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REVIEW

Insights into the Mechanisms of Fetal Growth Restriction-Induced Programming of Hypertension

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Abstract: In recent decades, both clinical and animal studies have shown that fetal growth restriction (FGR), caused by exposure to adverse uterine environments, is a risk factor for hypertension as well as for a variety of adult diseases. This observation has shaped and informed the now widely accepted theory of developmental origins of health and disease (DOHaD). There is a plethora of evidence supporting the association of FGR with increased risk of adult hypertension; however, the underlying mechanisms responsible for this correlation remain unclear. This review aims to explain the current advances in the field of fetal programming of hypertension and a brief narration of the underlying mechanisms that may link FGR to increased risk of adult hypertension. We explain the theory of DOHaD and then provide evidence from both clinical and basic science research which support the theory of fetal programming of adult hypertension. In addition, we have explored the underlying mechanisms that may link FGR to an increased risk of adult hypertension. These mechanisms include epigenetic changes, metabolic disorders, vascular dysfunction, neurohormonal impairment, and alterations in renal physiology and function. We further describe sex differences seen in the developmental origins of hypertension and provide insights into the opportunities and challenges present in this field.

Keywords: hypertension, FGR, placental insufficiency, LBW

Introduction: The Concept of Fetal Programming of Adult Disease

Recently, the theory of the developmental origins of health and disease (DOHaD), formerly known as the theory of fetal programming of adult disease, has gained traction as an important subject in both clinical and basic science medical research.[1–5] Research suggests that pre- or postnatal exposure to developmental insults, such as nutrient insufficiency, and environmental exposures may result in temporary or permanent changes in fetal or neonate anatomy, epigenetics, metabolism, and physiology of the fetus or neonate and subsequent early onset of chronic diseases in life.[1,3,6,7] David Barker et al were among the first groups to propose this idea with convincing epidemiological evidence linking low birth weight (LBW) to increased risk of morbidity and mortality from coronary heart disease as well as the development of insulin resistance and type II diabetes.[8,9] Since publication of these landmark studies, several clinical and animal studies supported this idea,[4,5,10,11] giving rise to the field of DOHaD.

LBW is defined as an absolute birth weight of less than 2500 grams, and this condition is a clinical surrogate of a variety of distinct pregnancy-related

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complications, including fetal growth restriction (FGR), prematurity, and small for gestational age (SGA).[12,13] Although LBW is closely associated with a high incidence of infant morbidity and mortality, the public health significance of this condition has risen in recent decades when it was discovered that poor adult health may be linked to compromised fetal growth.[8,9,14] In most cases, LBW is a sign of poor fetal milieu during pregnancy and can be caused by multiple factors such as maternal and fetal genetics, presence of adverse environmental exposures, and placental insufficiency.[12,14] Fetal growth restriction (FGR) is considered as a main cause of LBW. FGR results from insufficient uterine- placental perfusion, which leads to poor nutrient and oxygen supply to the fetus and consequently has detrimental outcomes on fetal growth and development and the diagnosis is based on the change in growth over time.[15] In contrast, some babies experiencing prematurity, defined as birth before gestational week 37, have LBW and show signs of FGR.[16] Note that not all premature babies are born with LBW. The recent statistic of the birth data in US for year 2019 reported 311,245 (8.31%) babies born with LBW but the number of premature babies is even higher as 382,061 (10.23%) babies born preterm.[17] Furthermore, sometimes LBW babies are SGA. A child is regarded as SGA when their abdominal circumference or weight at birth is below the 10th percentile or two standard deviations of the average abdominal circumference or weight for that specific gestational age, race, and gender.[18] Thus, infants in the category of SGA may or may not have growth restrictions.

Placental insufficiency is used to describe deficits in placental supply of oxygen and nutrients to the fetus, which becomes pathogenic by slowing fetal growth.[19,20] FGR is mainly caused by placental insufficiency, elicited by a variety of factors including failure of uterine and placental spiral arteries to remodel, gestational hypertension, and maternal malnutrition.[12,21–23] Suboptimal fetal nutrient supply and hypoxia may initiate preferential redistribution of blood to vital organs that are important for short-term survival such as the brain, myocardium and adrenal glands.[12,13] However, organs that are important for the long-term survival such as the kidneys and liver may be deprived of sufficient blood supply and nourishment leading to compromised growth and subsequent organ dysfunction in adult life.[24]

Since FGR is now considered a risk factor for adult hypertension,[25–27] we aim to give a synopsis of the current knowledge in the field of fetal programming of hypertension, with special attention to evidence from clinical and animal research. We further suggest possible underlying mechanisms, reasons for observed sex differences in this phenomenon, and conclude by discussing the challenges and opportunities available in this dynamic field.

Fetal Programming of Hypertension: Evidence from Clinical and Preclinical Studies

Genetics and lifestyle have been recognized as factors that promote hypertension development. However, several clinical studies now suggest that a suboptimal fetal environment can also initiate the progression of impaired blood pressure (BP) regulation.[3,14,28,29] David Barker et al laid the foundation of the theory of fetal origins of health and diseases.[9] In a cohort study of 22,846 adult men from the US, Curhan et al[30] found that LBW was associated with increased incidence of hypertension whereas high birth weight was linked to increased incidence of diabetes mellitus. In contrast, both LBW and high birth weight increased systolic and diastolic BP in a study carried out on children and young adolescents in China.[31] Several other studies support that LBW is directly associated with increased incidence of hypertension.[26,28,32,33] Although children who suffered growth restriction may experience hypertension,[27,34] the strength of association between LBW and essential hypertension becomes more pronounced in advanced age groups.[35] These observations suggest that secondary insults accumulate with age and may shape and exacerbate hypertension in adult populations that experience fetal growth restriction. In a population-based cohort study on young Swedish men, both severity of birth weight restriction and the extent of prematurity increased the rise in BP. This underscores how the degree of FGR may be influential on increasing the risk of hypertension in adulthood.[36] Human epidemiological research provides clear evidence that, to some extent, our fetal environment may determine the risk of developing hypertension in adult life.

Animal studies have advanced the field of fetal origins of health and diseases because they mitigate some of the confounding variable effects that influence the development of adult human diseases, such as genetic factors and postnatal environmental exposures.[37] Many animal models of FGR have been developed including by various intervention to the pregnant dams such as the use of surgical

methods to reduce blood flow to the placenta,[19,38] immunological intervention,[39] maternal protein restriction,[40,41] and exposure to environmental agents such as drugs.[42] Few genetically modified animal models in pregnant mouse and rat are also reported to develop spontaneous preeclampsia phenotype and produce FGR offspring.[43,44] Although the causes of FGR may differ from one animal model to another, most investigations suggest that regardless of cause, suboptimal fetal environments are closely associated with adult risk for hypertension.[11,40,42,45]

Potential Mechanisms Involved in Fetal Programming of Hypertension

Epigenetics as a Driver of Fetal Programming of Hypertension

Dynamic and inheritable modifications that change chromosome structure, but not gene sequence, are defined as epigenetics changes. These modifications regulate lineage-specific gene expression in several cellular processes including the pathogenesis of diseases and are a reflection of the interplay between DNA and environmental factors.[25,46] Gene expression is partly dependent on the accessibility of genomic regions like promoters, enhancers, and silencers. These regions are essential for binding transcriptional factors such as activator and repressor proteins to DNA when they regulate gene transcription.[47] Histone acetylation and methylation govern the accessibility of these genomic loci. In general, histone acetylation at lysine residues is associated with activation of gene expression while methylation may be associated with either transcriptional repression or activation, depending on gene specificity. Additional epigenetic modifications of histone proteins include sumoylation, ubiquitination, and phosphorylation. Methylation of DNA at specific cytosine regions of the promoter called CpG islands, is another form of epigenetic modification that regulates gene expression. Normally, promoter methylation is associated with transcriptional repression.[48–50] Gene expression can also be regulated by non-coding RNAs; these small molecule expression profiles may correlate with the upregulation or suppression of specific genes. It should be noted that not all gene regulation mediated by non-coding RNAs fall under epigenetics. Epigenetic traits must be inheritable,[51] which can be through mitosis and often encompasses the effects of maternal factors and early life experiences on long-term health. Epigenetic effects inherited through germline cells often manifest as paternal and transgenerational inheritance.[52] Epigenetics regulate various cellular and physiological functions including embryonic development, genome imprinting during blastocyte maturation, and compensation of gene dosage during X-inactivation.[46]

In addition to altering the development of key organs that regulate BP homeostasis, poor fetal environment has been shown to induce epigenetic changes which might influence predisposition to adult hypertension and the transmission of this phenotype to subsequent generations.[7,25,53] Inhibition of DNA methyltransferase (DNMTs) with 5aza2DC and antagonism of histone deacetylase (HDAC) with valproic acid during the fetal life of rats exposed to dexamethasone, inhibited the elevation of BP normally seen in adult rats exposed to glucocorticoids in utero.[54] In addition, epinephrine and phenylethanolamine N-methyltransferase enzyme expression were reduced in these adult IUGR rats, implicating the involvement of DNMTs and HDAC in the epigenetic programming of hypertension in FGR. Cortisol is a glucocorticoid implicated in stress response and regulation of vascular tone. The enzyme 11-HSD2 converts cortisol to its inactive form, cortisone, and its reduction is associated with increased vascular tone via amplified pressor response of angiotensin and catecholamines.[55] FGR has been shown to reduce 11-HSD2 protein and increase methylation of the gene that codes for this enzyme, which results in transcriptional repression,[56,57] thus providing further evidence of epigenetic involvement in fetal programming of hypertension.

Maternal calorie restriction in rats has resulted in pulmonary hypertension in offspring characterized by aberrant proliferation, migration, and angiogenesis in the pulmonary vascular endothelial cells (PVEC). PVEC derived endothelin 1 is thought to play a role in driving endothelial dysfunction in these animals. Epigenetic analysis of sperm and PVEC samples from first-generation IUGR animals revealed that there was reduced DNA methylation and enhanced trimethylation of lysine 4 of the histone 3 protein within the first intron of the endothelin 1 (ET1) gene. In addition, PVEC samples derived from second-generation IUGR animals continued to have significant demethylation of ET1 first intron. These observations indicate a transgenerational inheritance of endothelial dysfunction through epigenetics.[25]

Both maternal malnutrition and dexamethasone exposure have been shown to increase Angiotensin Receptor Type 1a (AGTR1a) expression in the hypothalamic paraventricular

nucleus, reduce DNA methyltransferase 3 (DNMT3) expression and its binding to the AGTR1a gene as well as increase DNA demethylation in that gene.[58] These epigenetic modifications may be associated with the increased salt sensitive hypertensive phenotype seen in adult FGR animals. Others have demonstrated that non-coding RNAs are another epigenetic mechanism involved in hypertension pathogenicity;[59] however, more research is needed to determine the extent that this type of epigenetic regulation is implicated in fetal programming of hypertension. Finally, it is paramount to note that while numerous studies have found an association between FGR/SGA/LBW and epigenetic modifications, there are few studies that have definitely linked epigenetic modifications to a phenotype, suggesting that this area requires further introspection.

Role of FGR Induced Vascular Dysfunction in Fetal Programming of Hypertension

Systemic vascular resistance is one factor that regulates BP homeostasis and is largely dependent on the patency of peripheral blood vessels. Increases in peripheral vascular resistance correlates with elevation of BP.[1] Several studies have reported that FGR is associated with increased vascular resistance in humans.[60–62] In both human and animal models, FGR has been shown to alter normal physical structure of blood vessels including increasing the intima media thickness[63,64] and smooth muscle cell number, reducing arterial elasticity and endothelial cell volume[65–69] as well as increasing collagen deposition.[70] The collective evidence suggests that vascular remodeling is one mechanism whereby FGR may program adult hypertension.

Angiogenesis defects are commonly seen in FGR and may also contribute to adult hypertension. Rat and sheep models of FGR demonstrate reduced micro vessel numbers in a variety of vascular beds.[71–73] In addition, during perinatal development angiogenic capacity is reduced in FGR due to deregulated expression of vascular growth and proliferation factors such as vascular endothelial growth factor (VEGF),[1,74] placental growth factor and insulin growth factor.[75–77]

Vascular response to physiological vasoactive compounds is an important determinant of BP regulation and subsequent risk of hypertension.[78] In some FGR animal models, suboptimal fetal environments have been shown to variably affect the response of different vascular beds to physiological vasodilator and vasoconstrictor agents.[1] Various in utero insults, such as maternal obesity,[79] endothelial nitric oxide synthase (eNOS) deficiency,[80] dexamethasone exposure[81] in mice, and maternal cocaine exposure[82] in rats have been shown to increase the response of mesenteric arteries to adrenergic agonists. However, some studies did not demonstrate this response,[83,84] suggesting that the effect of FGR on these arteries might be dependent on the type and timing of developmental insult. Increased sympathetic activity subsequent to FGR, particularly to the kidney, sometimes results in adrenergic receptor desensitization due to high circulating levels of catecholamines.[1] Angiotensin is an important target in hypertension treatment. Several developmental insults, such as reduced uterine perfusion,[85] maternal high sucrose diet,[86] fetal dexamethasone,[87] and nicotine exposure[88,89] alter this pathway in the vasculature (depending on the vascular bed). This leads to an elevated pressor response which may cause BP elevation. FGR has also altered endothelin resulting in an increased angiotensin pressor response.[25] Other vasoconstrictor mechanisms shown to be altered and potentiated by FGR include thromboxane[90] and serotonin signaling.[91] In addition, increases in myogenic tone in FGR animals has been reported.[92,93]

Defective endothelial function can be a precursor to development of hypertension.[94] FGR models of maternal nutrient restriction and high fat diet display signs of endothelial dysfunction by reduced vasodilator effects of acetylcholine in the mesenteric arteries and other vascular beds.[83,95] Females are normally protected from this phenomenon unless ovariectomized.[96] Vasodilatory pathways, such as eNOS, prostaglandin,[97] and endothelial dependent hyperpolarization[98] may be mechanisms altered by FGR and responsible for reducing the integrity of vascular endothelial function in FGR offspring.

Contribution of FGR Induced Neuroendocrine Impairment in Fetal Programming of Hypertension

Both the nervous and endocrine systems are important regulators of BP and any functional imbalance in these two systems can result in elevated BP.[99] Abundant evidence suggests that several neuroendocrine pathways are altered in FGR and may explain why disturbances in fetal life are closely associated with adult hypertension.[3,61,100–102]

Several endocrine pathways are altered in FGR. Endogenous or exogenous maternal exposure to

glucocorticoids may result in FGR, hyperactivation, and permanent alteration of the hypothalamic pituitary adrenal (HPA) axis and deregulation of BP homeostasis in offspring.[59,102] Since the HPA axis is heavily involved in regulating the stress system, alterations of this pathway in FGR may lead to hypertension through stress associated mechanisms and alteration of brain mineralocorticoid and glucocorticoid receptors.[102] In rats, maternal exposure to glucocorticoids increased the expression level of PNMT, an enzyme responsible for synthesis of epinephrine. Elevated epinephrine levels can increase sympathetic nervous activity resulting in hypertension.[103] Leptin signaling is another hormonal pathway altered by FGR[6,104–106] and impairment of this pathway may lead to a hyperphagic phenotype that becomes obese and consequently hypertensive. Alternatively, disruption in leptin signaling can lead to hypertension through sympathetic nervous activation and catecholamine secretion.[105,107] Both maternal nutrient restriction and placental insufficiency can suppress the renin angiotensin system (RAS), with kidney expression of angiotensin receptor 1 (Ang R1) and circulating angiotensin II (Ang II) reduced at birth.[108–110] The RAS is important in regulating nephrogenesis and kidney development. FGR rodents often have inappropriately activated Ang II-Ang R1 signaling when they become hypertensive in adulthood.[29,109] In addition, angiotensin (Ang)-(1-7), the pathway that opposes the Ang II-Ang RI signaling, was downregulated in adult glucocorticoid exposed sheep.[111,112] Collectively, these results suggest that the RAS system might be implicated in altering kidney structural development and physiology during fetal life and might result in hypertension in adult life. Testosterone is another hormone that is implicated in programming fetal origins of hypertension. Gonadectomy improved BP homeostasis in FGR but not in control rats in a study by Ojeda et al,[113] illustrating the importance of testosterone in the developmental origins of hypertension in these animals. FGR altered the energy homeostasis hormones, insulin and visfatin[104,105], which has the potential to indirectly contribute to the hypertensive phenotype through metabolic dysfunction.

FGR is often associated with sympathetic nervous system activation, presenting a potential mechanism leading to hypertension.[3,114] Bilateral denervation of renal nerves protects against the hypertensive phenotype in adult male rats exposed to placental insufficiency.[115] However, some investigations failed to show the association of FGR with increased sympathetic nervous activity,[116,117] implying that the role of sympathetic activity in the etiology of developmentally programmed hypertension might be dependent on sex, animal model, and type and timing of the developmental insult.

Impairment of Renal Anatomy and Physiology as Etiology of Fetal Programming of Hypertension

The renal system is essential in regulating BP and alterations in its physiology often results in secondary forms of hypertension. Renal artery perfusion pressure directly controls extracellular volume and sodium excretion in a process called natriuresis; dictating the activation of several vasoactive systems including the renin angiotensin aldosterone system (RAAS), which is central in regulating BP.[118] In addition, maladaptive changes in renal sodium and chloride handling have been associated with hypertensive conditions. One body of evidence suggests that renal nephron number and glomerular filtration rate are negatively associated with the risk of hypertension.[119,120] Furthermore, hypertension is often characterized with increased sympathetic activity to the glomerular afferent artery.[121,122] Ultimately, this data shows the importance of the kidney in maintaining BP homeostasis under normal and hypertensive pathophysiological conditions.

Alterations in kidney anatomy and physiology have been identified in IUGR and present potential links between FGR and risk for hypertension. Maternal protein restriction, hypoxia, placental insufficiency, and glucocorticoid exposure decrease nephron endowment and impair kidney anatomy in rodent offspring.[123–126] In humans, deficiencies in maternal folate, vitamin A, and total energy has been associated with kidney function impairment indicated by elevated proteinuria, reduced GFR, and abnormal creatine clearance in F1 offspring.[127] Crump et al showed that the risk of kidney disease was higher in preterm FGR individuals as young age as 9 years old.[128] Other studies have also observed alterations in kidney function and structure in human FGR individuals,[129,130] indicating that kidney development is very sensitive to developmental insults during fetal growth. Reduced nephron number may lead to hyperfiltration in the available glomerular nephrons. This may cause increased glomerular intracapillary pressure and hypertrophy which leads to diminished kidney function and subsequent hypertension.[131] Alterations in kidney physiology was also shown in animals exposed to FGR, particularly in RAAS system

suppression at birth and inappropriate activation in adult life.[108,109] Furthermore, offspring of protein deprived dams show increased expression of the following sodium transport proteins before development of hypertension: the renal thick ascending limb Na^+-K^+-$2Cl^-$ cotransporter, Na^+CL^- transporter[132] and both the α and β subunits of the apical Na^+-K^+ ATPase transporter.[23] However, the basal sodium excretory function in these animals was normal suggesting that renal sodium handling in these offspring might be compromised even before the progression to hypertension. Other studies have demonstrated that increased renal sympathetic activity might be responsible for the hypertensive phenotype seen in adult FGR animals since renal denervation reduces BP in FGR but not control animals.[115,133,134] Overall, these observations indicate that developmental insults on the kidney during fetal growth may have profound effects on the development of hypertension in adult life.

FGR Induced Obesity as Risk for Hypertension

FGR individuals are more likely to experience adult metabolic syndrome than normal birth weight individuals.[135] Metabolic Syndrome (Met S) is a group of conditions of metabolic origin which occur together and increase a patient's risk of developing cardiovascular disease. The components of Met S include but are not limited to insulin resistance, hypertension, central obesity, hyperglycemia, and dyslipidemia.[136] Increased risk of developing Met S in FGR individuals may be due to the "catch up growth" phenomenon often observed after FGR, which is characterized by childhood compensatory accelerated growth rate.[137] Rodent model investigations have shown that FGR programs a hyperphagic phenotype in infancy by increasing the expression of orexigenic pathways and suppressing anorexigenic brain signaling. This hyperphagic phenotype is thought to cause post-natal catch-up growth (PNCG) and exacerbate development of the metabolic syndrome later in life.[6,138]

Insulin and leptin are the two principal hormones regulating energy homeostasis; evidence indicates that FGR individuals tend to experience greater insulin and leptin resistance than their normal birth weight counterparts.[135,139–141] Children and young adult FGR individuals demonstrated decreased response to insulin.[142,143] Furthermore, FGR rodents demonstrated signs of insulin and leptin resistance, impaired glucose tolerance, and reduced food expenditure in early life.[101,144] Leptin resistance may also contribute to obesity and hypertension by affecting renal sympathetic flow and endothelial dysfunction as well as by altering the renin-angiotensin-aldosterone system (RAAS).[145–147] Although FGR newborns exhibit relatively decreased serum leptin due to lower adipose tissue, high leptin concentrations are observed in FGR individuals during catch up growth.[140,141] Adult rodent FGR models exhibit increased serum leptin and indicate resistance.[6] Thus, the dysfunction of this metabolic pathway may partly explain why adult FGR individuals often develop obesity and hypertension.

Sex Differences in Fetal Programming of Hypertension

In general, the prevalence of hypertension is higher in males than females,[148–150] suggesting sex differences in the development and progression of hypertension. Likewise, fetal programming of hypertension is associated with sex differences. Both male and female FGR offspring exhibit hypertension before puberty; however, females become normotensive during adolescence when estrogen production peaks,[113,151–155] whereas their male counterparts remain hypertensive. Ovariectomy significantly elevated BP in FGR but not in control rats, whereas estrogen administration returned BP to normal range in FGR animals.[151] These results indicate that sex hormones produced by ovaries, particularly estrogen, protect FGR rats from fetal programmed hypertension.

In males, castration protects FGR offspring from elevation of BP, whereas exogenous administration of testosterone rejuvenates the hypertensive phenotype.[113,156] In addition, testosterone has been shown to promote a hypertensive phenotype; animal studies have shown that its dosage is proportional to BP increases in animals.[157,158] Sex hormones also influence the RAAS. Testosterone seems to promote RAAS activation since BP of male FGR rat offspring respond greater to angiotensin II administration than male control offspring.[159]

Conclusion

Although our current knowledge of the mechanisms responsible for fetal origins of hypertension is still limited, a significant body of evidence from both human and animal models suggests that suboptimal fetal environments are associated with adult development of hypertension (Figure 1). More research is required to establish the causal relationship between FGR and adult hypertension. Currently, we

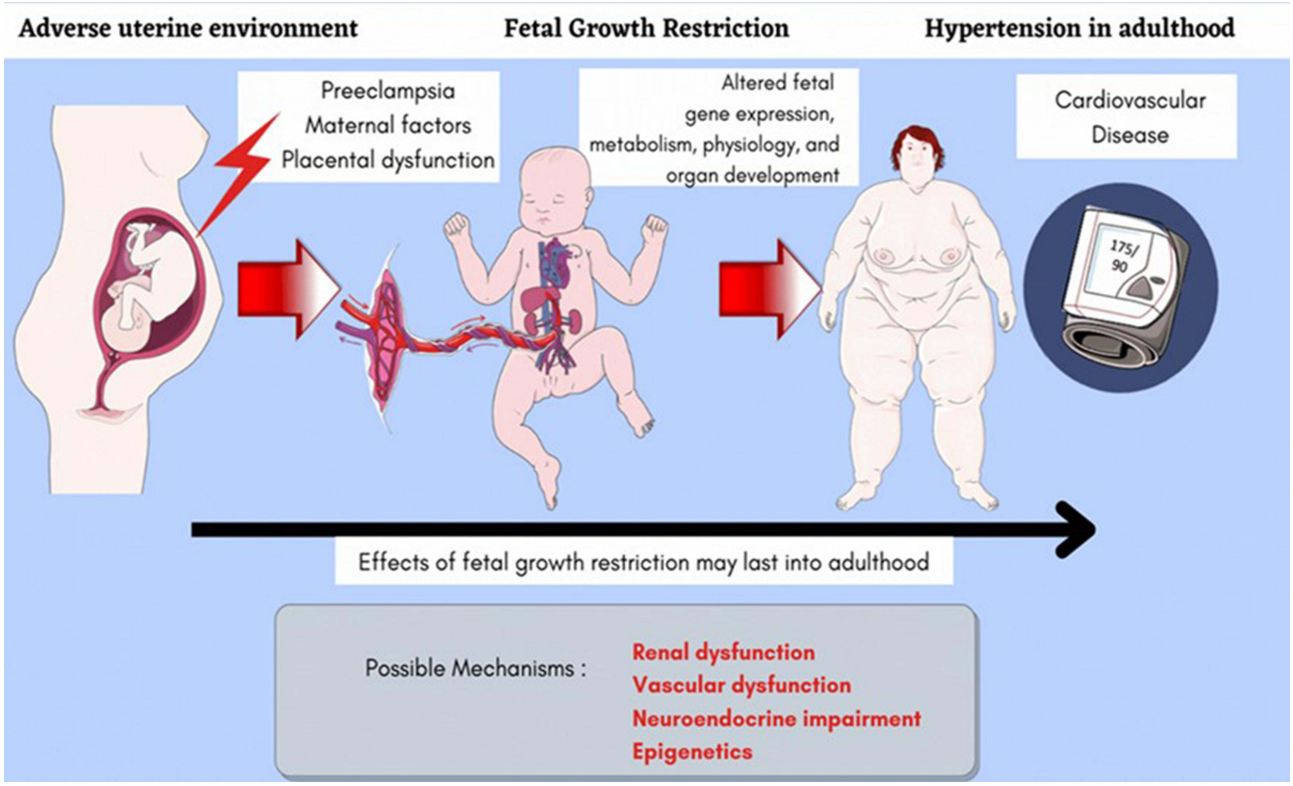

Figure 1 Mechanisms of fetal programming of hypertension, smart.servier.com.[160]

understand that FGR results in alterations in the development, anatomy, and function of several systems essential to maintaining normal physiological regulation of BP. These include the vascular, renal, neural, and endocrine systems. In addition, while huge advances in understanding fetal programming of hypertension have been made in recent decades, the therapeutic relevance of the biological pathways altered by FGR remains to be evaluated in human populations. Much research is needed if FGR pathway alterations (such as endothelin, leptin, angiotensin, and eNOS signaling pathways) can be utilized to develop drugs or prophylactic agents against hypertension in the FGR population. Lastly, more research is required to understand the time course of developmental origins of hypertension in both animals and humans. Identifying the developmental periods in which the majority of adverse adaptations occur to fetal development will allow researchers to develop time-informed interventions that may reverse or prevent these adaptations and improve the long-term health of FGR individuals.

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Disclosure

The authors report no conflicts of interest in this work.

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