile as the criterion would better identify individuals at a higher risk of adverse perinatal outcomes.[5] Moreover, low estimated fetal weight (<10th percentile), certain ultrasound findings of fetal growth (abdominal circumference <2.5th percentile) and altered Doppler velocimetry indices, such as abnormal umbilical artery waveforms or decreased pulsatility of the middle cerebral artery, that suggest abnormalities in fetal circulation are also indicative of IUGR.[6] To better understand abnormal fetal growth and to detect IUGR, specific computerized fetal growth charts that consider fetal gender and maternal characteristics such as height, weight, parity and ethnic origin were developed by Gardosi *et al.*[7] Pathological factors, including maternal systemic hypertension (HTN), diabetes, tobacco use and preterm delivery, were excluded from the model to predict the optimum weight that a baby can reach at term during a normal pregnancy. As it is necessary to distinguish between growth-restricted and constitutive 'small for gestational age' fetuses, longitudinal assessments of fetal growth trajectories are required to identify pathological fetal growth restriction, even if the altered growth trajectory is above the 10th centile limit.[8] More recently, universal standards of fetal growth have been proposed by the Intergrowth project.[9,10]

Risk factors for IUGR

IUGR can result from a multitude of risk factors, including maternal and fetal causes. Several maternal factors have been identified, such as undernutrition, which notably affects the activity and/or expression of placental nutrient and ion transporters;[11–13] chronic diseases, such as preeclampsia;[14] bacterial infection during pregnancy, particularly with *Escherichia coli*, *group B Streptococcus*, *Listeria monocytogenes*, *Treponema pallidum* or *Trichomonas vaginalis*; parasitic diseases, such as malaria; viral infection (e.g. human cytomegalovirus or rubella virus);[15,16] young age (adolescent pregnancy); and alcohol and/or tobacco consumption.[17] In addition, pregnancy-induced HTN, preeclampsia and placental insufficiency are known causes of asymmetrical IUGR (defined as restriction of weight followed by length).[18] Among the fetal causes, chromosomal anomalies (including trisomy of chromosome 13, 18 or 21; tri- and polyploidies; Mulibrey nanism; 3-M, Bloom and Turner syndromes; and Majewski osteodysplastic primordial dwarfism type II)[19] and fetal structural defects, such as congenital heart disease,[20] result in symmetrical IUGR (defined as global growth restriction), which is usually more severe than asymmetrical IUGR.[18]

Along with maternal causes, paternal health has also been identified as a possible contributor to IUGR. Insulin resistance, smoking habits, elevated blood pressure, endothelial dysfunction, upper body fat distribution and an atherogenic lipid profile have all been suggested as potential paternally determined factors that correlate with IUGR.[21] These factors presumably impact fetal growth through epigenetic processes.[22]

IUGR is now considered a critical public health issue because of its high perinatal mortality rate and long-term consequences. As numerous epidemiological studies have reported, infants born with fetal growth restriction have an increased risk of developing non-communicable chronic diseases, notably cardiovascular (e.g. systemic HTN and coronary artery disease) and renal [chronic kidney disease (CKD)] diseases, later in life. These observations are consistent with the concept of Developmental Origins of Health and Disease, which suggests that conditions affecting specific sensitive developmental periods, from conception throughout pregnancy to early infancy, 'program' tissue/organ structure and function throughout life in a process known as developmental plasticity that is adapted to short term, prevailing environmental conditions but possibly not to the further life course. The underlying mechanisms are not clearly defined. In parallel with the long-term effects of decreased nephron numbers and hyperactivity of the hypothalamic–pituitary–adrenal axis in these infants, endothelial dysfunction may also contribute to the development of certain chronic diseases in adulthood.

Endothelium dysfunction in individuals born with IUGR

The endothelium: a major role in vascular homeostasis

The endothelium plays a major role in maintaining vascular homeostasis and is one of the largest organs in the human body, consisting of more than 10^{14} cells lining the vascular network. It is intimately involved in the balance between vasodilation and vasoconstriction and between thrombogenesis and fibrinolysis, the inhibition and promotion of smooth muscle cell proliferation and migration, and the prevention and stimulation of platelet adhesion and aggregation.[23] All these functions are mediated by the release of numerous vasoactive factors, such as nitric oxide (NO) and endothelin. In this respect, the maintenance of endothelial structural and functional integrity is essential for vascular homeostasis; therefore, impaired endothelial function can lead to the development of vascular-related diseases.

Convincing evidence suggests that endothelial dysfunction during early childhood and persisting to adulthood in individuals born with IUGR is a key event in the development of HTN, atherosclerosis, coronary heart disease and CKD later in life. In these individuals, endothelial dysfunction primarily manifests as impaired endothelium-dependent vasodilation and vascular remodeling.

Impaired endothelium-dependent vasodilation in individuals born with fetal growth restriction

Endothelium-dependent vasodilation can be clinically evaluated using flow-mediated brachial artery tests, plethysmography or skin perfusion in response to acetylcholine using

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the laser Doppler technique.[24–26] Impaired endothelium-dependent vasodilation has been described in children (9–11 years)[27–29] and young adults (20–28 years) born with fetal growth restriction[30] and in umbilical and placental vessels derived from growth-restricted fetuses.[31]

An association between fetal growth restriction and impaired NO-dependent vasorelaxation has also been observed in several animal models, mainly in rats, mice and sheep. IUGR can be induced in rats by exposure to a maternal low-protein diet (LPD, containing 9% casein)[32] or restricted diet (50% of normal intake) and in sheep by single *in utero* umbilical artery ligation (at 105–110 days gestation); these diets and procedures result in low birth weight (LBW) offspring and lead to impaired endothelium-dependent vasodilation in small arteries,[33,34] the aorta[35] and coronary arteries[36] in adulthood.

The effects on endothelium-dependent vasodilation are more pronounced in males, whereas females seem to be protected by the NO-dependent vasoprotective role of estrogens. However, impaired endothelium-dependent vasodilation has been observed in female Wistar rats born with IUGR stemming from maternal undernutrition.[35] As suggested by Borwick *et al.*,[37] fetal undernutrition may decrease estrogen synthesis, ultimately leading to ovarian damage. Interestingly, estrogen-mediated vasoprotective activity has been reported in humans; specifically, postmenopausal women taking conjugated equine estrogens (0.625 mg for 28 days) showed improved vascular NO-dependent relaxation of the brachial artery.[38]

Vascular remodeling in individuals born with fetal growth restriction

Endothelial activation

Endothelial dysfunction is associated with leukocyte infiltration and the adhesion of monocytes, macrophages and low-density lipoprotein (LDL), which is oxidized to OxLDL in the arterial wall. This leads to foam cell formation and initiates atherogenesis. In addition, monocytes and macrophages secrete higher levels of cytokines and pro-inflammatory proteins such as interleukin-6 (IL-6), tumor necrosis factor-α and C-reactive protein (CRP).[39] These events create a vicious cycle: neutrophils and macrophages produce higher levels of IL-6 in response to inflammation, which in turn increases CRP production in the liver. CRP decreases NO availability and increases endothelin-1 production, thereby contributing to impaired endothelium-dependent vasodilation and leading to irreversible vascular damage.[39,40] Elevated levels of pro-inflammatory markers and endothelial activators are characteristic of middle-aged adults (45–64 years) born with LBW, indicating that endothelial dysfunction is patent in these individuals.[41]

Vascular structural changes

Histopathological analyses showed that the first atherosclerotic lesions begin to develop in the abdominal aorta.[42] Increased arterial wall thickness, measured using non-invasive assessments of the intima-media or carotid intima-media thickness, has been observed in newborns[43–46] and young children[47,48] and persists in adults (27–30 years) born after IUGR, and it is particularly apparent in those with exaggerated postnatal growth.[49]

Hypoxia and oxidative stress in vascular remodeling

Hypoxia and oxidative stress have been implicated in vascular remodeling.

Placental insufficiency is related to reduced nutrient and oxygen delivery to the fetus, contributing to the development of fetal growth restriction. Several maternal factors, such as living at a high altitude, HTN, anemia, pulmonary disease, preeclampsia, drugs and/or tobacco consumption can contribute to fetal hypoxia,[50] which can induce IUGR, LBW[51] and increase the risk of cardiovascular diseases (CVD) later in life.[52,53] During fetal development, hypoxia plays a crucial role by driving vasculogenesis/angiogenesis, hematopoeisis and chondrogenesis.[54] However, prolonged *in utero* hypoxia can lead to detrimental effects. In growth-restricted fetuses, circulating levels of angiopoietin-2, an angiogenic factor up-regulated by hypoxia, were increased at postnatal day 4 compared with appropriate-for-gestational age infants, thus contributing to postnatal vascular remodeling.[55]

Oxidative stress can be defined by decreased antioxidant defenses and increased reactive oxygen species (ROS) production. Under physiological conditions, ROS play an important role as a regulator of vascular functions such as migration, growth, smooth muscle and endothelial cell survival, and the secretion of extracellular matrix proteins. However, uncontrolled ROS production can contribute to vascular diseases.[56,57] ROS have been implicated in the hypertrophy and hyperplasia of vascular smooth muscle cells. In vascular cells (endothelial cells and vascular smooth muscle cells, adventitial fibroblasts), the main enzyme responsible for ROS production is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[58]

Angiotensin II (AngII), via Angiotensin type 1 receptor (AT1R), has been implicated in increasing superoxide anion levels followed by increased hydrogen peroxide production, which induces long-term outcomes of AngII, such as hypertrophy and hyperplasia of vascular smooth muscle cells.[59,60] The flavoprotein inhibitor diphenyleneiodonium (DPI)[60] and catalase overexpression[61] inhibit these vascular defects. In a rat model of IUGR induced by maternal LPD associated with adult HTN, we observed increased *ex vivo* vasoreactivity of the carotid rings to AngII, mediated by AT1R, which was normalized by DPI and apocynin (NADPH oxidase inhibitor) pre-incubation.[32]

The regulation of extracellular matrix proteins such as collagen and elastin can be modulated by ROS. Elastinolysis and collagenolysis play crucial roles in arterial remodeling and vascular diseases.[62] Metalloproteinases (MMPs) and their related tissue inhibitors of metalloproteinases are enzymes secreted by macrophages and vascular smooth muscle cells.

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MMP-2 and MMP-9 cleave gelatin, collagen and elastin, and have been associated with vascular diseases.[63] ROS have been demonstrated to activate MMPs.[64] Increased circulating levels of MMP-2 and MMP-9 and increased MMP-2/TIMP-2 and MMP-9/TIMP-2 ratios have been observed in children who were small for gestational age and are positively correlated with systolic blood pressure and vascular function.[65] In a developmental programming animal model of HTN induced by neonatal oxygen exposure, we observed increased aortic MMP-2 and TIMP-1 and reduced TIMP-2 staining as early as 4 weeks of age, indicating a shift in the balance toward degradation of the extracellular matrix and increased collagen deposition.[66] These data suggest that early changes could contribute to the onset of the elevated blood pressure and arterial stiffness observed at adulthood in this animal model.[67,68]

Mechanisms involved in endothelial dysfunction in individuals born with fetal growth restriction

Impaired NO bioavailability

The endothelium-mediated release of NO is widely accepted as the key determinant of endothelial function, and reduced NO bioavailability has been linked to most serious vascular pathologies.[69] In particular, the loss of NO production contributes to impaired endothelium-dependent vasodilation and to endothelium activation by improving the recruitment of pro-inflammatory cytokines, such as vascular cell adhesion molecule-1 and ICAM-1, and the infiltration of leukocytes into the vessel wall.[70–72] In normal pregnancies, NO synthesis is up-regulated, as reflected by increased nitrite/nitrate concentrations in maternal and fetal circulation, thus mediating maternal cardiovascular adaptations and the low systemic and umbilical vascular resistance in the fetus. In pregnancies complicated by IUGR, research findings are inconsistent. Some have displayed a decrease in NO metabolite concentrations in maternal and/or fetal serum, reflecting reduced NO synthesis compared with controls.[73,74] Other have found higher nitrite/nitrate concentrations in umbilical venous plasma[55] or an increase in endothelial nitric oxide synthase (eNOS) protein staining in placental vessels compared with normal pregnancies, suggesting that increased NO production could be a compensatory response to improve blood flow in the placenta.[75,76]

Decreased NO synthesis, evaluated in terms of nitrate/nitrite production, was observed in animal models of IUGR induced by a reduction *in utero* placental perfusion pressure[77] or maternal LPD[78,79] and in a rat model of developmental programming of HTN induced by exposing pregnant rats to androgens.[80]

Reduced NO bioavailability may result either from altered NO synthesis or from NO scavenging by other molecules, such as ROS.

Impaired eNOS functionality

Under physiological conditions, NO is synthetized in the vasculature by eNOS, using L-arginine (L-Arg) as a substrate and tetrahydrobiopterin (BH_4) as a cofactor. There are contradictory data on eNOS expression in individuals born after IUGR. In humans, independent studies have indicated that eNOS expression is increased in the umbilical arteries of babies born after fetal growth restriction, suggesting that activated NO synthesis may be a compensatory mechanism to improve placental blood flow.[31,81] However, these results are controversial because they could not be replicated.[82] Moreover, differences in eNOS expression have been observed in human endothelial cells isolated from the umbilical arteries (HUAECs) or veins (HUVECs) of IUGR newborns. eNOS expression is increased in IUGR-HUAECs but decreased in IUGR-HUVECs. These differences may be explained by the type of vessel (artery *v.* vein) or could be the consequence of altered blood flow and oxygen levels in pregnancies complicated by IUGR.[18]

In animal studies, eNOS expression varies depending on the animal model of IUGR used. In Dahl-S rats fed a high-salt diet to induce fetal growth restriction, the placental eNOS messenger RNA (mRNA) expression level was significantly increased compared with controls.[83] In an animal model of IUGR induced by placental insufficiency using hyperthermic exposure, placental and umbilical artery eNOS protein in the placenta was decreased at mid-gestation but increased near term.[84]

However, eNOS expression and activity and the gender effect seem particularly sensitive to undernutrition. In fact, decreased eNOS expression and/or activity have been reported in animal models of IUGR induced by intrauterine undernourishment.[35] In a rat IUGR model induced by intrauterine undernourishment,[35] eNOS expression was decreased only in males, whereas eNOS activity was decreased in both males and females. This reduction in eNOS activity in females, which is probably the consequence of decreased estrogen levels, could explain the impaired endothelium-dependent vasodilation observed in this animal model.[35] The modulation of eNOS activity by estrogens has been confirmed *in vitro*. Long-term estrogen treatment of cultured human and bovine endothelial cells up-regulates eNOS activity.[85]

Upregulation of the arginase pathway

Arginases produce urea and ornithine, using L-Arg as a substrate. By competing with eNOS for the bioavailability of L-Arg, arginases can indirectly contribute the reduction of NO synthesis by eNOS. Accordingly, arginase up-regulation is an important factor that drives endothelial dysfunction. Increased arginase-2 expression was observed in human umbilical endothelium from IUGR fetuses.[86] Pre-incubation with S-(2-boronoethyl)-L-cysteine, an arginase inhibitor, improved *ex vivo* endothelium-dependent relaxation in umbilical and placental vessels from babies born after fetal growth restriction[31] and in aortic rings from a rat IUGR model induced by maternal LPD (personal unpublished data). These data suggest that arginase activity was increased in these vessels.

Increased asymmetric dimethylarginine (ADMA) levels

ADMA, an endogenous NO synthase inhibitor, is also considered an early marker and mediator of endothelial dysfunction. ADMA acts as a competitor of L-Arg, thereby inhibiting NO synthesis by eNOS. However, the observations in human studies are controversial. In pregnancies complicated by IUGR, ADMA levels in maternal serum were found to be either increased[87,88] or decreased compared with those in normal gestations during the first (11–14 weeks), second (20–24 weeks) and third trimesters (28–35 weeks).[89] Estrogen therapy could improve endothelial function by reducing ADMA levels. Clinical data revealed that estrogen therapy, chiefly the oral form, decreased plasma ADMA concentrations and therefore improved NO production in healthy postmenopausal women.[90,91]

In animal models of atherosclerosis (rabbits and monkeys), endothelial dysfunction was associated with increased ADMA levels.[92,93] To the best of our knowledge, ADMA levels have not been assessed in animal models of IUGR.

Oxidative stress

Oxidative stress plays an important role in endothelial dysfunction. ROS, particularly the superoxide anion (O_2^-), play a central role in vascular physiology, and their overproduction is especially relevant to vascular pathologies.[94] In IUGR placentae, markers of oxidative stress, such as 8-hydroxy-2'-deoxyguanosine, redox factor-1,[95,96] malondialdehyde and oxidized LDL, are increased in venous cord blood.[97] Therefore, it has been suggested that oxidative stress is involved in both the short- and long-term modulation of endothelial function in individuals born after IUGR.[98] Oxidative stress affects the NO pathway by influencing NO synthesis and bioavailability. NO rapidly reacts with O_2^- to form peroxynitrite, a highly reactive and toxic species, which reduces endothelium-dependent relaxation[99] and accelerates the development of preatherosclerotic lesions.[100]

As mentioned above, L-Arg and BH_4 are crucial for NO production. A deficit in substrate and/or cofactor leads to enzymatic uncoupling, which causes eNOS to produce O_2^- rather than NO,[101] thus contributing to endothelial dysfunction and impaired endothelium-dependent vasodilation.[102,103] Decreased BH_4 bioavailability can contribute to eNOS uncoupling. Regardless of whether the BH_4 level is sufficient, the oxidation of L-Arg is coupled with the reduction of oxygen molecules to form L-citrulline and NO. However, BH_4 bioavailability can be decreased through reduced production,[104] increased oxidation[105] or impaired recycling of the oxidized form (BH_2)[106] therefore leading to eNOS uncoupling.

Increased O_2^- production up-regulates ADMA levels, thus worsening endothelial dysfunction.[107] In humans, impaired NO-dependent vasodilation in placental vessels from IUGR pregnancies is coupled with a higher sensitivity to oxidative stress.[108]

Increased O_2^- production mediated by NADPH oxidase and eNOS uncoupling was associated with defective endothelial function in a rat model of HTN induced by deoxycorticosterone and saline treatment[109] and in a rat model of IUGR induced by maternal diet restriction (50% of *ad libitum* intake throughout gestation) or LPD (9% casein).[32,110]

Endothelial progenitor cells (EPCs) dysfunction

Endothelial dysfunction is characterized by impaired vasculogenesis and decreased repair capacity, functions that are mediated by circulating EPCs. These cells are bone marrow-derived stem cells that can differentiate into mature endothelial cells, thus contributing to postnatal vasculogenesis and endothelial repair at damage sites.[111] EPCs subsets are differentiated by their phenotype and functional properties. The myeloid subset represents early EPCs, called colony-forming unit-endothelial cells, that appear early in cultures and display endothelial markers but do not form vessels *in vivo*.[112,113] Endothelial colony-forming cells (ECFCs), the true angioblasts, appear later and display properties such as proliferation, auto-renewal, migration and differentiation; additionally, they can support vascular growth and neovascularization. Both loss and impaired function of EPCs have been identified as markers of endothelial dysfunction, as described by Hill *et al.*[114] In adult men with different degrees of cardiovascular risk but without a history of cardiovascular disease, levels of circulating EPCs have been identified as a surrogate biological marker of vascular function and cumulative cardiovascular risk.[114] In pregnancy-related complications, most notably IUGR, aberrant vasculature and abnormal endothelial function were found on both the maternal and fetal sides of the placenta, and it is believed that altered fetal circulating EPCs contribute to these complications.[115] We and others have evaluated ECFCs isolated from LBW newborns and observed altered angiogenic properties *in vitro*, as evidenced by decreased numbers of colonies and sprouts,[116] and *in vivo*, as shown by a reduction in the number of perfused vessels.[117] Moreover, an imbalance between angiogenic and anti-angiogenic factors was noted.[117,118] These data suggest that the impairment of early angiogenic properties (structural and functional) could predispose LBW infants to endothelial dysfunction later in life.

Vascular senescence

Vascular senescence can contribute to endothelial dysfunction.[119] It is characterized by a state of irreversible (replicative senescence) or reversible (stress-induced senescence) growth arrest, the expression of negative cell cycle regulators (such as p53 and p16) and increased senescence-related β-galactosidase staining.[120] Senescent endothelial cells have a decreased ability to form new vascular structures; therefore, they contribute to impaired endothelial function. Sirtuins (SIRTs), particularly SIRT1, belong to a family of proteins involved in the regulation of many cellular processes, including senescence. SIRT1 is highly expressed in endothelial cells, wherein it regulates numerous functions, such as NOS expression and cellular senescence.[121] The depletion of SIRT1 expression in

endothelial cells led to endothelial dysfunction and premature senescence in several models of cardiovascular diseases, whereas overexpression of SIRT1 protected endothelial cells from senescence-associated morphological and molecular changes.[122] ECFCs from LBW newborns exhibit stress-induced vascular senescence characterized by growth arrest, increased β-galactosidase activity, and $p16^{INK4a}$ expression, all of which are mediated by decreased SIRT1 levels.[123] Therefore, stress-induced vascular senescence is coincident with impaired angiogenic properties and could participate in the endothelial dysfunction observed later in life in individuals born after IUGR.

Relationship between IUGR and cardiovascular and renal outcomes later in life

Early endothelial dysfunction observed in individuals born after IUGR could persist for the long term and lead to the onset of cardiovascular-related diseases.

Systemic HTN

Epidemiological studies have highlighted an inverse correlation between LBW and increased blood pressure in infancy,[124] adolescence,[125,126] young adulthood[127,128] and adulthood.[129–132] Some authors have questioned these results, suggesting that the data were inappropriately adjusted for confounding factors[133] that could potentially damage kidneys and/or vascular endothelial cells early in life (e.g. nephrotoxic drugs or umbilical catheter placement). Recent data have indicated that the risk of HTN is not only linked to birth weight but is also amplified by postnatal overfeeding, leading to exaggerated catch-up growth.[134]

Several animal models have shown that IUGR induced by ligation of the bilateral uterine vessels, prenatal exposure to hypoxia (11.5 *v.* 21% O_2) or glucocorticoids, maternal global undernutrition, caloric restriction or LPD during gestation induces HTN in adulthood[32,135–141] and is often associated with vascular dysfunction.[32,142,143] However, it is not well established whether HTN precedes endothelial dysfunction. Some clinical investigations have suggested that endothelial dysfunction is a primary defect in essential HTN that appears before the increase in blood pressure,[144] but other observations have hinted that endothelial dysfunction is a consequence of elevated blood pressure. Different animal models of HTN induced by aortic coarctation (rabbits),[145] a high-salt diet (rats)[146] or neonatal hyperoxia (rats)[67] showed selective impairment of endothelium-dependent vasodilation secondary to increased blood pressure. However, in an animal model of IUGR caused by maternal LPD during gestation, impaired endothelium-dependent relaxation preceded the onset of increased blood pressure (personal unpublished data).

Coronary heart disease

Impaired endothelial function plays a major role in the development and progression of atherosclerosis,[147,148] which ultimately leads to coronary heart disease. Many studies have proposed a relationship between birth weight and coronary heart disease: some showed an inverse relationship between LBW and increased risk of coronary heart disease,[149–151] whereas others found no significant correlation[152] or a positive correlation only in males.[153] Interestingly, the risk of coronary heart disease decreases with increasing birth weight. In fact, a 1-kg increase in birth weight was associated with a 10–20% decreased risk of coronary heart disease later in life.[151]

CKD

The role of vascular components in the renal system is of particular significance because the kidneys receive ~20–25% of the total cardiac output. However, the contribution of the endothelial compartment to kidney development has been the subject of many hypotheses. Previous experiments showed that a significant proportion of the renal endothelium is derived from a resident precursor, the metanephric mesenchyme.[154] Sprouting angiogenesis from the major renal vessels plays a significant role in forming the kidney endothelium, thus giving rise to most of the renal vessels and glomerular capillaries.[155] Endothelial dysfunction is involved in the development and progression of CKD.[156] Patients with CKD display microalbuminuria, which is thought to reflect endothelial damage in the capillary system of the renal medulla and increased endothelial permeability.[156–159] Capillary damage is characterized by increased plasma concentrations of endothelium-derived proteins, such as von Willebrand factor, tissue-type plasminogen activator and urokinase-type plasminogen activator, and increased concentrations of markers of endothelial cell injury, such as soluble thrombomodulin. Decreased endothelium-dependent vasodilation occurs in end-stage kidney disease.[160] Several epidemiological and experimental studies have shown that intrauterine insults are associated with the development of CKD. In humans, birth weight is positively correlated with glomerular number and inversely correlated with glomerular volume.[161] In a meta-analysis of 18 studies, infants born after fetal growth restriction appeared to have a significantly higher risk of albuminuria [odds ratio (OR), 1.81; 95% confidence interval (CI), 1.19–2.77], end-stage renal disease (OR, 1.58; 95% CI, 1.33–1.88), or a low estimated glomerular filtration rate (OR, 1.79; 95% CI, 1.31–2.45).[162] Similar to HTN, the impairment of glomerular and tubular function secondary to IUGR is further amplified by environmental insults, such as drug exposure during the neonatal period[163] or overweight in adulthood.[164]

Several animal models have enabled the identification of mechanisms involved in the development of renal dysfunction later in life. Rat models of IUGR induced by exposure to maternal LPD followed by early postnatal overnutrition during the lactation period or not according litter size reduction or increased protein intake to induce accelerated postnatal growth displayed alterations in renal structural development and a risk

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of chronic renal failure later in life.[165–169] Decreased glomerular number potentially leads to reduced filtration capacity, reduced salt and water retention and the subsequent development of HTN. Furthermore, early loss of nephron numbers/mass may result in a state of hyperfiltration in the remaining nephrons, which will lead to focal segmental glomerulosclerosis and further loss of glomeruli, thus initiating a vicious circle.[170] However, it is not clear whether endothelial dysfunction precedes or is a consequence of CKD. Regarding the impact of postnatal nutrition on renal maturation, rodent models could likely be more affected than humans because nephrogenesis is completed at ~36 weeks of gestation in humans, whereas in rats, this process is completed during postnatal life (between 7 and 10 days of life).

Potential preventive approaches

Several interventions have been identified to potentially prevent IUGR, improve endothelial function and thus antagonize the development of detrimental cardiovascular issues.

Breastfeeding

Breast milk could represent a promising approach, and the easiest one, for improving endothelial function in offspring. In fact, breastfeeding, as opposed to feeding with commercial infant formulas, is one of the best approaches for fighting neonatal oxidative stress because of breast milk's ability to 'trap' free radicals. Breast milk contains enzymatic and non-enzymatic components such as superoxide dismutase, glutathione peroxidase, vitamins (A, C and E), α-carotene, lactoferrin and trace amounts of iron. Breastfeeding could improve endothelial function, primarily due to the presence of lactoferrin, an iron-binding glycoprotein with antioxidant, anti-inflammatory, pro-angiogenic and NO-dependent vasodilator properties. Daily treatment with lactoferrin after unilateral hind limb surgery-induced ischemia in C57BL/6J mice promoted angiogenesis, activated endothelial function via an NO-dependent mechanism[171] and protected HUVECs against hydrogen peroxide-induced oxidative stress.[172]

Folate supplementation

Epidemiological studies have shown that folate deficiency is associated with increased cardiovascular risk.[173,174] Because of the homocysteine-lowering and antioxidant effects of folate and its ability to modulate eNOS activity and cofactor availability, folic acid supplementation could improve vascular endothelial structure and function.

In a study including patients with coronary heart disease, the circulating form of folic acid, 5-methyltetrahydrofolate, increased NO-dependent vasodilation, reduced vascular superoxide production, and improved enzymatic coupling of eNOS by increasing the availability of BH_4.[175] Folate supplementation in patients with acute ischemic stroke[176] or HTN[177] decreased plasma ADMA levels, suggesting that folate intake may also be beneficial in these contexts. Moreover, folic acid supplementation during pregnancy increased the birth weight of newborns.[178]

Folate deficiency in $ApoE^{-/-}$ mice was associated with the development of atherosclerotic lesions, which can be prevented by folate supplementation.[179] Moreover, folate supplementation of a maternal LPD diet prevented the development of increased blood pressure and restored endothelium-dependent vasodilation and eNOS mRNA expression[180] and enzyme activity.[181]

Vitamin supplementation

Studies of animal models of IUGR and developmental programming of CVD have demonstrated that maternal diet supplementation with vitamins C and E can prevent adverse perinatal and long-term outcomes. In an animal model of IUGR induced by high maternal cholesterol levels during the early stages of gestation, maternal dietary supplementation with vitamin E was found to prevent growth restriction in fetuses. Vitamin E has been shown to regulate molecular pathways controlling cell proliferation and viability[182] and to increase the release of vasodilator prostanoids from human aortic endothelial cells[183] and HUVECs,[184] thus improving placenta–fetal blood flow and thereby increasing nutrient delivery to the fetus.

Vitamin C was found to protect chick embryos against the developmental toxicity of ethanol. Indeed, concomitant injection of vitamin C and ethanol in chick embryos prevented the decreased survival, growth retardation and malformations induced by ethanol alone.[185]

However, in human studies, these treatments have failed to show clear benefits in terms of birth weight and associated long-term diseases.[186–189] A possible explanation is the potential confounding effects of maternal endogenous antioxidant defenses and redox status and maternal vitamin intake resulting from diversified nutrition. Differences in vitamin metabolism between humans and animals could also be involved in the discrepancy between human and animal studies.

Antioxidant therapy

Supplementation with resveratrol, a polyphenolic molecule found at high concentrations in red grapes, berries and peanuts, has been identified as a potential therapeutic strategy for the treatment of cardiovascular diseases, primarily due to its antioxidant properties and ability to modulate the NO signaling pathway. In spontaneously hypertensive rats, maternal dietary supplementation with resveratrol during the perinatal period prevented the onset of HTN in adult offspring.[190] Resveratrol also modulates SIRT1 expression. Pre-incubation with resveratrol restored angiogenic capacity and reversed the accelerated senescence of ECFCs from LBW newborns.[123]

Lazaroid is a potent inhibitor of free radical formation, notably O_2^--mediated lipid peroxidation. Treatment with Lazaroid reversed HTN in several rat models,[191,192] and the addition of Lazaroid to a maternal LPD diet throughout

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gestation increased birth weight and reversed later vascular dysfunction in offspring by decreasing oxidative stress.[143]

In a guinea pig model of IUGR induced by progressive uterine artery occlusion starting at mid-gestation, maternal *N*-acetylcysteine treatment during the second half of gestation restored *ex vivo* eNOS-dependent relaxation in the fetal aorta and umbilical artery and normalized eNOS expression in fetal and umbilical endothelial cells.[193]

Melatonin, a hormone with antioxidant and anti-inflammatory properties, is involved in regulating circadian and circannual rhythms[194] and could improve endothelial function. Melatonin exhibits direct scavenging activity on O_2^-,[36,195,196] up-regulates antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, and down-regulates pro-oxidant enzymes such as lipoxygenase,[197] thereby increasing NO production and improving its availability to induce vasodilation[198] in different vascular beds.[199–202]

L-citrulline supplementation

L-citrulline is a precursor of L-Arg. L-citrulline is a non-protein amino acid, which is absent from the regular diet, escapes liver metabolism, has high bioavailability, and is quantitatively converted to arginine *in vivo*.[203] Data have suggested that L-citrulline supplementation improves fetal growth in animal model of IUGR induced by *in utero* exposure to maternal LPD,[79] probably by improving maternal nutritional status and fetal growth through increased NO synthesis as a result of enhanced L-Arg availability in fetal circulation. L-citrulline can also exert a protective role on vascular endothelium. In fact, it has been proposed that L-citrulline supplementation could represent an alternative to L-Arg supplementation to improve vascular function,[204,205] and it attenuated blood pressure in young normotensive men.[206] In animal models, *ex vivo* pre-incubation with L-citrulline prevented endothelial dysfunction induced by ADMA in porcine coronary artery; indeed, such incubation favors L-citrulline to L-Arg recycling and the restoration of NO production, as a consequence of eNOS expression and activity up-regulation, the inhibition of superoxide anion production, and activation of the cyclic guanosine monophosphate (cGMP)[207] Such direct beneficial effects of L-citrulline on endothelium-dependent relaxation suggest that L-citrulline supplementation could be an efficient way to improve endothelial function in individuals born after fetal growth restriction.

Supplementation with L-Arg and NO mediators

It was reported that L-Arg could be administered to increase maternal NO levels to enhance birth weight and decrease neonatal morbidity.[74] More recently, the combined results of 10 small trials showed that L-Arg supplementation can increase the body weight and gestational age at birth of IUGR fetuses.[208] However, this study contrasts with others that reported no benefit of L-Arg therapy.[209,210] Such differences could be explained by the different route of administration (oral or intravenous). In fact, with oral administration, 40% of L-Arg is degraded by the small intestine and metabolized by arginase in the liver. Therefore, poor L-Arg availability in the blood could decrease its efficacy.[203,211]

Among NO modulators, phosphodiesterase inhibitors are promising agents for improving uterine perfusion in pregnancies complicated by IUGR. Type 5 phosphodiesterase (PDE5) is one of the enzymes responsible for the degradation of cGMP to GMP in smooth muscle. Therefore, inhibiting PDE5 delays the breakdown of cGMP and increases vasorelaxation. Sildenafil citrate (Viagra®) is probably the most famous PDE5 inhibitor. In women whose pregnancies were complicated by IUGR, sildenafil citrate improved fetoplacental perfusion[212] and decreased the *ex vivo* vasoconstriction (in response to the thromboxane analogue U46619) of myometrial small arteries.[213]

In animal models, parenteral administration of L-Arg (from day 60 of pregnancy to parturition) to underfed ewes prevented fetal growth restriction,[214] and in a rat model of IUGR induced by maternal LPD, pre-incubating the aortic rings with L-Arg restored impaired endothelium-dependent vasodilation (personal unpublished data). Sildenafil citrate supplementation reversed the maternal effects of preeclampsia by improving uteroplacental and fetal perfusion[215] in a Wistar rat model and increased fetal size in pregnant rats exposed to hypoxia at the end of gestation (18–20 days).[216]

Epigenetic markers of endothelial dysfunction

Epigenetics plays a major role in the developmental origins of health and diseases.[217] Epigenetics can be defined as a phenomenon of altered phenotypic expression of heritable genetic information without changes in the DNA sequence. Three main pathways can silence, activate or regulate the level and time of expression of many genes: DNA methylation, histone modifications (acetylation, methylation, ubiquitination, phosphorylation or ADP-ribosylation) and small non-coding RNAs, such as microRNAs (miRNAs).[218,219] In general, these three epigenetic mechanisms appear to work together to regulate gene expression. DNA methylation or histone modifications can alter the expression of miRNAs, which can in turn regulate the epigenetic processes of DNA methylation and histone modifications.

DNA methylation

DNA methylation has been known to be particularly sensitive to an adverse early environment. DNA methylation occurs through the binding of a methyl group in position 5 of the cytosine ring dinucleotide CpG sequences present in the DNA by DNA-methyltransferase, which can methylate and demethylate the DNA, thus making the modification reversible.[220] In general, low levels of DNA methylation (hypomethylation) are associated with increased gene activity, whereas high levels of methylation (hypermethylation) are associated with gene repression.[221] Moreover, hydroxymethylated

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cytosine [5-hydroxymethylcytosine (5 hmeC)] has been identified as another functional DNA modification, representing an intermediate state of active DNA demethylation and also influencing gene expression.[222,223]

eNOS expression in HUAECs and HUVECs of IUGR pregnancies can be controlled by DNA methylation levels. eNOS protein and mRNA levels were increased in HUAECs but decreased in HUVECs from IUGR pregnancies[86] and were associated in the eNOS promoter with decreased DNA methylation at CpG −352 in IUGR-HUAECs and an increased in IUGR-HUVECs. In addition, in human umbilical artery endothelial cells from patients with placental insufficiency, levels of 5 hmeC at the eNOS transcription start site directly correlated with elevated eNOS levels.[224] In a guinea pig model of IUGR, increased eNOS expression was associated with decreased DNA methylation levels in eNOS promoter of endothelial cells derived from aorta, femoral and umbilical arteries; such modifications were prevented by maternal administration of *N*-acetylcysteine.[193]

Histone modifications

In the nucleus, DNA is packaged into chromatin as repeating units of nucleosomes, which form a 'beads-on-a-string' structure that can compact into higher order structures to affect gene expression. Nucleosomes are composed of 146-bp DNA wrapped in histone octamers (composed of two H2A, H2B, H3 and H4) and are connected by a linker DNA, which can associate with histone H1 to form heterochromatin. Histone proteins contain a globular domain and an amino-terminal tail, which can be post-translationally modified. The post-translational modification of lysine (acetylation, methylation, ubiquitination, sumoylation), arginine (methylation) and serine and threonine (phosphorylation) are the most commonly described modifications.[218,225] In general, the acetylation of histones H3 and H4 is associated with increased gene expression and has been shown to regulate the angiogenic function of endothelial cells.

Levels of H3K9ac and H2A.Zac were significantly higher at the eNOS transcription start site and were directly correlated with elevated eNOS levels observed in the human umbilical artery endothelial cells from patients with placental insufficiency.[224] In addition, increased histone H3 acetylation in the endothelin-1 promoter of pulmonary vascular endothelial cells and in the peripheral leucocytes in a IUGR rat model induced by maternal undernutrition has been correlated with higher endothelin-1 expression, which could increase the risk of pulmonary disorders (pulmonary HTN or asthma) later in life.[226] Recently, we observed that SIRT1 repression in ECFCs from LBW newborns, associated with premature senescence, could be modulated by changes in 'active' or 'repressive' epigenetic marks. The 'active' marks trimethyl-H3K4 associated with the SIRT1 promoter were significantly decreased in LBW newborns compared with controls, whereas the 'repressive' marks trimethyl-H3K9, associated with heterochromatin formation, were increased.[123]

Non-coding RNAs

MiRNAs are small single-strand RNAs that do not encode proteins. Each miRNA binds to specific mRNAs, resulting in the degradation of target mRNA or the inhibition of its translation into protein. miRNAs regulate the post-transcriptional expression level of many genes and processes such as apoptosis, cell

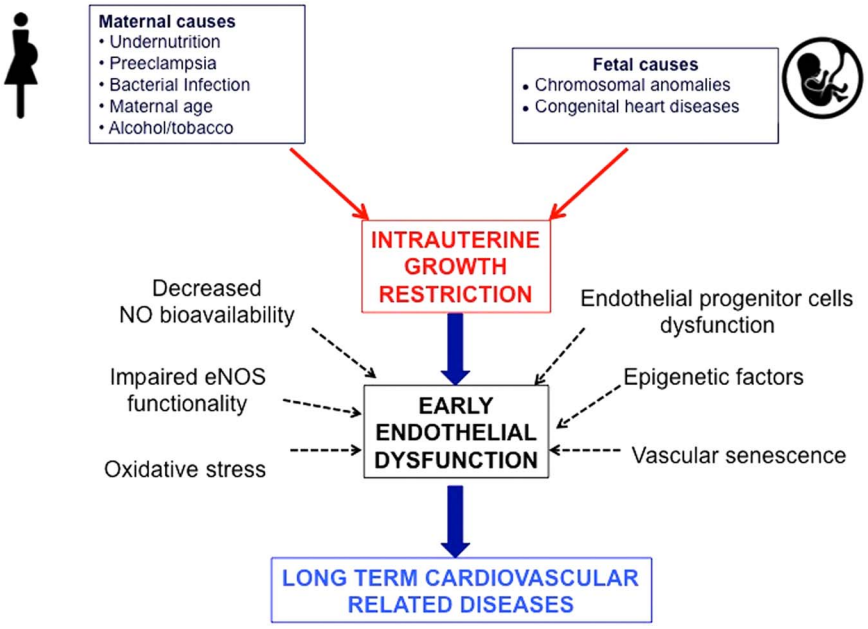

Fig. 1. Association between intrauterine growth restriction, early endothelial dysfunction and long-term cardiovascular-related diseases. eNOS, endothelial nitric oxide synthase; NO, nitric oxide synthase.

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growth and differentiation in a large range of tissues,[227,228] and notably in the regulation of endothelial functions. MiR-21 expression is increased in cases of shear stress, which helps to protect endothelial cells by decreasing apoptosis and increasing eNOS expression and NO production.[229] However, in atherosclerotic plaques, an up-regulation of miR-21 decreases the function of superoxide dismutase, which leads to increased ROS production and decreased migration of the progenitor cells.[230] MiR-221 and miR-222 are highly expressed in endothelial cells[231] and exert antiangiogenic, antiproliferative, antimigration and proapoptotic effects on endothelial cells,[231] which can be partly caused by reduced eNOS expression.[232] In addition, miRNAs can modulate SIRT1 expression. Increased expression of miR-217 and miR-34a have been observed in endothelial senescence, which leads to loss of SIRT1 function, notably by reducing eNOS expression.[233]

Conclusions

In individuals born after fetal growth restriction, early endothelial dysfunction plays an important role in the subsequent development of HTN, coronary heart disease and CKD. Decreased NO synthesis and bioavailability caused by defective eNOS function and oxidative stress, decreased EPCs number and function, and vascular senescence have all been shown to be involved in endothelial dysfunction (Fig. 1). Preventive approaches, including breastfeeding and supplementation with folate, vitamins, antioxidants, L-citrulline, L-Arg and NO modulators, represent promising and simple ways to prevent fetal growth restriction, improve endothelial function and vasodilation responses early in life and delay/prevent detrimental cardiovascular issues.

Epigenetic modulation of gene expression appears to be one of the main contributors to the long-term effects of an adverse perinatal environment. The identification of early biomarkers of endothelial dysfunction, especially epigenetic biomarkers, could allow early screening and follow-up of individuals at risk of developing CVD, thus contributing to the development of preventive and therapeutic strategies to avert the long-term effects of endothelial dysfunction in infants born after IUGR.

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Conflicts of interest

None.

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