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REVIEW

Fetal programming and early identification of newborns at high risk of free radical-mediated diseases

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Abstract

Nowadays metabolic syndrome represents a real outbreak affecting society. Paradoxically, pediatricians must feel involved in fighting this condition because of the latest evidences of developmental origins of adult diseases. Fetal programming occurs when the normal fetal development is disrupted by an abnormal insult applied to a critical point in intrauterine life. Placenta assumes a pivotal role in programming the fetal experience *in utero* due to the adaptive changes in structure and function. Pregnancy complications such as diabetes, intrauterine growth restriction, pre-eclampsia, and hypoxia are associated with placental dysfunction and programming. Many experimental studies have been conducted to explain the phenotypic consequences of fetal-placental perturbations that predispose to the genesis of metabolic syndrome, obesity, diabetes, hyperinsulinemia, hypertension, and cardiovascular disease in adulthood. In recent years, elucidating the mechanisms involved in such kind of process has become the challenge of scientific research. Oxidative stress may be the general underlying mechanism that links altered placental function to fetal programming. Maternal diabetes, prenatal hypoxic/ischaemic events, inflammatory/infective insults are specific triggers for an acute increase in free radicals generation. Early identification of fetuses and newborns at high risk of oxidative damage may be crucial to decrease infant and adult morbidity.

Key words: Fetal programming; Oxidative stress; High-risk newborn; Biomarkers; Perinatal medicine; Metabolic syndrome

Core tip: The adverse outcomes on the offspring born from altered gestation are already known. The consequences of these perturbations have been demonstrated even after many decades from birth. In this review we summarize gestational conditions associated to fetal programming and elucidate the mechanisms involved in such kind of occurrence. We also describe to what extent oxidative stress (OS) is involved in a very wide spectrum of genetic, metabolic, and cellular responses, through the gene expression

regulation, and cell growth modulation. By virtue of these properties, OS has been nominated as the lowest common denominator of adult disease programming.

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INTRODUCTION

The last century witnessed the rise in chronic cardio-metabolic diseases in which metabolic-syndrome (MetS) represents a major health problem regarding morbidity and mortality[1]. MetS is characterized by a number of related disorders, such as visceral obesity, glucose intolerance, disturbed plasma lipids concentration, high blood pressure, and increased risk of developing cardiovascular diseases and type 2 diabetes[2]. Smoking, high-fat diets, abdominal obesity[3-5], insulin resistance[6,7], physical inactivity[4,8], aging[9], and hormonal imbalance[10] have been identified as the main risk factors for several years.

Pediatricians have serious concerns with MetS because adult lifestyle is not the only determinant. In the last decades, a worldwide series of epidemiological studies have provided evidence for the association between perturbation of fetal environment and major risk factors for cardiovascular disease, diabetes, and MetS in adult life[11-15]. This has been called "fetal/early origins of adult disease" by David Barker. The hypothesis predicts that environmental factors, particularly nutrition, act in early life to program the risks for adverse health outcomes later in life[16]. Refinements of this idea of "fetal programming" focus on the processes of developmental plasticity, which in normal situations provide the settings for homeostatic mechanisms to ensure an adequate amount of nutrients to the most vital organs at the expenses of other less vital organs (the thrifty phenotype hypothesis)[17]. These changes in phenotype can become permanent and can generate a mismatch with adult environment that would lead to the development of metabolic diseases in adulthood[18]. The latter phenomenon gave rise to the new concepts of "metabolic memory"[19], "fetal primed"[20], and "developmental plasticity"[21].

The aim of this paper is to review all the gestational conditions associated to fetal programming and elucidate mechanisms involved in such kind of process. Identifying a lowest common denominator could be essential to contrive prevention strategies, treatment, and appropriate follow-up to high-risk newborns.

FETAL PROGRAMMING

Fetal programming occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or insult applied to a critical point in intrauterine life. Pregnancies complicated by diabetes, small for gestational age (SGA) or large for gestational age (LGA) offspring, pre-eclampsia and conditions such as hypoxia, oxidative and nitrosative stress are associated with programming. Placenta plays a key role in developmental plasticity. Vasculature and trophoblast are both involved in overall placental transport[22,23]. Changing developmental signals or the amount of substrate of the fetus produces an alteration of fetal development which ultimately leads to cardiovascular or metabolic diseases later in adult life[24]. Alterations in placental vasculogenesis[25], trophoblast expression of transporters[26], trophoblast enzyme activity, and hormone production[27] occur in pregnancies complicated by IUGR, pre-eclampsia or diabetes.

Mothers with insulin-dependent diabetes are prone to hyperglycemia in the first trimester of gestation that generates an up-regulation of Glut1 and System A (a sodium-dependent transporter of neutral amino acid) in the trophoblast leading to accelerated fetal growth in late gestation[28]. The activity of System A is reduced in placentas with intrauterine growth restriction (IUGR)[29,30]; moreover, inhibition of System A in rats causes growth restriction[31]. Glut transporters function and expression are also influenced by glucocorticoids, which are produced by trophoblast and regulated by the activity of 11-β-hydroxysteroid dehydrogenase (11βHSD). Exposure of the rat fetus to excess maternal or exogenous glucocorticoids causes growth restriction, hypertension and hyperglycaemia[32,33]. The trophoblast expresses 11βHSD-2 that converts cortisol to inactive cortisone and this may protect the fetus against high levels of maternal cortisol[34]. In humans, mutations in the 11βHSD-2 gene have been reported in association with low birth weight. Reduced 11βHSD-2 activity and increased fetal cortisol levels have been reported in association with IUGR[35].

Hypoxic conditions in pregnancy are strongly involved in fetal programming. Oxygen regulates development of the villous vascular tree and villous trophoblast proliferation due to hypoxic regulation of angiogenic mediators as vascular endothelial growth factor (VEGF) and placental growth factor (PLGF). Hypoxia acts *via* the transcription of hypoxia-inducible factor-1α (HIF-1α) that activates gene transcription in response to varying oxygen concentration. For example, at 10-12 wk of gestation, the trophoblast is exposed to a hyperoxic challenge during the transition from histiotrophic nutrition to intervillous blood flow vascularization[36]. Low oxygen tension inhibits trophoblast differentiation to the invasive extravillous trophoblast pathway, hence the switch in oxygenation activates trophoblast invasion and subjects the cell to oxidative and nitrosative stress. A pathological increase of oxidative stress (OS) is found in pregnancy complicated by pre-eclampsia or diabetes[37].

On the basis of the latter consideration, in order to

confirm the hypothesis of *in utero* programming process and analyze the mechanisms involved, many authors have conducted experimental studies throughout various animal models of fetal programming based on fetal insult induced by placental insufficiency, hypoxia, maternal undernutrition, and maternal exposure to stress and increased plasma glucocorticoids levels[38-44].

PROGRAMMING OF INSULIN RESISTANCE, OBESITY, AND TYPE Ⅱ DIABETES

Insulin resistance may come from fetal adaptation to an adverse intrauterine environment during a critical period, thus leading to programming of fetal gene expression[45,46]. Insulin plays a central role in fetal growth. During the first two years of life SGA newborns are usually able to catch-up growth by increasing their growth velocity and recovering the weight of AGA counterparts[47]. The dynamic changes that occur during this period suggest a critical role of adipose tissue in the development of metabolic complications. Ibáñez *et al*[48] stated that this early growth, in SGA newborns, was associated with development of central adiposity and insulin resistance between 2 to 4 years of age. The same correlation was found in early adulthood by Leunissen *et al*[49]. Following these epidemiological data, MetS was renamed as "the small baby syndrome"[50]. This fitted well with Hertfordshire's findings according to which the highest risk of cardio-metabolic diseases was in men and women who had evidence of early-life deprivation (considering weight at birth or in early childhood) and who had become overweight as adults ("small becoming big")[51]. However, we currently known that not only those subjects born with low birth weight, but also poor maternal nutrition increase maternal weight gain[52,53] and that large-for-gestational age newborns have increased metabolic risks[54].

Not only are diabetic mothers hyperglycaemic but they also have elevated circulating lipids and amino-acid. The fetal pancreas and liver are stimulated to secrete increased insulin and insulin-like growth factors that are growth-promoting hormones in the fetus. This results in the well-described diabetic mother's macrosomic infant. Low-grade inflammation has been reported to be a link between insulin resistance, obesity, and type 2 diabetes[55]. Adipokines and cytokines affect insulin sensitivity through their ability to interfere with insulin signaling[56]; these molecules also modulate inflammation[57]. Adiponectin, which is produced by the enhanced adipose tissue, acts as insulin-sensitizing, antiatherogenic, and anti-inflammatory hormone[58]. Some scholar have shown that women with gestational diabetes mellitus (GDM) express a decreased concentration of adiponectin and an increased level of TNF-α and IL-6[57,59]. Lihn *et al*[60] suggest that this happens due to TNF-α and IL-6 downregulation of adiponectin expression. Leptin, which is a hormone produced by placenta and by adipocytes principally[61], is involved in weight gain regulation by interacting with neuropeptide-Y in the hypothalamus[62]. Beyond its properties as appetite-suppressant agent, Leptin is also capable of regulating lipid metabolism. Atègbo *et al*[57] have shown high leptin level in mothers with GDM and, in contrast, a reduced level of leptin in their macrosomic children. Leptin, as pro-inflammatory factor, may contribute to the inflammatory state during gestational diabetes. Conversely, low leptin level in macrosomic babies may contribute to weight gain since leptin-deficient rodents[62] and human[63] have been shown to develop obesity. According to the hypothesis of "Metabolic Memory", these alterations may permanently increase the risk of trend in high food taking, overweight, obesity, and diabetogenic status in offspring during adult life[19]. An example of metabolic memory is revealed by Franke *et al*[64] who have shown that diabetic pregnancy in rats alters the differentiation of the newborns' hypothalamic neurons. The impairment of these neurons may be avoided by normalizing glycemia among diabetic pregnant rats[64]. This metabolic imprinting could generate an intergenerational effect in which children risk becoming overweight or obese post-natally. Furthermore, if the child is female, she risks becoming diabetic during pregnancy, thus exposing the fetus to another route of later metabolic risk[19].

PROGRAMMING OF HYPERTENSION AND CARDIO VASCULAR DISEASE

Experimental models of fetal programming induced by gestational protein restriction[65,66], maternal stress[67], hypoxia[68] or placental insufficiency[69] demonstrate that vascular dysfunction and hypertension are related to a marked increase in glucocorticoid (GC) expression and/or marked decrease in the expression of 11β-HSD2. In these studies, the exposure to exogenous GCs generates a reduction in nephron number[70], vascular dysfunction[71], alterations in the renin-angiotensin system (RAS)[72], disruption in hypothalamic-pituitary-adrenal (HPA) axis[73-76], and hypertension[77,78] in the litter. Reduction in nephron number may affect the renal excretory function, thus contributing to the fetal programming of hypertension. However, some models demonstrate that a decrease in nephron number is sensitive to the timing of the insult[77,79] and the early-mid nephrogenesis phase is the most critical window to promote the modification in fetal kidney[80]. This change in phenotype may alter the mechanisms of adaptation to renal damage in adult life[81,82]. Otherwise other systems, which are critical to the long-term control of blood pressure, may contribute to program hypertension. As is clearly known, vascular dysfunction is implicated in the pathophysiology of hypertension[83] and plays

a critical role in the development of cardio-vascular (CV) disease[84]. Many clinical studies have observed an impaired vascular function in healthy children with low birth weight[85,86], thus suggesting that vascular consequences of fetal programming may precede the development of adult CV disease. Vascular endothelial cell play a pivotal role in CV system by producing a collection of vasoactive agents whose functions include vasodilatation, vasoconstriction, and vascular growth[86]. This axiom is confirmed by animal models in which fetal insult, which is induced by nutritional restriction, placental insufficiency or hypoxia, leads to vascular dysfunction due to the impairment of endothelium-dependent nitric oxide (NO) availability[87-89]. During hypoxia, an imbalance in potent vasoactive factors is generated and an increase in total peripheral resistance is programmed, thus contributing to the development of hypertension. The RAS is another system strongly involved in blood pressure regulation and CV disease programming[90]. In the rat, RAS blockage during the nephrogenic period leads to a marked reduction in nephron number[91,92]. Although suppression of the RAS is observed at birth, hypertension is established by inappropriate activation of the RAS later in life[93-95]. According to the thrifty phenotype hypothesis, blood flow redistribution to critical organs such as the brain and heart occurs at the expense of other organs such as the liver, kidney, muscles and skin, thus resulting in exposure to hypoxia, with modifications in the hypoxia inducible factor (HIF) pathway[21]. HIF regulates several pathways, including the sympathetic nervous system, *via* stimulation of tyrosine hydroxylase[96]. Numerous models of fetal programming confirmed an increased amount of circulating catecholamines during placental insufficiency and gestational protein restriction[97-99]. The data are supported by the evidence that renal denervation delays the development of hypertension in prepubertal offspring[100] and abolishes hypertension in adult male IUGR offspring[101]. All these alterations in phenotype appear to contribute to hypertension in response to certain fetal insults, thus highlighting the complexity of the pathways involved in the fetal programming of hypertension and CV disease.

OS FETAL PROGRAMMING HYPOTHESIS

OS occurs when the production of free radicals (FRs) exceeds the capacity of antioxidant defenses[102]. It represents an imbalance between the production of reactive species and the capacity of biological system to readily detoxify the reactive intermediates or repair the resulting damage.

FRs can be produced through many processes. FR are generated primarily within the mitochondrial respiratory chain, which is fundamental for ATP production in mammalian cells. During the respiratory process, oxygen (O_2) is utilized as an electron acceptor and completely reduced to water through the acquisition of four electrons. Once this process is completed through subsequent steps, radical formation becomes possible. NO can be also a FR source because it contains an unpaired electron in the outer orbital.

Nitric oxide synthase (NOS) catalyzes the formation of NO. It reacts relatively slowly with O_2 thus producing the orange-brown gas nitrogen dioxide ($^{\cdot}NO_2$), a highly reactive FR[103]. Hypoxia-ischemia sets in motion several pathways involving intracellular calcium release and activation of nitric oxide synthetase leading to increased FR generation[104].

Other potential endogenous sources of FRs include inflammatory cell activation (through Nicotinamide Adenine Dinucleotide Phosphate Reduced oxidase of phagocytes and some endothelial cells), monoxygenase system, nitric oxide synthase, and several other enzymes involved in the inflammatory process[105]. The burden of FR can be further amplified by the presence of "free" metals such as iron, copper, and manganese that are released from metalloprotein complexes[106]. Iron, can damage tissues by catalyzing the conversion of superoxide and hydrogen peroxide to FR species through the Haber-Weiss and Fenton reactions when it is unbound to plasma proteins[107].

Additional endogenous sources of cellular FR are activated neutrophils, eosinophils, and macrophages[108]. Notwithstanding the source of FRs, they are really dangerous because of their toxic effects that are able to damage all cell components, including proteins, lipids and DNA. OS may operate directly through the modulation of gene expression or indirectly through the adverse effects of oxidized molecules at critical developmental windows.

Therefore, OS causes a very wide spectrum of genetic, metabolic, and cellular responses and many oxidative conditions are able to modulate gene expression, stimulate cell growth or cause a protective temporary growth-arrest[109]. Necrosis is the most extreme outcome and involves direct cell destruction.

Recently, Leal *et al*[110] have shown that there is a change in the prooxidant and antioxidant defences strictly related to pregnancy process. During pregnancy, OS plays a major role in maternal-fetal interface insofar as it is essential for embryo and tissue development. Maternal diabetes, prenatal hypoxic/ischaemic events, inflammatory/infective insults are specific triggers for an acute increase in FRs, thus generating an adverse intrauterine environment with impaired fetal development[111,112]. Pro-OS is also a common feature for adverse (poor or excessive) fetal growth, preterm birth, smoking, malnutrition, overnutrition, infection and inflammation[113-116]. Consequently, OS may be the key link underlying the programming associations between adverse fetal growth/preterm birth and elevated risks of chronic diseases.

The role of OS in the pathogenesis of insulin dependent diabetes mellitus has been implicated in several

studies[117,118] and there is evidence that both free-radical production and antioxidant defences are disturbed in Diabetes[119]. Hyperglycemia leads to an increased production of FRs through different metabolic pathways. In short, hyperglycemia increases formation of advanced glycation end product (AGE) and activates the hexosamine biosynthetic pathway, thus leading to the formation of glucosamine-6-phosphate that competes with glucose-6-phosphase dehydrogenase and limits the synthesis of nicotinamide adenine dinucleotide (NAD). As is clearly known, NAD is necessary for reduced glutathione (GSH) rebuilding. Moreover, activation of the polyol and protein kinase C pathways, together with oxidases activation, may also be responsible for increased FRs production[120]. Hence, end products of abnormal glucose metabolism lead to an increased formation of FRs. When FRs production overcomes fetal and placental antioxidant capacity, transcription factors (TFs) such as nuclear factor-κB, activator protein-1, and HIF-1 are activated and lead to insulin resistance due to the phosphorylation (inactivation) of insulin receptor substrate-1 (IRS-1). Inhibition of IRS-1 leads to reduced membrane translocation of glucose transport protein as glucose transporter-4 (GLUT-4), thus generating a reduction of glucose insulin-dependent uptake. Moreover, FRs are able to down-regulates GLUT-4 transcription directly[120]. Consequently, extracellular hyperglycemia occurs. However, glucose can enter all cells virtually through insulin-independent GLUTs such as GLUT-1 and GLUT-3. This raises intracellular glucose concentration and enhances FRs generation, which, again, impairs insulin and signals the establishment of a vicious circle. TFs may also directly induce the expression of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α or monocyte chemoattractant protein-1 that will cause insulin resistance. Recent studies in animal models have observed that manipulating anti/pro- oxidant balance in pregnancy could alter blood pressure and vascular reactivity in rat offspring[121,122]. Such emerging evidence confirms that both the insulin functional axis and blood pressure could be sensitive targets to OS programming.

OS has been demonstrated in pregnancies with fetal growth restriction[123]. Fetal growth restriction is often complicated by intrauterine hypoxia and impaired blood flow to the fetus. Intrauterine hypoxia may induce FRs generation and fetal OS. It has been demonstrated that increased isoprostanes concentrations, which are reliable markers of lipid peroxidation in amniotic fluid, indicate fetal growth restriction and also induce damage to amniotic epithelium and chorioamniotic collagen. This aspect is clarified by recent data demonstrating that F2-isoprostanes concentrations are significantly higher in pregnancies with premature rupture of membranes than in normal ones[123]. FRs may disrupt amino acid binding in proteins and polyunsaturated fatty acids of the membrane lipid bilayers, thus causing cell dysfunction, modification of chorioamniotic biology and predisposition to premature rupture of membranes.

By favouring intracellular release of NPBI into plasma, asphyxia and acidosis supply redox-cycling iron, thus predisposing to OS[124-127]. NPBI leads to the catalysis of superoxide anion ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), and the generation of the damaging hydroxyl radical ($^{\cdot}OH$). In presence of free iron, huge increases in FRs generation are possible and likely to cause tissue damage. Plasma NPBI may leak into the brain through a damaged barrier and is particularly damaging insofar as it is taken up by cells directly. When NPBI gains access to the extracellular space, its uptake by cells is enhanced by intracellular calcium and paradoxically also by increased levels of intracellular iron. Differentiating oligodendrocytes are particularly vulnerable to FRs damage because they are rich in iron, which is required for differentiation[128].

A recent *in vivo* and *ex vivo* rat model of IUGR underlines that delays in oligodendrocyte differentiation and myelination are probably due to bone morphogenetic protein 4 (BMP4) up-regulation induced by OS. When BMP4 expression in oligodendrocyte increases, impaired differentiation occurs. A normal myelination has been observed abrogating BMP signaling[129].

Down syndrome comes from an exceeding chromosome 21 in cellular karyotype. Superoxide dismutase (SOD) gene is localized on chromosome 21. This enzyme has the capacity to detoxify cells from superoxide anion *in vivo* with the participation of catalase and glutathione peroxidase. Consequently increased SOD production leads to high H_2O_2 generation, which can itself be toxic and also interfere with SOD activity[130]. An increased level of 8-iso-PGF2a isoprostane, was found in amniotic fluid of pregnancies with a Down syndrome foetus[131]. The immature oligodendroglial cells are glutathion peroxidase and catalase deficient so overexpression of SOD can be dangerous, instead of being protective. The early occurrence of OS in pregnancies with trisomy 21 and their subsequent oxidative damage as major contributing factor in brain aging and cognitive function decline are probably due to the overexpression of SOD, which comes from the supernumerary chromosome. SOD is also overexpressed in the immature brain, especially under stressful conditions (such as hypoxia)[132].

CONCLUSION

During early life, many gestational conditions may represent an important determinant of future health. Whereas the dominant focus of experimental studies to date has been on defining the phenotypic consequences of fetal-placental perturbations, the emphasis has now shifted to determining those initiating mechanisms underlying the programming process. The size and scope of this field has grown to include OS as the lowest common denominator.

During normal pregnancies, oxidants have many physiological functions, which promote and control cellular fate and which play a crucial role in normal development through cellular signalling. In absence of a parallel increase in antioxidative activity, OS will result. Overproduction of reactive oxygen species can lead to massive cellular damage by acting on proteins, lipids, and DNA. This unbalance may change the course of pregnancy and generate a cascade effect that leads to the genesis of *in utero* programming of adult diseases. It is clear that placenta is not simply a passive participant in pregnancy supplying maternal substrates to the fetus. It adapts to the maternal environment and changes both its structure and function. Placenta thus assumes an active role in programming the fetal experience *in utero* that leads to disease in adult life. Since placenta serves as barrier against oxidative insult to maintain the homeostasis of fetal intrauterine environment, it is plausibly that placenta adaptation occurred in response to such altered maternal environment may be the general underlying mechanism that links altered placental function to fetal programming. It can also been hypothesized that programming process is extended in early postnatal life for premature infants. Premature neonates experience a hyperoxic challenge as they have to grow up in an oxygen-rich environment post-natally. Moreover, these biological systems are prone to oxidative insults because of their resilience and maturity stage at the time of insult. There could be a different timing of insult, plausibly prenatal and early postnatal periods are the most critical "windows" to OS programming insults.

The challenge for the future is to develop new effective antioxidant therapies and to demonstrate their benefits in treatments. However, whether antioxidant supplementation, or a diet rich in antioxidants, can avoid consequences of OS programming in the off-spring or not is yet to be elucidated. Longitudinal studies evaluating the panel of OS biomarkers and elucidating the molecular mechanisms that engender OS in perinatal period are needed before antioxidant therapies are accepted in clinical practice.

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