

Foetal programming in the pathogenesis of arterial hypertension

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Abstract

Pathogenesis of arterial hypertension is complex and in spite of the decades of studies is not yet entirely understood. In recent years, attention has been paid to the phenomenon of foetal programming and its relationship to arterial hypertension in adult life. It has been shown that low birth weight predisposes to the development of arterial hypertension. The relationship between the number of nephrons and blood pressure and the risk of hypertension also has been found. Blood pressure and the number of nephrons depend on both genetic and environmental factors affecting pregnant females. The aim of this review is to summarize the current knowledge concerning the role of foetal programming in the pathogenesis of arterial hypertension in adults.

key words: arterial hypertension; foetal programming; foetal development

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Introduction

Pathogenesis of arterial hypertension is complex and in spite of the decades of studies is not yet entirely understood. All potential risk factors contributing to the pathogenesis of arterial hypertension can be divided into three groups: genetic factors (e.g. monogenic forms of hypertension), congenital factors (e.g. low birth weight) and acquired factors (e.g. renal artery stenosis). According to the Barker's hypothesis (i.e. foetal programming hypothesis), harmful factors such as limited intake of nutrients, placenta dysfunction, hyperglycaemia and cigarette smoking during pregnancy result in occurrence of chronic diseases such as arterial hypertension, ischaemic heart disease, chronic kidney disease and metabolic syndrome in adult life [1, 2]. The aim of this review is to summarize the current knowledge concerning the role of

foetal programming in the pathogenesis of arterial hypertension in adults.

Low birth weight

A low birth weight according to the WHO definition is the weight of live-born infants lower than 2,500 g or below the 10th percentile for the gestational age (small for gestational age — SGA). A meta-analysis of 20 clinical trials showed 21% higher risk of arterial hypertension in adult life in subjects with low birth weight compared with those with normal birth weight [3]. Subjects with a birth weight lower than 2,500 g are characterized by 2.6 mm Hg higher systolic blood pressure [3].

Kidney development, nephron number and blood pressure

Intrauterine growth retardation affects the kidney development. There is a lot of evidence that kidney plays a crucial role in pathogenesis of arterial hypertension. Rettig *et al.* in experimental study trans-

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planted a kidney from a spontaneously hypertensive rats (SHR) to rats with normal blood pressure. After the transplantation normotensive rats (WKR) developed hypertension [4]. In another experimental study, transplantation of the kidney from normotensive donor rats lead to decrease in blood pressure in recipient rat with hypertension [5]. In humans, in the 4.5-year follow-up of 6 patients with chronic kidney disease due to hypertension, after kidney transplantation it was observed not only normalization of blood pressure, but also partial regression of the hypertensive organ complications [6].

A number of both experimental and clinical studies suggest the relationship between low nephron number and arterial hypertension. In humans there is high variability of the number of nephrons between individuals. Puelles *et al.* in the study of 800 autopsies found that the number of glomeruli in human kidney varies between 210,000 and 2,700,000 [7]. Keller *et al.* in autopsy study compared the number of glomeruli in patients with essential hypertension and those without hypertension [8]. They found that the number of glomeruli per kidney was significantly lower in hypertensive patients than in normotensive subjects (890,869 *vs* 1,666,805). This observation was confirmed in other study [9]. In humans nephrogenesis is finished in 34 weeks of gestational age and there is no further nephron number increase to the end of life [10]. Therefore, the number of nephrons is determined in the foetal period. Glomerular adaptation to the increased size of the body during growth in humans is through glomeruli hypertrophy, only.

Factors affecting the nephron number

Manalich *et al.* performed an autopsy study in newborns. They showed that the number of glomeruli significantly depends on the birth weight [11]. Interestingly, Hughson *et al.* in another autopsy study have shown that 1-kg increase in the birth weight results in an increase in the number of glomeruli by over 250,000 [12]. Studies on white newborns identified some polymorphic variants of the human tyrosine kinase receptor gene (RET) associated with a reduction by 10–23% of newborn kidney volume [13]. It has been shown that kidney size correlates positively with the number of glomeruli per kidney [14, 15]. In Swiss Kidney Project on Genes in Hypertension (SKIPOGH) observational study involving 793 subjects from 205 families it has been shown that the length of the kidney depends on genetic factors in 50% [16]. Therefore it can be assumed that

nephron number depends on environmental factors in the remaining 50%.

Environmental factors

Different environmental factors may influence nephrogenesis and may affect the foetus' number of nephrons and blood pressure in adult life (Fig. 1). First of all it concerns the amount of protein intake during pregnancy. It was shown that the offspring of mothers who had experienced a limited amount of protein intake during pregnancy were characterized by a lower number of nephrons and higher mean arterial blood pressure [17, 18]. In various studies, both experimental and clinical, it has been estimated that the reduction of the number of functioning nephron due to reduced protein intake ranged from 11% to 30% [19]. In experimental studies on rats, Burdge *et al.* demonstrated that the protein intake restriction during pregnancy reduced DNA methylation of PPAR alpha gene in the offspring [20]. In addition, such a maternal diet reduced the expression of AT₁ and AT₂ receptors in the offspring [21]. Another factor contributing to the decrease of the nephrons number in offspring is a vitamin A deficiency during pregnancy [22]. In humans it was shown that there was reduction of the kidney volume in the offspring of mothers who had decreased plasma concentration of vitamin A during pregnancy [23]. Results of experimental studies suggest the negative effects of iron and zinc deficiencies in mothers on the number of nephrons in offspring [24–27]. The number of foetal nephrons is also affected by the

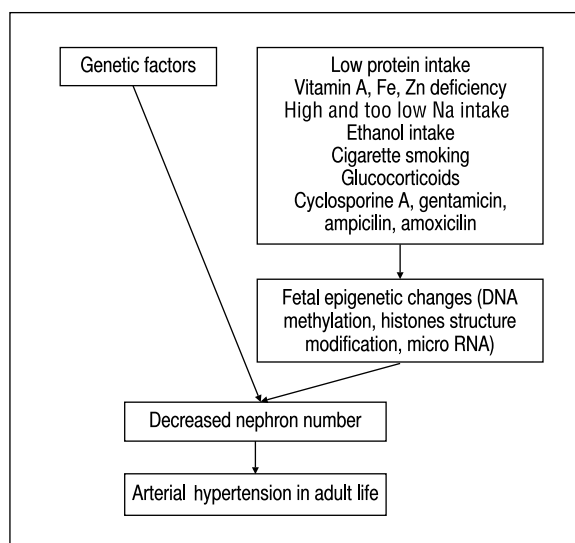


Figure 1. Pathomechanism of foetal programming in the pathogenesis of arterial hypertension

sodium intake during pregnancy. This relationship is however complex [28]. Both too high and too low sodium intake lead to the nephrons number reduction in offspring. High sodium diet reduced the renin-angiotensin system activity. Intact foetal kidney RAA activity is necessary for the proper kidney growth. On the other hand, too low sodium intake decreases the blood flow through the placenta. Both of these mechanisms seems to affect adversely the number of nephrons in the kidneys of the foetus. It has been shown in the experimental studies that the consumption of ethanol during pregnancy reduces the number of nephrons in the foetus and results in blood pressure increase during adult life [29, 30]. Also cigarette smoking adversely affects the development of foetal kidneys by reducing the number of podocytes, as shown by experimental study in rats [31]. In observational studies in humans systolic blood pressure was increased in those whose mothers smoked cigarettes during pregnancy [32]. Other studies have confirmed an increase of blood pressure both in childhood and in adult life in the offspring of mothers who smoke during pregnancy [33, 34]. In children of mothers smoking during pregnancy, a reduction of renal volume in ultrasound examination was also observed [35].

Drugs affecting foetal kidney development

The number of nephrons in the foetus is also affected by several drugs used by pregnant female.

In many experimental and clinical studies the negative effects of glucocorticoids on number of nephrons in the foetus and blood pressure in offspring have been shown [36–39].

Doyle *et al.* in a cohort study of 210 14-year-old children compared individuals exposed to antenatal corticosteroids with those who did not have such an exposition. Children exposed to corticosteroids during foetal period had higher systolic and diastolic blood pressure [37]. There is expression of 11 β -hydroxysteroid dehydrogenase type 2 in placenta during pregnancy, which protects the foetus against an excessive amount of both endogenous (e.g. severe stress in the mother) or exogenous glucocorticoids [40]. In experimental studies on pregnant rats carbenoxolone, an 11 β HSD2 inhibitor, was administered. This resulted in blood pressure increase in the offspring [41]. It was also shown that protein restriction in the diet reduced 11 β -HSD2 activity [42]. Therefore malnutrition during pregnancy may result in the more intensive exposure of foetus on glucocorticoids.

Another drug influencing the development of the kidney in the foetus is calcineurin inhibitor, cyclosporine A. Experimental study in rats has shown that administration of cyclosporine A during pregnancy reduces the number of glomeruli, increases glomeruli volume and increases blood pressure in the offspring [43]. Also, administration of amoxicillin and ampicillin during pregnancy in rats contributed to the deterioration of kidney development in its fetuses [44]. Moreover Gilbert *et al.* in studies on guinea pigs have shown the negative effect of gentamycin exposition during pregnancy on foetal kidney development [45]. The clinical relevance of these observations needs, however, further studies.

Mechanism of prenatal programming

It is known that the mechanisms involved in foetal programming are epigenetic. Epigenetic changes involve modification of gene expression without changing the genetic material. They consist of modifying the DNA structure or function by DNA methylation, histones modification and micro RNA.

The most important of epigenetic changes are DNA methylation. Methylation modifies genes' structure by attaching a methyl group to cytosine. These may change the gene expression. In the past few years, some studies have shown a relationship between exposure to nutrients during pregnancy and the change of foetus DNA methylation [46]. Hogg *et al.* observed increase in DNA methylation in placentas of pregnant women with hypertension compared with women with normal blood pressure [47]. There are some studies that have shown that factors that increase DNA methylation causes the development of cardiovascular disease, including hypertension [48]. Experimental studies on rats have shown that increased folic acid intake during pregnancy enhanced methylation in glucocorticosteroid receptor gene and results in an increase in blood pressure in susceptible offspring [49]. The mentioned above 11 β -HSD2 enzyme activation is regulated by histone methylation of its gene [50]. In experimental studies on mice it has been shown that the methylation of lysine residue 79 at histone H3 reduces 11 β -HSD2 gene expression [51]. An abnormal increase of methylation of 11 β -HSD2 promotor seems to lead to hypertension. It has been shown that calcium deficiency in pregnant rats leads to a reduction of methylation 11 β -HSD1 gene and glucocorticosteroid receptor NR3C1 in the offspring [52]. It is known that increased plasma cortisol concentration leads to hypertension [53]. In addition, a low protein diet

Table 1. Environmental factors affecting the foetus causes decreasing of nephron number

Dietary factors	Drugs	Others
Low protein intake Vitamin A deficiency Iron deficiency Zinc deficiency High or too low sodium intake	Glucocorticoids Cyclosporine A Antibiotics (gentamicin, ampicillin, amoxicillin)	Ethanol intake Cigarette smoking

during pregnancy causes hypomethylation of AT_{1b} angiotensin receptor gene in the adrenal glands of the offspring [54].

Second mechanism of epigenetic regulation is a post-translational modification of histones (PTMs). It has been shown that histone acetylation plays a key role in the development of hypertension associated with glucocorticoids [55]. Furthermore, histone acetylation plays an important role in upregulating 11 β -HSD2 activity in human placenta [56]. Glucocorticoids may program the foetus through epigenetic modifications to the development of hypertension [57]. It has been shown that dexamethasone leads to a reduction of the interferon-gamma gene expression by histone deacetylation [58]. This leads to the development of hypertension in the offspring [59].

Third mechanism of epigenetic regulation may be a regulation based on micro RNA (miRNA). These small fragments of RNA inhibits the degradation of messenger RNA (mRNA) and translation. It has been shown both *in vitro* and *in vivo* that glucocorticosteroid receptor expression and activity is reduced by miR-124 and miR-18 [60]. Other studies have demonstrated that the other types of miRNA reduce glucocorticoid receptor expression in the adrenal glands in mice [61]. These mechanisms may be also involved in pathogenesis of hypertension in the offspring.

Summary

In summary, the factors affecting the development of foetal kidneys may also predispose to the development of arterial hypertension in the adult life. For this reason, prevention against development of arterial hypertension should start already during pregnancy. The most important elements of such a prophylaxis should be balanced diet, healthy lifestyle, avoiding smoking cigarettes, alcohol consumption and drugs affecting the development of the foetal kidneys, such as corticosteroids and probably some immunosuppressive drugs or antibiotics.

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