Impact of Fetal Programming, Birth Weight, and Infant Feeding on Later Hypertension

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The concept of developmental origins of adult disease derives from both epidemiologic and basic sciences. This brief review considers the impact of the intrauterine milieu, intrauterine growth retardation, premature birth, and infant feeding on later hypertension and kidney disease. *J Clin Hypertens (Greenwich).* 2012; 14:365–371. ©2012 Wiley Periodicals, Inc.

The concept of developmental origins of adult diseases derives from several different types of observations. The thought that there were critical or "sensitive" periods of development originated more than 50 years ago and was put forward by Widdowson and McCance,[1] who demonstrated that malnutrition led to distinct and different effects, depending on when the life cycle malnutrition occurred. In the 1980s, epidemiologic data in which an association was observed between birth weight, as well as placental size, and subsequent cardiovascular disease led to the understanding that the perinatal environment was important in the risk of future disease.[2–4] The implications of such epidemiologic observations were brought to prominence by the work of David Barker and colleagues, and the data mesh well with the hypothesis put forth nearly concomitantly by Brenner and colleagues,[5] who hypothesized that the final number of nephrons, which is fixed by term birth in humans, might explain subsequent hypertension and chronic kidney disease. In the decades since the work in this area began, the data have shifted from phenomenology to a current emphasis on seeking mechanisms for these observations. In this brief review, we examine the information available to explain the pathogenesis and mechanisms of what has been widely termed perinatal programming or developmental origins of health and disease. In 2001, Bateson[6] suggested that a better term for the subtle changes that occur in the perinatal period but have long-ranging effects might be phenotypic induction, a label that may better combine the various forces at work—both environmental and epigenetic—that lead to time-spanning changes in the individual. This paper considers the impact of the intrauterine milieu, intrauterine growth retardation, premature birth, and infant feeding on later hypertension and renal disease.

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PRENATAL STRESS AND THE INTRAUTERINE MILIEU

A number of perinatal perturbations have been associated with subsequent hypertension—maternal malnutrition, exposures to medications or toxins during pregnancy, and dietary deficiencies.[7–10] The influence of dietary alterations and stress on the developing fetus or immature (premature) newborn may be very mild, changing the developmental sequence very subtly, yet permanently (Table and Figure). Such changes may include alterations in the distribution of cell types within an organ or differences in gene expression within given cells within the organ. The effects of stress may vary, depending on when the stress occurs. For example, embryos of dams exposed to a low-protein diet only within the preimplantation period had decreased inner cell mass in the early blastocyst and, in the mid to late blastocyst, a decreased number of cells were found in the trophoectoderm.[11] While the mechanism is unclear, such decreased cell numbers may lead to long-term changes in the developing organism. It is thought that increases in maternal glucocorticoid levels via stress may transduce some of the changes observed in the offspring. The placenta normally has 11-beta-hydroxysteroid dehydrogenase type 1, which inactivates maternal glucocorticoids. During stress, placentas express less of this enzyme, and the fetus is exposed to higher glucocorticoid levels as a result (summarized in Baum[9]). It has been demonstrated that glucocorticoids at critical windows lead to decreased nephrogenesis, at least in the rat, likely by inhibition of branching morphogenesis and, ultimately, resulting in a relatively low nephron number.[12,13]

NORMAL KIDNEY DEVELOPMENT

The antecedents of the human kidney form in three successive waves: the pronephros, the mesonephros, and the metanephros. The initial functioning of nephrons is present by about 9 weeks of gestation, and no new nephrons are formed after 34 to 36 weeks (after 7–10 days postnatal in rats). Several hundred genes are involved in orchestrating renal development.[14,15]

The vasculature begins to develop early in the first trimester, but within the kidney, vasculogenesis continues

TABLE. Stressors and Developmental Origins of Health and Disease

Timing of Stressor	Exposure Type	Effects in Models	Observations in Humans
Preimplantation	Malnutrition/low-protein diet	Cell deficiencies in blastocysts	–
Placental	Placental insufficiency, multiple pregnancies	Models of placental insufficiency associated with intrauterine growth restriction	Infants with intrauterine growth restriction often have small placentas; placental size correlated with birth weight and with future cardiovascular disease in initial Barker studies
Intrauterine	Hormones (folate, glucocorticoids)	Impaired glucose tolerance test/ diabetes mellitus reduced β-cell mass	Impaired glucose tolerance test/diabetes mellitus reduced β-cell mass
	Methylated compounds	Obesity; impaired nephrogenesis	Obesity; impaired nephrogenesis
	Protein-calorie malnutrition; Hyperglycemia High glucocorticoids Renin angiotensin system alterations Inflammation Free fatty acids	Increased type 1 angiotensin II receptor expression; cardiorenal abnormalities, vascular structural changes; hypertension	Low nephron number, vascular structural changes; hypertension
Perinatal	Malnutrition Overnutrition Toxic substances Hypoxia Oxidative stress Trace metal deficiencies	Epigenetic changes observed Future cardiorenal syndrome Future metabolic syndrome	Future cardiovascular disease Future metabolic syndrome

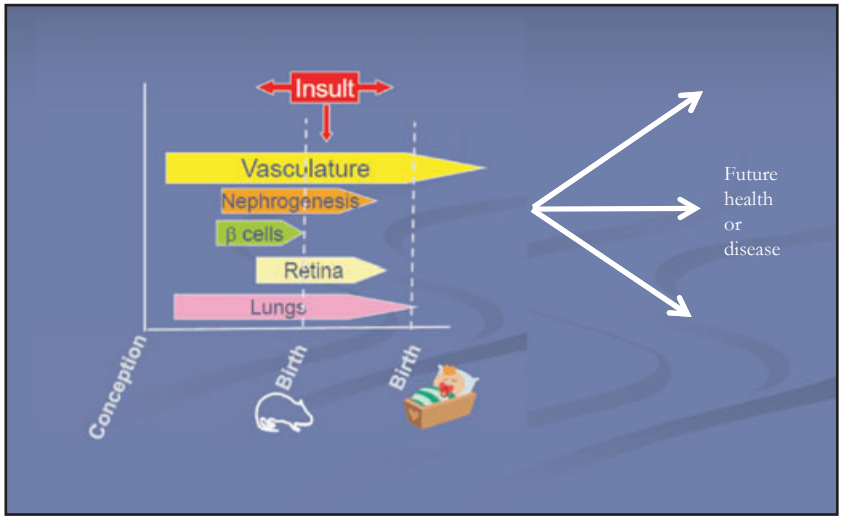

FIGURE. Perinatal stressors, growth, and cardiorenal endowment. This figure shows the length during which certain organ systems of interest develop, as well as potential timing of insults. Depending on whether there are intrauterine or perinatal challenges will inform the potential trajectories of health and disease throughout subsequent development and in adult life.

as nephrons form. Major vessels are visible by the start of the third week of fetal life in the human, and the heart is formed by the 9th week. In the human embryo, vasculogenesis begins by about day 18, at which point cells from the splanchnopleuric mesoderm differentiate to become endothelial progenitors and, then, embryonic endothelial cells, which begin to form vessel networks. Subsequently, periendothelial smooth muscle cells, essentially for the formation of actual vessels, also appear. Vasculogenesis continues as organs develop.[14,15]

Nephrogenesis and renal vascularization are intimately linked. Both glomerular and tubular epithelia are induced by the ureteric bud, which branches. Around the ureteric bud tip, there is a condensation of mesenchymal cells, which ultimately develop into glomeruli.[14,15] Concomitantly, the vasculature develops, and if coordination is not synchronized, the kidneys are markedly abnormal. The process is well-traced in the mouse and some other mammalian models, but, for obvious reasons, is not well studied in humans.

INSULTS DURING ONGOING NEPHROGENESIS

Animal models and ex vivo studies indicate that intrauterine insults such as those imposed simply by a maternal low-protein diet, may lead to decreased nephron number. There appear to be specific "windows," at least in rodent models, during which exposure to stress has maximal effects. For example, the timing of the administration of a maternal low-protein diet and also maternal glucocorticoid administration greatly impacts its effect. In rats, the provision of a low-protein diet to pregnant dams during the second half of gestation but not during the first half results in a nephron deficit in the offspring. The administration of glucocorticoids at E13–15 leads to hypertension in rats, but not later or earlier.[14,15]

The strategies that have been employed to examine the impact of challenges to the maternal-fetal environment have included total caloric restriction, as well as low-protein diet, high-fat diet, vitamin A and D deficiencies, high-salt diet, ethanol exposure, trace metal deficiencies, and glucocorticoid exposure or interruption to endogenous glucocorticoids.[16–18]

VASCULATURE AND INTRAUTERINE EVENTS

Both experimental models and epidemiologic data suggest that intrauterine events can affect both vasculogenesis and endothelial function, as well as vascular wall structure. Both endothelium-independent and -dependent vasodilatation (well-recognized precursors of hypertension and atherosclerosis) may be impaired in low-birth weight infants and may persist to adult life.[18–22] Some differences in vascular reactivity are evident, even in the first week of life in small-for-gestational-age neonates.[19] At 9 years of age, children who were low–birth-weight neonates had evidence of aberrant response to acetylcholine but normal response to the endothelium-independent vasodilator sodium nitroprusside. Experimental data also indicate exaggerated vasoconstrictor response to angiotensin II in such offspring.[23]

There is experimental evidence of decreased vascular arborization during development that leads to microvascular rarefaction in the fetus or neonate exposed to adverse conditions.[24–26] Microvascular rarefaction (which comprises reduced density of arterioles and capillaries) is associated with hypertension.[27] Capillary and microvascular rarefaction can increase peripheral vascular resistance and are generally considered a consequence rather than a cause of hypertension.[28] However, experimental data have shown capillary rarefaction in major sites of peripheral resistance in newborn but not in fetal rats exposed to a maternal restricted protein diet that is prior to blood pressure elevation,[25,26] suggesting that microvascular rarefaction can be a primary event in the development of hypertension associated with earlier fetal stress. It can therefore be postulated that the increase in blood pressure could at least be, in part, an adaptation mechanism allowing sufficient capillary recruitment to maintain adequate perfusion to the peripheral tissues.[29] Reduced retinal vascularization and lower peripheral skin blood flow have been reported in young adults born at term but who had evidence of intrauterine growth restriction[30,31] or were born preterm (these persons were not diagnosed with formal retinopathy of prematurity during their neonatal period).[32]

Mechanisms underlying microvascular rarefaction associated with fetal and/or neonatal stress is incompletely understood. Experimentally, there appears to be an attenuated angiogenic potential early in life based on explants of aortic rings in pups exposed to a maternal restricted protein diet.[26] However, there have been studies indicating that a number of factors known to be participants in angiogenesis—AT_1 receptor subtype; endothelial nitric oxide synthase, angiopoietin 1 and 2, the Tie 2 receptor, vascular endothelial growth factor (VEGF), VEGF F receptor-2, and platelet-derived growth factor. Controls were not affected. More recent data indicate that vascular progenitor cells could be affected by perinatal adverse conditions. Neonatal mice exposed to 10 days of hyperoxia have lower endothelial progenitor cells in the blood and lungs.[33] Furthermore, circulating endothelial progenitor cells from prematurely born children who were exposed to supplemental oxygen demonstrate impaired growth and proliferation when compared with endothelial progenitor cells taken from either premature infants who remained in room air or from term infants.[34]

Low birth weight and premature birth are associated with increased arterial stiffness when tested later as adults, and also in children and adolescents who had such birth histories[].[35–38] The proportion of elastin vs rigid collagen in the arterial wall is a major determinant of arterial stiffness, which is a key factor in increased systolic and pulse pressure in adults.[39] The main structural change in the artery wall associated with increased stiffness relates to relatively increased collagen and reduced elastin content. Elastin synthesis in vessels peaks in late gestation, decreases rapidly after birth, and is minimal in the adult aorta.[40] Experimental data indicate that extracellular matrix composition can be altered by fetal and/or neonatal stress and thereby contribute to resulting vascular and blood pressure changes.[41,42]

TRAJECTORY OF DEVELOPMENT AFTER PERINATAL CHALLENGES

The inverse relationship between birth weight and blood pressure[43,44] is not present during the neonatal period or very early childhood, but it has been reported from the age of 4 and appears to increase with age.[45] Similarly in experimental models of developmental programming, animals are not born with hypertension but undergo an age-dependent and earlier-than-expected increase in blood pressure.[25,46]

Studies that consider gestational age (and therefore prematurity) in addition to low birth weight are

relatively more recent. In a study of 430 Swedish men, aged 49 years, the authors estimated that every additional week of gestation achieved before birth was associated with a decrease in adult systolic blood pressure of 7.2 mm Hg.[47] Former preterm adolescents and young adults are also reported to have higher blood pressure.[48] Such impact of shortened gestation rather than or in addition to intrauterine growth restriction (IUGR) was noted by additional[43,49] but not by all studies.[50,51] Interestingly, in many studies, IUGR participants do not seem to differ from those who were born at an appropriate size for gestational age, within both the premature and term groups, suggesting that preterm birth per se plays an important role in the programming of later-life cardiovascular function.[52]

White and colleagues[53] looked at 31 case-control and cohort studies that included data on more than 49,000 individual persons and data from more than 2 million persons in one record-linkage report. Their analysis showed that the combined odds ratios for developing kidney disease supported a link between low birth weight and subsequent chronic kidney disease, although not all studies were consistent.

MECHANISMS (EPIGENETIC AND POST-GENETIC)

Growing evidence suggests that epigenetic modifications might explain many of the changes noted in perinatal programming.[54–56] Epigenetic changes consist of modifications to nucleic acids that do not change the sequence of base pairs. Such changes consist mainly of chemical reactions—5′-methylation of cytosines in CpG dinucleotides, phosphorylation, ubiquitination of histones, ADP ribosylation, and other covalent modifications such as acetylation.[54–56] Noncoding RNAs may also influence and change the organization of chromatin. Of importance, epigenetic changes may change conformation and function of chromatin, modulating gene expression and binding of transcription activators and repressors. Methylation of DNA is associated with long-term changes, while histone modifications lead to short-term effects.

The term *imprinting* has multiple meanings. Genetic imprinting connotes alteration of a gene or its expression based on the observation that some genes will have differential expression that depends on maternal or paternal derivation. This expression is a function, in large part, of the epigenetic regulation of a gene. Generally, the methylation pattern of a gene is involved, with more methylation of imprinted regions, which renders them relatively less transcriptionally active. (Note that the term "imprinting" is also used in the field of developmental origins to describe a variety of metabolic changes that occur with intrauterine stresses that are transmitted to a fetus; this is an inexact term that has been used nearly interchangeably with programming and is not considered here.)

Epigenetic changes can and do occur at multiple points in the lifecycle. However, there are major epigenetic changes in the germline—when the germ cells move to the developing gonads and then during early embryonic life, when both maternal and paternal haploid genomes lose much of their DNA methylation and then undergo histone modification. The demethylation that occurs in the paternal genome is extensive, but it does not take place in genes that are paternally imprinted.[54–57] Some repetitive sequences and heterochromatin near some centromeres may not be demethylated. Thus, these processes erase much of the epigenetic information from the previous generation, although some sequences may remain.

A growing body of data suggests that epigenetic changes do occur with intrauterine stress. The low-protein intake model of perinatal programming has been used to examine the role of epigenetic changes. Bogdarina and colleagues,[58] for example, examined the offspring of dams that were given low-protein intake during gestation (8%) as compared with offspring of dams that were given normal protein intake (18%). The investigators examined adrenal expression of renin-angiotensin system components and reported changes in the expression of genes of the RAS in the offspring at 1 day and at 12 weeks of life. They also reported that differences appeared to be due to demonstrable evidence of epigenetic changes. In particular, the AT_{1b} receptor had a lower-than-normal amount of methylation. As in vitro, the AT_{1b} gene is dependent on promoter methylation, the intrauterine effects of a low-protein diet might permanently alter the gene expression of an important receptor for angiotensin II action.

In another series of experiments in a rat model, Vaiman and colleagues[59] examined the level of IUGR-induced deregulation of the transcriptome and noted that organs are differentially affected by insults such as a low-protein diet. In general, organs that develop function late are affected more severely than are those that function early. For example, the kidney would be more markedly affected than the heart. In a recent study, Vaiman and colleagues examined offspring of normal protein dams (22%) vs those offspring of dams that had a low (9%) protein diet. They then examined the organ-specific intensity of growth restriction, looked at clustering of the effects of organ response to stress, and analyzed specific gene groups. They examined epigenetic regulators, imprinted genes, and chromosome-specific alterations of gene expression and concluded that many alterations would be permanent, affecting organ function well into adult life.

OTHER FACTORS

Among the many factors implicated in adverse perinatal conditions and developmental programming of hypertension, oxidative stress seems an important common denominator. Infants are exposed upon birth to relatively high concentrations of oxygen compared with intrauterine life. Indeed, under physiologic conditions the fetus is hypoxic compared with the adult.

While human maternal arterial oxygen partial pressure is approximately 90 mm Hg, the highest arterial or venous oxygen partial pressure in the late gestation fetus rarely exceeds 30 mm Hg. In the fetal to neonatal transition, blood oxygen content and oxygen availability abruptly increase in the first few minutes after birth to adult values, eliciting the generation of a burst of oxygen-free radicals.[60–62] Small-for-gestational age and premature infants have lower and less inducible antioxidant defenses because it is only during the last trimester of a normal pregnancy that antioxidant enzyme levels increase.[63–66] Therefore, the combination of immature antioxidant system to face this surge in oxygen partial pressure plus the need for therapy with oxygen supplementation because of lung immaturity, unstable lung dynamics, and sepsis altogether, can lead to significant oxidative stress in the immediate neonatal period.[67–69] In immature newborns, exposure to supplemental oxygen can halt microvessel growth in the lung and retina, leading to serious short-term complications such as bronchopulmonary dysplasia and retinopathy of prematurity.[70,71] The possible long-term consequences of early-life vascular oxidative injury in susceptible individuals are only starting to be explored, and experimental data indicate a premature arrest in cell proliferation in developing organs with accelerated differentiation and oxidative DNA damage.[72,73]

MANAGEMENT: WHAT CAN ONE DO TO AMELIORATE THE EFFECT OF ADVERSE PROGRAMMING?

How do we identify those who are at risk for long-term sequelae of an adverse intrauterine and perinatal experience? What do we know about managing them? Data from animal models suggest that progeny born to mothers who had a deficient diet during pregnancy remain normotensive and live longer if they remain on a restricted diet during postnatal life. Other studies demonstrate that rat pups born to dams that had uteroplacental insufficiency, owing to uterine vessel ligation, were ''rescued'' by cross-fostering to normal mothers. There are data in humans that suggest that the pattern of weight gain after birth, if controlled, can lead to less hypertension and chronic kidney disease.

Enhancing vasculogenesis postnatally can be promoted by exercise. Children randomized to daily school exercise lessons (vs twice a week for the control group) for 1 year improved their physical fitness and significantly increased the number of circulating progenitor cells.[74] Therefore, evidence so far indicate that common sense healthy life habits (limiting calories and regular exercise) can be particularly critical for the significant proportion of children and adults who were born with low birth weight or prematurely.

UNANSWERED QUESTIONS

At present, we do not have a method of assessing vascular and nephron endowment during early infancy in humans. Postmortem studies that assess nephron number strongly suggest that intrauterine events influence cardiorenal endowment,[75–78] but noninvasive means that could assess nephron number are still needed, as those infants with a nephron number deficit would likely be at high risk. Thus, practical means to distinguish whether all small-for-gestational age infants are at high risk would be of benefit. Whether fitting postnatal diet to endowment would impact later metabolic and cardiovascular diseases is unknown, although animal models suggest that such an approach would be of benefit.

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