Early programming of hypertension

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ABSTRACT
Hypertension (HTN) is a modifiable risk factor for cardiovascular disease (CVD) and should be included in the study of developmental origins of health and disease (DOHaD). During intrauterine and perinatal development, different environmental factors have an impact on the early programming of noncommunicable diseases (NCDs). This review provides a summary of the evidence that connects the fetus’ plasticity and adaptive changes to unfavorable environmental factors that alter the adult phenotype in the development of HTN. Such adaptive changes result from epigenetic changes that favor the development of HTN and CVD in adulthood with intergenerational implications. Lastly, we mention preventive strategies to limit or reverse any variable that may alter developmental programming leading to HTN later in life.

Key words: blood pressure, hypertension, fetal programming, DOHaD, epigenetics. https://decs.bvsalud.org/es/

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INTRODUCTION
Hypertension (HTN) is a major modifiable risk factor for the development of cardiovascular disease (CVD) in adults and originates during childhood; its prevalence is estimated at 3.5 - 5% in pediatrics.1-5

Given the large impact of adult CVD in public health, strategies have been proposed to identify risk factors to reduce the population’s morbidity and mortality.3,5

In this regard, the introduction of the concept of developmental origins of health and disease (DOHaD) assigns the alteration of normal development before conception, during intrauterine and perinatal life, and the first years of life a critical role as a triggering factor of noncommunicable diseases (NCDs). Certain environmental factors and an adverse maternal environment during gestation and perinatal life may affect developmental plasticity, during which the fetus adapts to environmental conditions that pose a future risk for HTN and CVD in adulthood, as well as other metabolic, neurodevelopmental, and immune diseases.3,5

The evidence also demonstrated that the effects of programming in the case of parental exposure to environmental challenges may be transmitted from one generation to the next.5

Therefore, it is important to know and detect the effects of adverse environmental conditions on fetal and perinatal development, epigenetic mechanisms, and other adaptive responses that may be key in the early programming of HTN in future life, and assess strategies aimed at reducing the risk.5

ENVIRONMENTAL IMPACT ON THE DEVELOPMENT OF HTN
Recent epidemiological studies have demonstrated that the stages prior to conception and the fetal and perinatal periods may contribute to the development of HTN and other risk factors for CVD in the future (Table 1).3,4,6-10

This hypothesis, initially proposed by Barker, states that a low birth weight (LBW) induced by gestational malnutrition produce certain adaptations in the fetus that predispose or “program” the development of HTN and CVD later in life, a process known as “fetal programming,” which then originated the concept of DOHaD.10,11

LBW, prematurity, and intrauterine growth restriction (IUGR) usually result from developmental plasticity to adverse factors, including...
nutrient deficiency, either due to an inadequate maternal diet—as demonstrated in studies about the offspring of populations that suffered from hunger during gestation—or placental insufficiency.3,4,9,12,13

There is evidence that indicates an association between LBW, prematurity, the effect of a rapid postnatal growth in infants with a LBW (Helsinki cohort and Nord-Trøndelag Study), and changes in body mass index (BMI) during childhood and the risk for HTN later in life.3,4,13-18

Another study agreed that a history of preterm birth was the event most commonly associated with blood pressure (PA) during adulthood. It reported a significant increase of 4.2 mmHg in systolic BP, an increase of 2.6 mmHg in diastolic BP, an increase of 3.1 mmHg in 24-hour ambulatory systolic BP, and a greater risk among women.19

According to the evidence, there are critical periods during fetal development (organogenesis) and the early postnatal period which are considered the most sensitive ones to nutritional deficiency and a risk for future development of HTN.13,20

It is important to note that both LBW and excessive fetal growth (macrosomia) predispose subjects to a higher risk for CVD in adulthood. This is the case of children born to mothers with a high BMI or diabetes. Maternal metabolic status, pre-gestational obesity, and excessive weight gain during pregnancy may be implied in a transgenerational vicious cycle of early programming of BP.21

Cohort studies in humans showed that both gestational HTN and early-onset preeclampsia were associated with the development of HTN in their offspring, especially during the neonatal period, which demonstrates the role of placental insufficiency in the programming of BP.22

In addition, other causes of fetal stress also result in inadequate fetal growth and correlate to

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**Table 1. Adverse environmental factors and developmental origins of health and disease**

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>Type of exposure</th>
<th>Effects in experimental models</th>
<th>Observations in humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preimplantation</td>
<td>Malnutrition or low protein diet</td>
<td>• Blast cells deficiency</td>
<td></td>
</tr>
<tr>
<td>Placental</td>
<td>Placental insufficiency, Multiple pregnancy</td>
<td>• Models of placental insufficiency associated with IUGR</td>
<td>• Placenta size in correlation with birth weight and future cardiovascular conditions in initial Barker’s studies</td>
</tr>
<tr>
<td>Intrauterine</td>
<td>Hormones (folate, glucocorticoids), Methylated compounds</td>
<td>• Impaired glucose tolerance test, diabetes mellitus, reduced β-cell mass, Obesity, impaired nephrogenesis</td>
<td>• Impaired glucose tolerance test, diabetes mellitus, reduced β-cell mass, Obesity, impaired nephrogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Protein-calorie malnutrition, Hyperglycemia, Glucocorticoid excess, Altered renin-angiotensin system, Inflammation, Free fatty acids</td>
<td>• Increased expression of angiotensin II type 1 receptor, Cardiorenal abnormalities, Structural vascular changes, Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Low nephron number, Structural vascular changes, Hypertension</td>
</tr>
<tr>
<td>Perinatal</td>
<td>Malnutrition, Overnutrition, Toxic substances, Hypoxia, Oxidative stress, Metal deficiency</td>
<td>• Epigenetic changes, Future cardiorenal syndrome, Future metabolic syndrome</td>
<td>• Future CVD, Future metabolic syndrome</td>
</tr>
</tbody>
</table>

a higher prevalence of HTN during adolescence and adulthood. As an example, it is worth noting hypoxia; maternal stress (environmental, emotional, and physiological); microbiota changes; early exposure to glucocorticoids; exposure to toxic substances, such as nicotine and tobacco smoke; alcohol use; and maternal sleep deprivation.23-36

Changes in microbiota may affect BP by regulating sensitivity to salt. Early exposure to high glucocorticoid levels alters placental autoregulation of 11β-hydroxysteroid dehydrogenase type 2, which has a lower activity in males, increasing cortisol levels in fetal circulation. Such adaptation may be associated with IUGR, altered nephrogenesis, high BP, changes in fat metabolism, insulin resistance, and variations in the hypothalamic-pituitary-adrenal axis during adolescence and adulthood. Exposure to toxic substances, such as a mother who smokes (nicotine), or tobacco smoke causes vasoconstriction and a reduced placental blood flow, with impaired vascular development and a lower kidney size and increased BP during early childhood. Fetal exposure to alcohol and cocaine may also affect multiple organs and potentially increase the risk for organ dysfunction and disease during adulthood. Sleep restriction during pregnancy may increase the BMI and BP levels of the offspring due to alterations in glucose metabolism, inflammatory pathways, and a predisposition to preterm birth, with more marked effects in female children. In animal models, sleep restriction may increase BP due to changes in kidney development.23-36

ADAPTATIONS IN PROGRAMMING OF HTN

As a result of an interaction between the genome and an unfavorable intrauterine environment, the fetus produces structural and functional responses that, in the short term, become adaptive and promote survival chances; however, in the long term, they may have adverse consequences. Changes in cardiovascular, renal, and autonomic nervous system development have been suggested to be related to BP regulation.5,37

Renal alterations
The renal phenotypes that have been reported in developmental programming of HTN include small kidney size at birth with a reduced nephron number (if the adverse effect occurs during the period of greatest nephrogenic plasticity, before 34 weeks of gestation); alterations in renal function, sodium transport, renin-angiotensin-aldosterone system (RAAS), and sympathetic renal nerves that regulate renal function.5

Maternal factors, such as nutrient restriction that limits nephron endowment couple with age-related nephron loss, have been associated with HTN programming in adulthood.38

Brenner and Chertow suggest that the risk for essential HTN during adulthood increases as a result of an impaired renal development implied in IUGR. This hypothesis is supported by studies in humans that demonstrate that a lower nephron number in subjects with LBW, with a smaller glomerular filtration area, causes compensatory glomerular hyperfiltration and, eventually, glomerular hypertrophy, kidney injury (microalbuminuria, proteinuria), and glomerulosclerosis, and favors the development of HTN.38-41

Other observations suggest a direct relationship between birth weight and nephron number, a reverse association between birth weight and HTN in adulthood, and a reverse association between nephron number and BP, regardless of whether the number of nephrons reduces congenitally or in the postnatal period.40,41

The developmental programming of HTN demonstrated that the glomerular filtration rate reduces after protein-calorie dietary restriction during pregnancy, as well as with the administration of glucocorticoids, alcohol, and maternal diabetes.5

Programmed HTN models showed tubulointerstitial injury and alterations in the pathways that regulate fibrosis, inflammation, oxidative stress, and changes in gene and/or protein expression in sodium, calcium, and water channels that may affect tubular function and sodium homeostasis.5

In experimental animal models, the hypothesis proposed was that the early changes in the kidney cortex microenvironment alter sodium management, resulting in an increased sensitivity to salt. In some preterm or LBW infants, BP values are increased with an excessive sodium intake due to alterations in related regulation mechanisms, either due to a smaller glomerular filtration area associated with a reduction in nephron number or a higher
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sodium tubular reabsorption. There is little information about renal nerves and their potential role in programmed HTN, although sympathetic innervation plays a major role in BP regulation and sodium transport.

Cardiovascular alterations

Cardiovascular structural and functional alterations may significantly contribute to HTN and are present in programmed HTN models.

The cardiac phenotype typically presents a reduced number of cardiomyocytes and/or increased cardiac hypertrophy in the offspring following maternal protein restriction, vitamin D deficiency, and restriction of placental function in experimental models of fetal programming associated with LBW. Cardiac hypertrophy was also observed in male offspring and systolic and diastolic dysfunction in male and female offspring for 3 months in the case of a fat-rich diet during gestation in animals.

Children with a history of fetal stress and LBW showed a more reduced endothelium-dependent vasodilation, regardless of current BMI. These data indicate that children with a LBW develop endothelial dysfunction. Experimental studies support the possibility that fetal stress may affect vasculogenesis and cause endothelial dysfunction and vascular remodeling. Such phenotypic and functional changes in vascular smooth muscle cells arise in response to vasoconstriction and vasodilation mediators secreted by endothelial cells. This process is characterized by changes in vascular structure, such as an alteration in wall thickness and lumen diameter (with a major role played by metalloproteinases) and changes in vascular mechanical properties, which may develop or be precursors of HTN over life.

In the case of IUGR, it was suggested that elastin synthesis is altered during the fetal stage, a period of rapid vascular growth, which may lead to changes in vascular mechanics, reduced arterial elasticity, and development of HTN in the long term.

This hypothesis is supported by the association between LBW and arterial rigidity observed in preterm infants when high pulse wave velocity was measured, a clinical indication of accelerated vascular aging.

Autonomic nervous system alterations

There is strong evidence that the increase in sympathetic nervous system activity contributes to the pathogenesis of essential HTN and that it may originate since the beginning of development through sodium reabsorption in renal tubules. Such sympathetic hyperactivity may be a common underlying mechanism of HTN induced by maternal obesity.

In addition, bidirectional interactions occur between the sympathetic nervous system and the immune system. Particularly, the relationship between T cell adaptive immunity and the enteric nervous system, which increases, through microbiota composition, proinflammatory cytokines and alters intestinal permeability by intervening in the programming of salt-sensitive HTN.

MECHANISMS CONTRIBUTING TO HTN PROGRAMMING

The organ system alterations mentioned above may be associated with varying changes in mediators. The most relevant ones are the RAAS, the epigenetic modulation of certain genes (especially those related to the insulin-like growth factor [IGF]), and reactive oxygen species (ROS).

All RAAS components were affected by developmental programming of HTN in several models, including the administration of glucocorticoids, a diet rich in fat, sodium, sucrose, fructose and low in proteins, which may account for the alterations in renal and vascular function.

The findings common to these models suggest that a maternal diet with protein restriction leads to a perinatal suppression of the intrarenal RAAS and a subsequent impairment of nephrogenesis and reduced nephron number, and predisposes to HTN in adulthood. In addition, differences have been reported between males and females in BP programming during nephrogenesis.

The epigenetic modifications in the beginning of the embryonic stage account for changes in gene expression and regulate their function, but without altering the DNA sequence. Such changes may be transmitted to future generations.

Such epigenetic mechanisms entail DNA methylation (the most studied mechanism in models of developmental programming of HTN), histone modification, control of gene expression by non-coding RNA, and chromatin formation.
Experimental studies in humans and animals suggest that epigenetic changes are one of the mechanisms responsible for fetal programming that may explain both organ system alterations and vascular dysfunction and HTN in the offspring. These epigenetic changes consist in modifications in genes related to the RAAS, angiotensin type 1 receptor, vascular tone, ion channels, epithelial sodium channels, Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter, an increased expression of micro-RNA that regulates the translation of angiotensin-converting enzyme-1, micro-RNA associated with cardiac injury, angiogenesis, and cell changes, modifications in endothelial nitric oxide synthase (eNOS), and HSD11B2 hypermethylation, among others (Table 2).\(^{3,4,68-70}\)

Studies in humans who suffered calorie and nutrient restriction during the intrauterine period showed modifications in IGF gene methylation and in genes involved in cardiovascular function and inflammation.\(^{71,72}\)

It is also worth noting that DNA methylation occurring in cytosine-phosphate-guanine sites is mediated by enzymes that depend on adequate micronutrient levels, such as choline, niacin, folic acid, vitamins B6 and B12, vitamin C, methionine, glutathione, zinc, selenium, and retinoic acid. Such micronutrient deficiency may cause the fetus to suffer lower tissue oxygenation, increased oxidative stress, activation of apoptosis due to mitochondrial dysfunction, and alteration in organ development and may predispose to metabolic syndrome and HTN in adulthood.\(^{31,54,73,74}\)

The paternal environment, in case of calorie restriction before and during puberty, also plays a role in the programming of metabolic and cardiovascular disorders.\(^{75}\)

Another major contribution of molecular biology that should be taken into consideration, and that is related to the fetal origin of NCDs, is telomere shortening. Telomeres are made up of repeated segments of DNA at the end of chromosomes and their main function is to confer structural stability and regulate the life of cell lines. Telomere shortening, in the case of adverse events during the intrauterine period, is associated with the development of chronic, cardiovascular, and metabolic diseases and a shorter life expectancy.\(^{76}\)

In relation to oxidative stress, it has been proposed that it is another of the most plausible mediators between adverse fetal growth and a higher risk for CVD and metabolic disease in adulthood.\(^{77}\)

Excess ROS produced by vascular, immune, and dendritic cells and enzyme systems may account for several organ system alterations, such as endothelial dysfunction with increased vascular tone, which has been demonstrated in animal models subjected to protein restriction during gestation.\(^{8,54,78}\)

The evidence indicates that maternal malnutrition, sodium overload during pregnancy, and placental dysfunction are associated with higher oxidative stress and nitric oxide-ROS imbalance in the fetal kidney, which is capable of programming renal disease and HTN in adulthood.\(^{54,79}\)

<table>
<thead>
<tr>
<th>Table 2. Some factors involved in early programming of HTN(^{4})</th>
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<tr>
<td><strong>Epigenetic regulation</strong></td>
</tr>
<tr>
<td>DNA methylation</td>
</tr>
<tr>
<td>Histone modification</td>
</tr>
<tr>
<td>Non-coding RNA</td>
</tr>
<tr>
<td>Chromatin formation</td>
</tr>
</tbody>
</table>

HTN: hypertension; RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species; Na\(^+\)-K\(^+\)-ATPase: sodium-potassium adenosine triphosphatase; NADPH: nicotinamide adenine dinucleotide phosphate; NKCC2: sodium-potassium-2 chloride cotransporter; Na\(^+\)-Cl\(^-\) cotransporter: sodium-chloride cotransporter.

*The table columns are not related to each other.*
STUDIES OF EXPERIMENTAL MODELS OF PERINATAL PROGRAMMING OF BLOOD PRESSURE

The studies with experimental models of the mechanisms of developmental fetal programming of HTN and CVD in adulthood help to better interpret the results obtained in humans and allow to conduct long term studies. The most representative ones are the model of nutritional restriction during gestation, placental insufficiency, hypoxia, and exposure to glucocorticoids (Table 3). \(^{3,4,6,8,23}\)

These models establish that, among cardiovascular risk factors, HTN is more frequently associated with IUGR due to nutritional imbalances. \(^{3,4}\)

PREVENTIVE MEASURES IN THE POPULATION AT RISK FOR HTN

The current evidence suggests that several mechanisms are involved in the development of HTN programmed by an unfavorable prenatal, perinatal, and postnatal environment. \(^{3-5}\)

Clinical prevention strategies aimed at avoiding the risk for HTN since critical development periods suggest controlling and identifying risk factors. It is important to assess the presence of a history of infection and medication, alcohol, drug or tobacco use and to perform clinical and ultrasound controls. Weight, height, BP, and metabolic status should be recorded and different dietary micronutrient or mineral intake should be monitored. \(^{3,4,6,7,50,80,81}\)

And in the case of infants with a LBW, preterm birth, macrosomia, and a family history of HTN, it is necessary to carry out a clinical follow-up during their childhood and adolescence, with BP and glycemia controls and warranting breastfeeding and complementary feeding, implementing a healthy lifestyle and physical activity to reduce the possibility of developing obesity, metabolic syndrome, diabetes, and HTN. \(^{1,4,6-8,23,50,80,81}\)

CONCLUSION

The accumulation of adverse factors during conception, intrauterine growth and development, and in the first years of life causes epigenetic changes that favor the development of HTN and CVD in adulthood with intergenerational implications. Such adverse factors may be reversed or controlled through a primordial preventive approach and strategies aimed at improving maternal, paternal, and child health, which will allow to reduce the global burden of HTN and CVD later in life. □

REFERENCES

3. Sinha MD. From Pregnancy to Childhood and Adulthood:

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Studied species</th>
<th>Number of nephrons</th>
<th>Glomerular histology</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calorie restriction</td>
<td>Rats, mice, Guinea pigs</td>
<td>Reduced</td>
<td>Glomerular hypertrophy</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Low protein diet</td>
<td>Rats, mice, Guinea pigs, sheep</td>
<td>Reduced but variable</td>
<td>Glomerular hypertrophy</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Diet with multiple deficiencies</td>
<td>Rats</td>
<td>Reduced</td>
<td>Glomerular hypertrophy</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Rats, mice, Guinea pigs, sheep</td>
<td>Reduced or unmodified</td>
<td>Glomerular hypertrophy or segmental glomerulosclerosis</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Mice, rats</td>
<td>Reduced or unmodified</td>
<td>Glomerular hypertrophy</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Partial uterine artery ligation</td>
<td>Rats</td>
<td>Reduced</td>
<td>Glomerular hypertrophy</td>
<td>Normal or high</td>
</tr>
</tbody>
</table>

Table 3. Examples of experimental models of early programming of hypertension}

\(^4\)
39. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive


