Perinatal Programming and Blood Pressure

7

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Abstract

Adverse intrauterine and perinatal events may have profound effects on the fetus and neonate. This chapter discusses both epidemiologic data and experimental models that elucidate those factors involved in perinatal programming and developmental origins of adult disease. Persons who have been born after exposure to an adverse intrauterine environment may be at higher risk of future diseases than those born after uneventful gestation. This phenomenon has been called "perinatal programming," a term suggesting the importance of the milieu during organogenesis to future events. The mechanisms by which perinatal programming occurs are multiple, involving subtle changes in development, changes in expression of various proteins, and, likely, epigenetic changes. Infants who are small for gestational age or are premature appear to be at high risk to be subject to the effects of programming. Whether such people should be considered as having an "extra" risk factor for hypertension and cardiovascular disease, as well as for metabolic syndrome and other conditions, is discussed in this chapter.

Keywords

Developmental origins of health and disease • Perinatal programming • Nephron endowment

Introduction

In the 1980s, British epidemiologist David Barker mined national records kept since the early part of the century to examine the relation between maternal health during pregnancy and cardiovascular disease of their offspring in later life, specifically non-hemorrhagic stroke [1]. A few previous publications had noted a statistical

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association between birth weight and hypertension in later life [2–4], and Barker subsequently formulated the hypothesis that prenatal and perinatal environment can impact later-life phenotype [1, 5, 6]. From his observations on stroke victims, who died at ages 55–74 years, he postulated that hypertension may be the link between low birth weight and later-life cardiovascular disease [1]. Initially called the "Barker hypothesis," the concept has since been variously called "prenatal programming," "perinatal programming," "developmental origins of health and disease," abbreviated as DOHaD, "developmental programming," or "developmental plasticity." As the latter terms imply, the concept has expanded to explain phenotypic characteristics other than diseases induced or caused by prenatal and early-life events. During the past two decades, the phenomenon of developmental programming has been a focus of intense study, but many of its aspects remain highly controversial and lack consensus, in part, because unraveling the underlying physiological mechanisms has proven elusive.

Of later-life disorders, hypertension has received the most attention in this field, and the bulk of the evidence supports the concept that the in utero environment can modify adult blood pressure patterns. It is important to note, as discussed below, that low birth weight may only be a marker of intrauterine stressors and may not have a causal role in the subsequent development of hypertension. There is also considerable evidence to suggest that the susceptible period extends to postnatal factors in early life.

Epidemiology of Low Birth Weight and Subsequent Hypertension

Geography, Ethnicity, and Gender

Most epidemiologic and other human studies about developmental programming have focused on the association of birth weight with subsequent events. Barker's early reports [1, 5, 6] took advantage of records available in a relatively limited geographic area (England and Wales). However, the association of LBW with hypertension has now been described in cohorts from numerous countries in Northern and Southern Europe [7, 8] [Finland, Norway, Sweden], North America [9–12], Central [13] and South America [13, 14], the Caribbean [15], Asia [16, 17], and Australia–New Zealand [18, 19]. The findings have largely been similar in all ethnic groups studied, including the indigenous peoples of Australia [18, 20]. The possible exception are persons of African ancestry in whom the findings have been ambiguous [13, 21, 22] or even the opposite, with LBW subjects having lower BP [23, 24]. Interestingly, a recent paper reported that Colorado residents of Mexican heritage appeared to be partially protected from the adverse effect of low birth weight [25].

Most reports have compared persons who had a low birth weight, often defined as <2,500 g, to those with "normal" birth weight. Very low birth weight (<1,500 g) persons may be at an even higher risk for later hypertension [26–29], and the risk may be inversely correlated to immaturity at birth [30].

Most studies in people report no gender difference in the association between birth weight and later hypertension [7, 9, 10], with some exceptions. While female subjects were more affected in a twin study published by Loos et al. [31], other reports have shown a predominant effect in males [32].

Studies in identical twins have been employed to control for potential confounding genetic and other factors common to both twin pairs. Several studies have concluded that even between twins, the twin with the lower birth weight is likely to have higher blood pressure in adult life [31–33], suggesting an effect within the fetoplacental unit, rather than from maternal factors shared by both twins. Not all studies agree. For instance, a Belgian long-term cohort study of 418 twin pairs reported no correlation between intrapair birth weight and blood pressure in young adulthood, although an effect of birth weight was observed between pairs [31]. The fact that perinatal programming of hypertension can be induced in both inbred and outbred animal species indicates that the in utero environment may confer an effect independently of the inherited genome [33].

A few epidemiologic studies have disputed the relationship between birth weight and

hypertension [34]. For example, Seidman et al. [35] found no association of BW and later blood pressure in a cohort of >30,000 17-year-old men and women. Skepticism about the concept of prenatal programming has centered on the difficulty in controlling for all confounding variables in epidemiologic studies [36–38]. It has been noted that low birth weight is frequently associated with many other factors known to be associated with hypertension, such as maternal size, socioeconomic status, educational level, and geographic region in which the mother lives. These concerns were recently addressed in a large US longitudinal study of 39–56-year-olds [39]. The study demonstrated that while socioeconomic factors during early life predicted adult hypertension, there were significant independent contributions by birth weight, even between siblings [39]. Taking the data together, the link between low birth weight and later-life hypertension seems well established. Negative results may be explained by studies with small subject numbers and other confounding risk factors, and the young age of study subjects who have not yet become hypertensive.

Intrauterine Growth Restriction Versus Prematurity

Most large cohort studies in adults were unable to distinguish between low birth weight resulting from intrauterine growth restriction (IUGR) or from premature birth and, therefore, do not clearly indicate whether premature babies without IUGR (BW appropriate for gestational age) are at an increased risk for later hypertension. The strength of the evidence now suggests that prematurity by itself is a risk factor, causing organ and metabolic pathology similar to those seen in IUGR, including later-life hypertension [28, 40–43]. Therefore, it is possible that early postnatal stress has effects analogous to prenatal stress on a very immature organism. Some studies have suggested that prematurity may be a stronger independent predictor of subsequent hypertension than LBW [43]. This is an important point because in developed countries, prematurity is a much more common cause of LBW than IUGR.

Body Proportion and Postnatal Growth

It is possible that the postnatal catch-up growth that follows IUGR may have later effects on BP. Several studies have suggested that IUGR places the offspring on a trajectory to increased postnatal weight gain, which may be an additional factor leading to a programmed increase in BP. The reported sensitive time periods for detrimental weight gain have varied from 1 to 13 years of postnatal age [23, 44–48].

An additional point is that a "thin" body habitus (low ponderal index) at birth may be independently associated with later increase in BP, which may be independent of BW but amplified by large postnatal weight gains [13, 46, 47, 49, 50]. For example, in the Helsinki birth cohort [46], men in their early 60s who already knew they had a diagnosis of hypertension in midlife were generally insulin resistant and obese but at birth had been thin and short but had caught up by age 11 years. Others who had previously undiagnosed hypertension were overweight with an abnormal lipid profile. They had been short at birth and had been thin and short at age 11.

Magnitude of the Effect of Programming

Many studies have quantified the relation between BW and later blood pressure, either as absolute differences in mmHg in systolic and diastolic BP or as an incidence of hypertension. Increased BP is more readily demonstrable in adults and may reflect pathophysiological amplification with age [48]. The magnitude of the BP effect ranges from 1 to 10 mmHg on systolic BP and slightly less on diastolic BP during adulthood. Several studies have reported a predominant effect on systolic BP, sometimes with no effect on diastolic pressure, with a resultant higher pulse pressure [48, 51].

Published studies attempting to link birth weight with subsequent BP and the magnitude of the elevation do not necessarily concur. A large prospective US study concluded that there is no relation between birth weight and BP at 7 years

of age in either white or black children [23]. Some studies have reported an inverse relation between blood pressure and birth weight in children [14], even in infants [52]. Yiu et al. reported that in 7-year-olds, there was a 1.3 mmHg decrease in systolic blood pressure and 0.6 mmHg decrease in diastolic blood pressure for each 1 kg increase in birth weight [12]. Others have found no correlation, even in older children [18]. In general, with advancing age, the correlation seems to become stronger and more readily demonstrable. Besides a more subtle impact in young subjects, many other factors, including methods of BP determination and small subject numbers, may account for the lack of statistical differences.

In absolute terms, the magnitude of BP increase in persons who were LBW neonates is small, once analyses are adjusted for confounders, and LBW should, therefore, best be considered as another risk factor for hypertension and cardiovascular disease. However, because of the high incidence of LBW, even a small population-wide statistical increase in mean BP would lead to a considerable number of additional persons being diagnosed as pre-hypertensive or hypertensive by the current diagnostic criteria. The large US studies by Curhan et al. documented a 39–43 % increase in diagnosed hypertension in 25–55-year-old women whose BW was below 5.0 lb and a similar 26 % increase in 40–75-year-old men [9, 10]. A recent meta-analysis of 78 studies reported a 21 % increase in the risk of hypertension in persons of relatively lower BW [53]. Pediatric studies have generally not observed frank hypertension, despite statistical increases in BP, supporting the hypothesis that there is amplification of the pathogenetic mechanisms with age.

In contrast to the epidemiologic data, most experimental animal models of developmentally programmed hypertension have shown a large increase in BP. In rat and murine models, the increase in systolic BP measured by tail-cuff method in adult animals is reported to be 20–30 mmHg above control levels [54–58]. As in humans, the increase in BP does not appear to be present or is only modest early in life [54, 59]. These animal data have come under scrutiny with the introduction of continuous intra-arterial radiotelemetric BP recording in rodents. In some models, the BP increase is only demonstrable with exposure to stress such as physical restraint [60]. In other reports, the effect on intra-arterial BP has been relatively small [57, 61, 62], absent, or even reversed [63]. Increased mean arterial pressure of approximately 6–10 mmHg by direct intra-arterial measurement has also been described in sheep after prenatal steroid treatment [64, 65]. Nevertheless, the large amount of experimental data taken together indicates that developmental programming of BP in association with lower birth weight does occur.

It is important to note that birth weight likely serves only as a crude marker of adverse prenatal environment and is not causally related to the programming phenomenon; this marker phenomenon may explain the mixed results of some of the human experience. As discussed below, much remains to be learned about the pathogenesis of programming.

Potential General Mechanisms of Developmental Programming

Glucocorticoids

Relatively little is understood about the programming signal(s) from the mother or the environment to the offspring. A leading hypothesis states that fetal exposure to excessive glucocorticoid levels constitutes a major programming signal [66]; this concept is supported by the finding of elevated cortisol levels at term in fetuses with intrauterine growth restriction [67].

Under physiological conditions, the fetus is protected from maternal glucocorticoids by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βDH2), which metabolizes glucocorticoids into inactive metabolites. High maternal cortisol levels due to maternal stress or glucocorticoid administration may overwhelm the capacity of 11βDH2, allowing the active hormone to cross into the fetus [64, 66]. The long-term effect of glucocorticoid administration to

the mother to accelerate fetal lung maturation has been examined is several studies, with variable results; some investigators have reported increased BP and obesity in the offspring [68], while others have observed no measurable difference [68]. Prenatally programmed hypertension has been induced experimentally in several species by maternal glucocorticoid administration during a sensitive period of gestation [56, 64, 65, 69]. Both negative and positive results have been reported in sheep; the differences may be attributable to the timing of the exposure or the type of glucocorticoid used [70]. Additional work on the maternal glucocorticoid hypothesis is provided by experiments in rats showing that offspring programming of hypertension is prevented or ameliorated by pharmacologic inhibition of maternal glucocorticoid synthesis or by maternal adrenalectomy [71–73].

Increased fetal exposure to glucocorticoids could also result if there is decreased placental 11βDH2 activity. There is evidence that activity of the enzyme may be impaired by maternal stress [74] or by intrinsic placental dysfunction, as seen in preeclampsia [75], and the level of the enzyme activity has been correlated with fetal weight [76]. Administration of a 11βDH2 inhibitor, carbenoxolone, to pregnant rats causes fetal IUGR and programs adult hypertension [55, 77]. Also, surgical reduction of uterine blood flow in rats or embolization of uterine vessels in sheep, either of which may cause placental ischemia and results in programmed hypertension in the offspring [57]. Thus, there is considerable evidence to support a role of fetal glucocorticoid exposure in developmental programming, but other factors may be equally important and require further study.

Epigenetic Imprinting of the Fetal Genome

Epigenetic mechanisms can be defined as heritable changes in gene expression that are not caused by changes in DNA sequence [78–80]. Epigenetic gene regulation is largely responsible for the fact that, despite identical genomes, different cells and tissues of the organism exhibit vastly different phenotypes. Although direct evidence is still scant, it is likely that epigenetic phenomena are operative in developmental programming [81, 82]. Epigenetic regulation can take place via at least three different mechanisms – first, DNA methylation affecting the binding of certain DNA-binding proteins; second, modification of chromatin configuration through methylation, acetylation, or phosphorylation of histone proteins, the "packaging proteins" of DNA; and third, silencing of specific mRNAs by microRNA molecules.

The majority of the embryonic genome is demethylated in the early postconceptual period, followed by large-scale methylation to establish a new methylation pattern, and this process may be susceptible to variations in maternal or paternal diets [83]. Maternal undernutrition during the preimplantation period appears to impair methylation in the embryo [84] and program increased blood pressure in the offspring [85–87]. In addition, paternal undernutrition may also have important effects [85, 88].

Later in gestation, the effects of impaired methylation, as well as changes in histone protein modification and RNA silencing, may be organ specific and depend on the developmental state of the given organ. This may explain why, for instance, maternal protein restriction in the rat during the second half of pregnancy programs a reduction in the number of nephrons [54]. There is experimental evidence that the effects of prenatal programming may be alleviated by maternal treatment with the methyl donor folic acid [89, 90], and preliminary data in humans suggest that folic acid supplementation reduces the risk of low birth weight and prematurity [91, 92]. Possible targets of epigenetic programming relevant to the development of hypertension include the renal 11βDH2 enzyme, renal and adrenal angiotensin II type 1 receptor, and the glucocorticoid receptor [93–96].

Of both interest and concern are the findings that in experimental rat models, the effects of prenatal programming appear to carry across to the next generation [97, 98]. For instance, rat offspring from low-protein pregnancies passed on

the phenotype of low nephron number and hypertension to their progeny via both maternal and paternal lines [97, 98].

Oxidative Stress and Fetal Programming

There is growing evidence that oxidative stress during fetal life may be a major factor in fetal programming [99]. Some of the adverse effects may be reduced by tempol, which is an ROS scavenger [100]. Recently, Chang et al. [101] have shown that hypertension programmed by maternal diabetes could be ameliorated by engineered overexpression of catalase in the renal proximal tubule. In that study, it was shown that the overexpression of the catalase triggered the Nrf–HO-1 defense system.

Maternal and Placental Risk Factors

Maternal Nutrition

Maternal nutrition is well known to affect fetal growth. A variety of maternal nutritional factors have been associated with developmental programming of hypertension (Table 7.1). Most, but not all, are associated with low birth weight. A striking example of overall nutrient restriction is provided by the long-term follow-up studies of people whose mothers were exposed to the Dutch famine in 1944–1945.The global nutrient deprivation lasted for a sharply defined period. As adults, the offspring who were exposed for at least 10 weeks had an increased rate of hypertension and cardiovascular disease [32, 102–104]. Other examples of global nutritional deprivation come mostly from underdeveloped countries. For instance, maternal nutrient status during pregnancy was linked to BP increase in 10–12-year-old Jamaican children [105]. Experimentally, programmed hypertension is inducible by global food restriction in several species, including the rat and the sheep (Table 7.2) [106–108].

Deficiencies in specific nutrients have also been implicated, but the evidence is less clear. As noted previously, folic acid supplementation during pregnancy appears to reduce the risk of fetal growth restriction, but its effect on later blood pressure is not known [109, 110]. Other implicated nutrients include vitamin A [111], zinc [112], iron [113], sex hormones [114], and micronutrients in general [110].

Maternal overnutrition and obesity [115] or high salt intake [116, 117] may also induce later-life hypertension in both human subjects and experimental models.

Table 7.1 Maternal exposures or conditions and prenatal programming

Maternal extrinsic exposures and future hypertension in offspring
Global reduction in protein and calories
Low-protein diet and isocaloric protein restriction
High-salt diet
Vitamin A deficiency
Folic acid deficiency
Iron deficiency
Nephrotoxic drugs
Tobacco exposure
Alcohol exposure
Maternal conditions and future hypertension in offspring
Placental deficiency
Maternal diabetes
Maternal obesity
Maternal CKD

Table 7.2 Animal species for the study of programming

Rodents – rat, mice, guinea pig
Sheep
Nonhuman primates
Good reviews may be found as follows: (a) Nathanielsz [187]; (b) Bertram and Hanson [188]; (c) Ozanne et al. [189]

Other Maternal Factors

There is a reported association between birth weight in persons whose mothers' mothers had either gestational or non-gestational diabetes and later development of the metabolic syndrome and hypertension in the offspring [118]. In particular, larger fetal and newborn size appears to be

associated with increased risk of obesity in later life [119]. One study reported elevated BP in the offspring of such pregnancies as early as at 3 years of age [118]. Other causes of LBW that are associated with later hypertension include maternal smoking [120], alcohol [62], and caffeine intake [121]. Unadjusted data from a cohort study in Western Australia suggested that maternal smoking might be associated with reduced birth weight and, later, with higher BP in young (1–3 years) offspring, but an adjusted analysis that included potential confounding factors ablated the BP effect from low birth weight [120].

Maternal Glucocorticoid Treatment

The long-term effect of glucocorticoid administration to the mother [122–124] to accelerate fetal lung maturation has been examined in several clinical studies, with variable results; some investigators have reported increased BP and obesity in the offspring [122], while others have observed no measurable difference [125]. This is discussed further in Chap. 26. Cortisol and other stress hormones are also implicated by studies linking maternal stress to developmental programming of cardiovascular disease, including the metabolic syndrome and hypertension [126].

Prenatally programmed hypertension has been experimentally induced by maternal glucocorticoid administration in several species, including the rat and the sheep [56, 64, 65, 69]. In both species, there seems to be narrow window of susceptibility to glucocorticoids, during the third trimester in rats and first-trimester sheep; it should be noted that sheep are much more mature at birth. However, not all investigators were able to demonstrate an effect in sheep; the difference may be attributable to the timing of the exposure or to the type of glucocorticoid used [64, 65].

The Placenta and Programming

Preeclampsia and placental dysfunction are the most common causes of LBW in developed countries and has been associated with hypertension in the offspring [57, 127]. Clearly, placental dysfunction has metabolic consequences for the fetus that may contribute to developmental programming [75, 128], but the available data are very limited except for that about the placental 11β-hydroxysteroid dehydrogenase type 2 (11βDH2) enzyme, discussed earlier.

It has been suggested that placental size and size discrepancy between the newborn and its placenta correlates with adult blood pressure [32, 49, 129, 130], but further studies are required to confirm and elucidate this observation.

Programming Targets in the Offspring

Kidney

Much of the research on programmed hypertension has been devoted to the role of the kidney. Experimental data indicate that the three renal compartments – vascular, glomerular, and tubulointerstitial – may all have structural and/or functional aberrations, but the role of the number of nephrons after an in utero insult has received the greatest attention. In humans, kidney development begins during the 6th week of gestation, and nephrogenesis (new nephron formation) is completed around the 36th week of gestation.

Nephron Number

It is well established that diseases that cause extensive renal damage and chronic kidney disease are frequently associated with loss of functioning nephrons and hypertension. The consequent progressive kidney injury is hypothesized to be mediated by increased flow and filtration in the remaining glomeruli, the so-called hyperfiltration theory. There is a wide variation in the number of glomeruli in the human kidney, ranging from 300,000 up to 2,000,000 [131]. It is therefore attractive to speculate that a congenitally low number of nephrons, even in the absence of renal disease, may lead to later hypertension. Strong support for this speculation was provided by an autopsy study by Keller et al. [132] which, though small (ten hypertensive and

ten normotensive persons who had expired due to accidents), indicated that hypertensive young adults without renal disease had a lower number of nephrons than control subjects. Because of the young age of the autopsied subjects, the low nephron count was suggested as congenital [132].

Later studies have confirmed an inverse correlation between number of nephrons and birth weight on one hand and adult BP on the other in American Caucasians. However, interestingly, such correlation was not present in African Americans, who generally have a higher incidence of hypertension [140, 141]. The nephron number per kidney in these studies was measured by the unbiased but cumbersome dissector/fractionator stereological method, explaining the paucity of human studies [131]. This method determines the total number of nephron in the whole kidney in three-dimensional space. More commonly, investigators have employed a counting method in histologic slides, measuring the number of glomeruli in a two-dimensional plane. A possible source of error with this methodology is the change in relative volume of different renal compartments (glomeruli, tubules, interstitium) as a result of intrauterine pathology. However, such histologic studies do in general agree with the stereological method in showing a reduced number of nephrons in LBW babies [133].

A few studies have been done utilizing indirect evidence, using kidney size, measured by ultrasound, as a surrogate for nephron number in children. The results are inconsistent; kidney size was reduced in LBW children in some studies but not in others [134, 135]. Additionally, kidney size may not be a reliable marker of nephron complement because of compensatory hypertrophy. Interestingly, persons born with a single kidney generally do not develop hypertension. Additional human studies are clearly needed to clarify the issue of nephron endowment and subsequent BP.

Experimental studies strongly support the association between the number of nephrons present at the end of nephrogenesis and later hypertension. In several models of genetic hypertension, there is a strong association between congenitally low nephron number and hypertension [136, 137]. However, crossbreeding experiments between spontaneously hypertensive rats SHRs and the normotensive WKY controls hint that filtration surface area, which has been linked to the development of high blood pressure, may not always be related [138]. The study looked at F1 and F2 offspring from this cross. BP was measured weekly from ages 5 to 15 weeks, and the animals were euthanized at 15 weeks, at which time glomerular number, size, and surface area were determined. Although the offspring exhibited the expected wide range of nephron numbers and BPs, no association between the two was noted in the F2 generation, in which there is random segregation of the genes from the WKY and SHR.

That being said, low nephron number has been documented in several experimental models of programmed hypertension and/or IUGR, both by true stereological methods and by other methods. Moreover, neonatal uninephrectomy in the rat induces later hypertension [139].

In summary, although studies in experimental animals do link low nephron count to hypertension, human studies are less conclusive and suggest that additional factors are in play, especially in African Americans.

Renal Vessels

Aberrant renal arterial vasculature has been described in experimental models of programmed hypertension [140, 141], but further studies are needed. Some investigators have described decreased capillary density in the kidney [140], but this too awaits confirmation. Similar information in humans is, to our knowledge, lacking. However, it is reasonable to expect that vascular abnormalities similar to those found in systemic vessels (see below) also apply to the kidney. Indeed, it has been hypothesized that renal microvascular disease may be a primary abnormality in programmed hypertension, leading to tubulointerstitial injury as discussed below [142].

Tubulointerstitial Factors

Renal tubulointerstitial pathology or functional alterations may be important in the genesis of hypertension [39]. It has been proposed that renal tubular transport aberrations, induced by injury to the tubulointerstitial microenvironment, may

underlie many types of hypertension by causing renal dysregulation of sodium balance and chronic volume expansion [39, 143]. Increased salt sensitivity, reported in some in children and adults with low birth weight, supports such dysregulation in prenatally programmed hypertension [144, 145]. Further, upregulated renal tubule sodium reabsorption has been directly documented in a rat model of programmed hypertension [146–148]. Factors involved in the accompanying tubulointerstitial injury may include oxidative stress and inflammation. Indeed, expression of oxidative pathways is upregulated in kidneys in relevant rodent models [149, 150], and treatment with reactive oxygen species scavenger or immunosuppressive drugs has been reported to decrease BP in a rat model [150]. One may speculate that an initial tubulointerstitial injury initiates salt-sensitive hypertension by chronically upregulating renal tubular sodium reabsorption and leading to chronic extracellular volume expansion [151]. Possible causes of tubulointerstitial injury include ischemia due to intrarenal microvascular abnormalities, heightened sympathetic activity, and increases in certain circulating vasoactive substances (see below).

Other factors may contribute to interstitial disease. For example, in a retrospective review, Feig et al. noted that children with incident hypertension had relatively elevated uric acid levels. Additionally, such children had evidence of lower birth weights and displayed markers of endothelial dysfunction [152]. In a pilot study, Feig and colleagues treated youngsters with hypertension and elevated uric acid with allopurinol and noted improved BP. In a subsequent article [153], the authors speculated that abnormalities in uric acid may be involved in aberrant intrarenal microvasculature (see Chap. 5).

The Intrarenal Renin–Angiotensin–Aldosterone System and Programming

The kidney contains a local renin–angiotensin–aldosterone system (RAAS) in which all components are present; this intrarenal RAAS appears to function locally, distinct from the systemic RAAS, contributing to maintenance of normal renal physiology, and also participates in many pathologic states [154]. The intrarenal RAAS is critical for normal kidney development [155, 156]. There is strong experimental evidence that developmentally programmed hypertension is associated with an altered intrarenal RAAS during prenatal life and in the perinatal period. Rat pups born to protein-restricted dams exhibit changes in levels of intrarenal components of RAAS, including increased expression of renin and angiotensin II type 1 receptors, decreased expression of angiotensin II type 2 receptors, as well as decreased angiotensin II levels [59, 93, 157–159]. In ovine models of programming, the administration of glucocorticoids to the fetus or maternal food restriction [160–162] is associated with changes in intrarenal RAAS expression. Similar information is not, to our knowledge, available in human newborns.

Thus, it appears that changes in the intrarenal RAAS occur in developmental programming. Exogenous alteration of the RAAS by administration of an angiotensin receptor blocker in rat pups still undergoing nephrogenesis results in a decreased number of nephrons and later hypertension [163]. Prenatal suppression of the RAAS would also be likely to cause abnormal renal vascular development, and one might speculate that such suppression could lead to tubulointerstitial ischemia and oxidative stress that may ultimately mediate dysregulation of sodium balance.

Renal Nerves

Much data suggest that the renal nerves participate in BP regulation either via effects on renal hemodynamics or on renal sodium transport. Renal denervation has been shown to alleviate severe treatment-resistant essential hypertension [164]. The role of renal nerves in developmental BP programming in humans has not been established, but in a rat model the sympathetic outflow to the kidney appears increased, and renal denervation prevents or ameliorates the development of hypertension [165, 166]. It is attractive to speculate that increased renal sympathetic stimulation, as a part of generalized sympathetic overactivity, is a key element in promoting renal Na by the mechanisms discussed above, hence leading to increased extracellular volume and hypertension.

Systemic Vasculature

Large numbers of human and experimental studies have examined changes in the systemic vasculature in IUGR offspring and whether these could have a role in the development of hypertension. Whether primary intrinsic structural defects are present is not clear. A few human studies have shown decreased reduced arterial diameter in large vessels in adults [167] and [168–170] children with LBW, but others have failed to find any effect of BW on arterial diameters [171, 172]. Arterial stiffness, a possible indicator of an abnormal arterial wall, has also been variably noted in large vessels in humans with LBW [170].

Abnormal vascular endothelial function has been hypothesized as an important contributor to the development of hypertension. Relevant studies have included determination of vascular relaxation in response to increased flow or acetylcholine (endothelium-dependent relaxation) and to NO donor (endothelium-independent relaxation). Impaired endothelium-dependent relaxation was reported in children and adults with LBW [169, 171, 172]. However, some reports show no change [173, 174]. Further, the presence of such changes in some infants and children without elevated BP [175] suggests that the alterations may be a direct consequence of the intrauterine environment rather than hypertension. Of interest, one report documented the presence of such functional abnormalities in subjects whose LBW was due to IUGR but not in others with LBW due to prematurity [169].

In contrast to aberrant vasorelaxation, abnormal vasoconstriction in response to stimuli is not consistently found in humans or experimental models. Microvascular dysfunction was examined in 3-month-old infants in whom skin perfusion was measured in response to acetylcholine or an NO donor. Response to acetylcholine, but not to the NO donor, appeared impaired in LBW infants, a possible evidence of a primary defect in NO-cAMP generation [176]. A study by the same investigators in 9-year-old normotensive children provided similar results [171].

As noted earlier, abnormal uric acid metabolism has emerged as a potential mediator of endothelial dysfunction and hypertension [153] and has been proposed to be important in prenatal programming of hypertension [152]. In addition to alterations in the systemic vasculature, uric acid might promote hypertension via vasoconstriction or other effects on intrarenal vessels.

Thus, there is evidence to support the presence of both structural and functional abnormalities in both the macrovascular and microvascular circulation, but whether these changes result in the development of hypertension has not been unambiguously established.

The Sympathetic Nervous System and Stress

Several studies of human subjects with low birth weight or prenatal stress documented changes in stress reactivity and sympathetic nervous system function in the offspring. For example, when studied at an average age of 58 years, people exposed to the Dutch famine in utero displayed an exaggerated BP response to stress if their prenatal exposure was during early gestation [177]. Reactivity to stress in adult life has been approached by producing mild psychosocial stress and then measuring plasma or salivary cortisol levels before and after the intervention [178–180]. Results have varied. For example, de Rooij et al. found no differences in cortisol responses after stress, while Kajantie et al. [179] reported an inverse U-shaped relationship between cortisol levels and birth weight with psychosocial stress. The lowest ACTH and cortisol levels were observed in the participants who weighed the least at birth.

A study of preteen children showed increased urinary catecholamine excretion in subjects who were born preterm or had evidence of IUGR at term, but there were no differences in baseline or stress-induced BP as compared to control subjects [181].

Stronger evidence that stress reactivity and sympathetic activity can be programmed prenatally comes from experimental studies. Increased BP response to stress has been described in both rats and sheep; however, the baseline BP was not

invariably elevated [182–184]. An exaggerated increase in BP was also described after amphetamine-induced catecholamine release in rats that had been exposed to dexamethasone in utero [183]. Increased cortisol level in response to stress has been described in sheep that had been exposed to betamethasone in utero [182].

Thus, responses to stress appear to be modified by prenatal conditions or exposures in certain experimental models, and there are hints that this may be the case in humans. However, the role of hormones released by stress or of the sympathetic nervous system in the development of hypertension has not been clearly established. Because sympathetic overactivity may be a predictor of future hypertension [185, 186], intrauterine stress may be considered as a possible risk factor associated with prenatal conditioning.

Speculation about Prognosis, Prevention, and Suggestions for Management

Persons who have been born after exposure to an adverse intrauterine environment may be at risk of having undergone perinatal programming. Such people should be considered as having an "extra" risk factor for hypertension and cardiovascular disease, given the growing number or reports, summarized above, which indicate that such persons may develop hypertension and other "programmable" traits such as obesity, dyslipidemia, and metabolic syndrome [185]. Risk for these other conditions may be at least as important as changes in BP. For example, one study reported that CV mortality in LBW subjects is only minimally mediated by BP [185].

Prenatal programming may be avoidable. At this time, there would appear to be sufficient epidemiologic and experimental data to suggest healthful measures that would lower the chance of an adverse intrauterine milieu. Thus, before conception and during pregnancy, mothers should have adequate protein–calorie intake and should avoid smoking and alcohol. Folic acid supplementation still remains controversial with respect to the prevention of future cardiovascular disease, though adequate intake is important for all.

After birth, at-risk children should be followed, but to what extent is not clear. Excessive postnatal weight gain should be avoided, but there are presently insufficient data for guidelines. However, it makes sense to encourage a healthy diet that avoids excessive salt, as well as a healthy lifestyle. Further, monitoring the BP in such children as they mature should permit early intervention if hypertension develops. Currently data are not sufficiently robust to make a recommendation that at-risk children should have their renal size monitored or be screened for microalbuminuria. Further, there are not enough data to indicate whether treatment with ACE inhibitors or ARBs in at-risk persons would be helpful.

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