

INTRAUTERINE GROWTH RESTRICTION - AN IMPORTANT EPIGENETIC PREMISE FOR ADULT CARDIOVASCULAR DISEASES

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Abstract: *Given multiple causalities, the fetus develops an intrauterine growth restriction that compensatory stimulates the adaptative phenomena; both, the determining cause of intrauterine growth restriction and the adaptative reactions, will initiate epigenetic changes which will affect the long-term structure and functionality of the heart and will modify the cardiovascular reactivity. The study is based on a systematic review of 20 existing studies that certifies a link between epigenetic changes and adult cardiovascular disease. Against the background of epigenetic changes, postnatal nutritional and behavioral factors are added which lead to pathologies in adult life, so the proper functioning and development of the body starts from the first moments of intrauterine life and continue postnatal, creating the premises for a healthy life. However, it is difficult to assess the environmental factors that interact with the human body and how this combination of factors determines a predisposition to cardiovascular disease.*

Key words: *Intrauterine growth restriction, intrauterine programming, epigenetics, cardiovascular diseases*

1. Introduction

The term „epigenetics” refers to the processes in which the expression of genes determines the individual phenotype, processes that have their beginning either in the gametogenesis

phase or in the prenatal phase, these having a role in heredity and remaining stable throughout life. Epigenetics also involves mechanisms in which environmental factors, including maternal nutrition or exposure to certain chemicals during pregnancy, can influence the fetal

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and neonatal phenotype as well as the development of certain pathologies [1].

In the contemporary world, cardiovascular diseases are the main cause of death for both sexes. Epidemiological studies suggest a link between low birth weight and high rates of adult mortality and cardiovascular morbidity, supported by clinical studies showing that intrauterine growth restriction (IUGR) causes adaptive cardiovascular changes [2].

2. Methods

This paper is a review of the literature on the long-term effects of intrauterine growth restriction (IUGR) on adult cardiovascular diseases and the mechanisms involved in intrauterine programming and its critical stages. For its elaboration, 20 articles were selected and the conclusions and the results were synthesized and presented in this paper.

3. Result and discussion

Critical stages of genetic programming and the mechanism of intrauterine programming

Dynamic and inherited changes that alter the structure of chromosomes, but not the sequence of genes, are defined as epigenetic changes which regulate the expression of line-specific genes in some cellular processes, including the pathogenesis of disease. They also are a reflection of the interaction between DNA and environmental factors. Gene expression depends, partially, on the accessibility of genomic regions such as promoters, enhancers, and silencers [3]. These regions are essential for binding

transcriptional factors, such as DNA-activating and repressing proteins, when regulating gene transcription. Acetylation and methylation of histones have major impact in the accessibility of these genomic loci [3]. In general, acetylation of histones in lysine residues is associated with the activation of gene expression, while methylation may be associated with either transcriptional repression or activation, depending on the gene specificity [6]. DNA methylation to certain cytosine regions of the promoter called CpG islands is another form of epigenetic modification that regulates gene expression. Gene expression can also be regulated by non-coding RNAs; these expression profiles of small molecules can be correlated with the up-regulation or suppression (down-relegation) of specific genes.

Environmental aggressors cause changes in the programming of the fetal phenotype, when they act during the developing stage, and even more, in certain key points, when they will put their mark even more strongly on the postnatal evolution.

In the preconceptional or preimplantational period, oxygen levels, nutrients and hormone levels interfere with the development of the oocyte and further with the blastocyst, affecting the cell distribution between the trophoblast and the rest of the embryonic cell mass [3]. In animal models, it has been shown that contraceptive exposure to elevated levels of progesterone or metabolites such as urea, leads to above average birth weight. At the same time, dietary restrictions during the contraceptive period seem to shorten the duration of pregnancy, and also to cause maternal hypertension and dysfunctions in the hypothalamic-pituitary axis [4]. Changes

before the implantation of the egg affect multiple cell lines, even if during the pregnancy there are compensatory changes such as up-regulation of transplacental transport. With the onset of placenta formation, intrauterine programming is performed to support its development [5]. Harmful factors that act during organogenesis, produce discrete structural alterations, but permanent and with long-term effects, affecting the functional capacity of the organ in question.

If aggression occurs during gametogenesis, the reproductive potential of the next generation is compromised [6]. If the pathological changes occur during the period of rapid fetal growth and affect the intake and use of nutrients, tissue growth suffers, therefore, the cell cycle moves from the proliferation phase to the differentiation phase, resulting a decrease in the total number of cells [7,8]. Given the fact that tissues and organs have different growth rates, pathological changes that occur during intrauterine life affect morphologically and especially functionally various structures when they appear in the latter part of pregnancy. This is due to overlapping with the maturation processes of the fetal organism and its preparation for extrauterine life. Maturation and differentiation processes are mainly glucocorticoid-dependent and can be activated prematurely by early exposure to corticosteroids. Physiological systems of extrauterine maturation and adaptation, that are latent during pregnancy, are normally activated during birth, so that their early activation, in relation to the moment of birth, can have negative effects on the starting point of the health of the newborn.

Intrauterine programming can begin at any level of the affected system and consists of structural and functional changes in genes, cells, tissues and finally organs.

The relation between cardiovascular diseases and intrauterine growth restriction

The subclinical stage of cardiovascular diseases has an early onset, with some studies suggesting it before birth, the risk factor in this case being the restriction of intrauterine growth. Epidemiological studies have shown that low birth weight is associated with an increased risk of myocardial infarction [9, 10], hypertension [11-13], low glucose tolerance and non-insulin-dependent diabetes [14-16]. The biological phenomena underlying these associations are called "fetal programming" and represent structural, metabolic and functional changes that occur as an adaptive response to environmental factors that negatively influence fetal development, these changes persisting in the postnatal period.

In relation to cardiovascular diseases, fetal programming involves metabolic changes and cardiovascular remodeling. Metabolic changes have been implied as the first hypothesis to explain the relationship between adult cardiovascular diseases and low birth weight. The caloric restriction and, implicitly, of nutrients during the epigenetic programming period, especially during the intrauterine life, determine the development of some ways that compensate the alterations produced by them by selecting some "saving" genes [17-19].

Because nutrient availability will be within normal limits in postnatal life, this

fetal programming will promote a higher incidence of metabolic diseases such as obesity and diabetes but also a metabolic syndrome that can secondarily lead to cardiovascular diseases (CVD) [20,21]. Although metabolic changes are factors that contribute to the determination of CVD, they cannot per se explain the epidemiological association between IUGR and CVD [22].

Cardiovascular remodeling and adaptative cardiovascular changes in IUGR

Placental insufficiency has two major effects on fetal development of the cardiovascular system. Firstly, the reduced intake of oxygen and nutrients disrupts the growth of cardiomyocytes and the architecture of muscle fibers and secondly, villous hypoplasia causes an increased placental resistance and chronic cardiac load [23]. Thus, the developing myocardium shows a variety of changes in micro- and macrostructure and cardiac function which are defined as cardiac remodeling in order to maintain ventricular flow [23]. Initially, the heart has a spheroidal shape that allows the systolic volume to be maintained under a lower contractile force, while reducing the parietal stress in order to better tolerate a pressure overload [24, 25]. This occurs either in both ventricles (globular phenotype) or in one ventricle (elongated phenotype, where the right globular ventricle pushes the interventricular septum and lengthens the left ventricle). In more severe cases, increased sphericity is not enough and muscle hypertrophy develops over time to increase contractility and reduce parietal stress. Thus, cardiomegaly is a characteristic change with 3 different phenotypes

(elongated, globular and hypertrophic) suggesting a progression of severity [25]. Early-onset IUGR is associated with hypertrophic changes while late-onset IUGR causes elongated or globular phenotypes [25]. Cardiac morphometric evaluation such as sphericity index may be more useful in such cases for the evaluation of cardiovascular remodeling compared to functional parameters.

M mode and tissue Doppler show reduced longitudinal myocardial movements [26] that reflect subclinical systolic dysfunction. Diastolic dysfunction occurs in the early stages as increased pulsatility in the venous duct and abnormal E/A ratios [26, 27]. Recent studies show that biomarkers of cardiac dysfunction such as NT-proBNP and those that reflect heart injury such as troponin, have high levels in the umbilical cord blood of girls with IUGR in both early and late onset [28-30]. Echocardiography in newborns with IUGR shows changes similar to intrauterine modifications that include cardiac morphometric changes (dilated left atrium, intraventricular septal hypertrophy), diastolic (increased E/A ratio), and systolic changes (reduced contractility and low cardiac output) [30]. Some studies have reported global longitudinal deformity in the first 5 days of life and also systolic and diastolic heart dysfunction [31, 32].

Cardiovascular changes associated with IUGR persist in childhood, with early and late forms being associated with cardiac remodeling, with globular hearts and reduced longitudinal movements and myocardial relaxation disorders [29]. Children with late onset IUGR show reduced longitudinal movements apparently offset by increased radial function [33]. In severe cases, it is no

longer compensated so it reduces the systolic volume and is accompanied by a compensatory increase in heart rate to keep the arterial pressure within normal limits. Vascular changes include microvascular endothelial dysfunction and increased blood pressure [33]. A recent study shows that cardiac remodeling persists into preadolescence with spherical ventricles and reduced arterial pressure [34]. Another study shows low aortic size in young adults born with severe IUGR [35].

There are limited data on cardiovascular changes in adults. A study of a cohort of 3596 subjects aged 34-49 years showed a reduction in systolic volume but normal sphericity index values and normal diastolic function. Another study showed a slightly increased systolic blood pressure.

Placental phenotype and hypertension

The development of hypertension is determined by the lack of sufficient nutrient intake in the uterine life but also by the surface and the shape of the placenta. A study conducted in Bristol, UK, on 13,971 births, found the relationship between the number of placental lobes on the mother's side and blood pressure in 9-year-olds as a result of these pregnancies [36]. A number of lobes between 4 and 10 is associated with high blood pressure in these children. In terms of gender distribution, in boys, the number of lobes was described as directly proportional to increased systolic and diastolic blood pressure, without an increased pulse pressure. As a consequence, the number of placental lobes becomes an important index in assessing the long-term risk of developing hypertension.

A Swedish study concluded that low birth weight men developed high blood pressure, with a predominance of diastolic hypertension. [37]. In 10-year-olds with low birth weights, an increased blood pressure and pulse at rest were found. These children and their mothers had a lower height than the population group from which they came, associating the genetic component, in addition to the environmental one [38]. Another Danish study reported the negative effect of IUGR and rapid weight gain up to the age of 7, targeting obesity and hypertension [39].

Huxley, through his study, established an inversed proportionality between systolic blood pressure, weight and cranial circumference at birth. In fact, his study proposes accelerated postnatal growth as a factor which promotes adult hypertension [40]. In order to start from the origin of the previous arterial hypertension changes, the intrauterine factors have been intensively researched. Hypoprotein diets have been shown to increase peripheral vascular resistance, with a low ventricular rate, in the absence of cardiac hypertrophy [41]. A nonspecific reduction in maternal nutritional intake was shown to be less unfavorable than specific protein deficiency [42-47]. The maternal protein deficiency associated with Omega 3, unsaturated fatty acids, from conception to week 9 of gestation, was materialized in the increase of blood pressure in experimental studies in rats [48]. Another premise for hypertension is maternal malnutrition in the pre-implantation period, which acts through genetic regulatory mechanisms. The maternal diet must contain a donor of methyl groups for DNA methylation, the way in which the genetic material is formed is imposed from the first days

after fertilization. In this way, the preimplantation period can also be considered as a "critical period" in embryonic development. The ideal conditions are to ensure optimal serum levels of folate and low homocysteine during the period of conception.

Chronic cardiac failure

The relevance of epigenetics in adapting to chronic heart failure (CHF) has been highlighted in adults by the presence of specific prints of DNA changes in heart cells [49, 50]. A recent analysis of DNA methyloma in cardiomyocytes from healthy adults and adults with CHF shows the dominant role of DNA methylation as a reversible and dynamic process in the development of cardiomyocytes [51]. In intrauterine life, a recent study shows that the treatment of laboratory animals with hypoxia causes hypermethylation of DNA, which is associated with the early transition from mononuclear to binucleate cardiomyocytes and an increased risk of ischemic injury [52]. Data on the reduced length of sarcomeres that negatively influence circulatory dynamics have been reported [53]. Other studies have detailed the mechanism of chronic hypoxia that has led to changes in cardiac structure and function by increasing collagen production [54], cardiomyocyte proliferation and apoptosis and postnatal changes in protein isoforms involved in sarcomeric structure (tinin, myosin) [55, 56, 57].

Ischemic heart disease and myocardial infarction

Based on observational studies, it has been hypothesized that newborn males with the lowest birth and at-one-year

weights have the highest chance of dying from ischemic coronary heart disease as adults [58]. Although this link is valid for all newborns, cardiovascular diseases secondary to intrauterine growth restriction occur predominantly in men [59]. In a retrospective study of adult men, the concentric dilatation of the left ventricle was found to be a predictor of coronary heart disease [60].

The renin-angiotensin-aldosterone system (RAAS)

The fetal renin-angiotensin-aldosterone system is activated by IUGR [61]. This dysfunction tends to persist in adults born with IUGR, maintaining the same pattern throughout life. Surprisingly, the predisposition developed in intrauterine life by hypertension seems to have other developing mechanisms than the activation of RAAS [62].

An explanation for the low plasma renin values in girls with IUGR is the nephron deficiency demonstrated in these individuals. The study conducted by Multiple studies concluded that IUGR is associated with a lower number of nephrons, which leads to increased pressure in the glomerular capillaries and secondary to glomerular sclerosis [63,64]. This sclerosis further reduces the number of nephrons and thus forms a vicious circle of self-sustaining hypertension. Studies using fetal ultrasonography as main tool of research, have shown reduced kidney growth between weeks 26-34. The reduced renal dimensions are based on the decrease of the antero-posterior diameter and not on their length [65]. Based on these premises, hypertension would only be an adaptation for maintaining homeostasis [66].

Related to the cardiovascular system, IGF-1 is an important factor in the growth of blood vessels [67] and this may explain the relationship between rapid postnatal weight growth and the development of hypertension in adulthood.

Reduced compliance of the aorta is an important marker of cardiovascular disease [68], being associated with hypertension and also with left ventricular hypertrophy [69,70]. A study performed on a group with a mean age of 50 years, correlated low birth weight with a low compliance of the large arteries accessible to direct examination, respectively at the level of the lower limbs [71]. This vascular deficiency is similarly started and programmed in the intrauterine life, with the formation and distribution of elastin. IUGR associates a reduced amount of elastin in the arteries, which become more rigid, increasing vascular resistance [72-74]. The most important areas in which the effects of this vascular deficit become significant are the descending aorta and the cerebral vascularization [75]. The mechanism responsible for these vascular changes is the centralization of circulation, due to the suboptimal blood supply to the fetus and the adaptation of the cardiovascular system to protect the brain to detriment of other organs and systems [76-78].

Vascular dysfunction

Systemic vascular resistance is a factor that regulates homeostasis and blood pressure and is heavily dependent on the permeability of peripheral blood vessels. Increases in peripheral vascular resistance are correlated with increases in blood pressure. Some studies have reported that restriction of intrauterine growth is

associated with increased vascular resistance. In both, human and laboratory animals, IUGR causes altered blood vessel structure, increased thickness of the intima, [79] and proliferation of smooth muscle cells [80,81].

The vascular response to physiological vasoactive compounds is an important determinant of the regulation of blood pressure and the risk of developing hypertension [82]. In some animal models with IUGR, the unfavorable maternal environment variably affects the response of different vascular beds to physiological vasodilators and vasoconstrictors [83]. Pathologies such as maternal obesity, endothelial nitric oxide synthase deficiency (eNOS) and dexamethasone exposure in animal models have increased the response of adrenergic agents to the mesenteric artery [84-86].

Increased sympathetic activity due to fetal growth restriction, especially in the kidneys, causes desensitization of adrenergic receptors due to increased circulating levels of catecholamines [86]. At the same time, a diet rich in carbohydrates, exposure to dexamethasone and nicotine can cause these desensitizations, which can lead to high blood pressure [87].

Females are protected from this phenomenon unless ovariectomy is performed [88]. Vasodilator substances such as eNOS, prostaglandins and endothelial-dependent hyperpolarization may be mechanisms altered by intrauterine growth restriction and are responsible for reducing the integrity of vascular endothelial function in those with IUGR [89, 90].

The above evidence suggests that there is a correlation between intrauterine growth restriction and the development of

cardiovascular disease (CVD) in adults with a history of IUGR. However, it is difficult to assess the environmental factors that interact with the human body and how this combination of factors determines a predisposition to cardiovascular disease. The hypothesis that genetic and epigenetic factors invariably require another triggering factor for the manifestation of clinical stage of CVD is well accepted in the field of oncology. Therefore, it can be stated that cardiac remodeling present in IUGR, which is a subclinical stage, involves an increased predisposition to cardiovascular damage, but must be associated with other risk factors, is not a sine qua non condition in adult CVD.

Another topic of interest is the existence of "windows of opportunity" which represent moments during intrauterine life when stopping / reducing certain environmental factors can cause the involution of phenomena induced by IUGR [23]. As shown in animal models, changes in metabolism or epigenetic patterns that are caused by prenatal exposure are correctable if taken early. Whether or not there is a "window of opportunity", the evidence suggests that early intervention has strong positive effects on the evolution of these cardiovascular changes.

Observational and in-vivo studies have shown that breastfeeding and the consumption of polyunsaturated fats during childhood have benefits in terms of vascular remodeling in individuals born with IUGR [91]. Similarly, consumption of eicosapentaenoic acid and alpha-linoleic acid has beneficial effects on children and adolescents born with IUGR but has no effect on those with normal birth-weight [92].

The challenge for future studies in this field is to establish ways in which fetal cardiovascular programming can induce adult cardiovascular disease. Although the evidence supports this statement, the identification of specific groups with high risk and finding the mechanisms of action of the environmental factors that promote accelerated progression to CVD in subjects with IUGR could influence the therapeutic attitude in some cases, even the life-quality in adulthood. Given that IUGR affects 5-10% of the total number of pregnancies [93], the possibility of reducing morbidity in some cases would be an important step in the medical field.

3. Conclusions

IUGR has a strong influence on cardiovascular health and the identification of prenatal risk factors can implement preventive strategies that lead to the reduction of morbidity and mortality through this pathogenesis. Whether there are specific subgroups in which differences related to IUGR-induced changes persist or worsen remains a question that requires further study.

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