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Authors

Chu, Alison
De Beritto, Theodore

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The Perinatal Origins of Cardiovascular Disease

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Alison Chu, MD; and Theodore De Beritto, MD, MS

Abstract

In recent decades, with advances in neonatal intensive care, extremely premature infants are now surviving into adulthood. Epidemiologic data on the health of these ex-premature infants have begun to reveal a concerning motif—that is, prematurity, in and of itself, seems to be a risk factor for cardiovascular and metabolic disease in later adulthood. The mechanisms underlying this increased risk are unclear, but it is believed that both adverse fetal environment and postnatal exposures for a premature infant likely contribute to the developmental programming of disease by altering the normal trajectory of maturation and aging of multiple organ systems. This article specifically focuses on perinatal factors that may affect risk for cardiovascular disease. [*Pediatr Ann.* 2015;44(11):e254-e259.]

Alison Chu, MD, is an Assistant Professor-in-Residence, Department of Pediatrics, Division of Neonatology, University of California, Los Angeles, David Geffen School of Medicine, Mattel Children's Hospital. Theodore De Beritto, MD, MS, is a Pediatric Resident, Department of Pediatrics, University of Chicago, Pritzker School of Medicine, Comer Children's Hospital.

Address correspondence to Alison Chu, MD, 10833 Le Conte Avenue, MDCC B2-375, Los Angeles, CA 90095; email: alisonchu@mednet.ucla.edu.

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Recent advances in neonatal and perinatal medicine have led to increasing survival of premature infants, and data on the long-term outcomes of these surviving premature infants are now becoming available. Epidemiologic studies have consistently identified a strong association between prematurity and increased risk for developing cardiovascular disease (CVD) during adulthood. These findings suggest that events occurring during the perinatal period may lead to alterations in the normal trajectory of maturation and aging of multiple organ systems, including the cardiovascular system. Although the mechanisms underlying these changes are unknown, multiple research groups have evaluated potential pathways and how they are altered in low birth weight and premature infants, and contribute to eventual propensity for disease in adulthood.

During gestation, interactions between the mother and the fetus are critical for optimal growth and development. Barker's hypothesis¹ was based on observations in large, longitudinal cohort studies that fetuses exposed to maternal undernutrition were at increased risk for cardiovascular and metabolic disease when they were adults. Many studies since then have validated these findings, and have also demonstrated that birth weight and prematurity are independent risk factors for coronary heart disease, hyperlipidemia, hypertension, stroke and diabetes in adulthood.¹ Consequently, several experimental models have examined the impact of altered intrauterine environment on long-term adverse outcomes. These studies provide evidence that fetal adaptation to the altered environment in-utero leads to epigenetic modification and altered gene expression that in later life results in mismatch between physiologic set-points and resource availability, thus manifesting as adult disease (**Figure 1**).

PREMATURITY AND RISK FOR CARDIOVASCULAR DISEASE IN ADULTHOOD

Although the concept of developmental programming was borne from observations that low birth weight is associated with adult disease, studies now have demonstrated that prematurity, independent of birth weight, contributes to markers of

During gestation,
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cardiometabolic dysfunction, including hypertension, increased serum cortisol levels, and insulin resistance.² A study³ of ex-premature infants showed that even at age 2.5 years, these toddlers demonstrated higher systolic and diastolic blood pressures than their full-term counterparts. The effect was greater in boys, consistent with findings in several epidemiologic studies that girls are relatively protected against programming of cardiometabolic disease.³ Interestingly, this effect was even more dramatic in patients with mothers who smoked, those that took steroids for antenatal fetal lung maturation, and those who were diet restricted. Many of these factors were likely contributors to low birth weight and/or prematurity. It is theorized that this vascular dysfunction self-perpetuates as the child ages, and in adolescence, this manifests as cardiovascular growth arrest, myocardial remodeling, altered autonomic control, and adrenal overactivity.⁴ In adulthood, this vicious cycle results in increased risk for

hypertension, coronary heart disease, and stroke.

PRENATAL FACTORS

Maternal Nutrition

Nutrition is of the utmost importance in the fetal and neonatal period and can significantly contribute to developmental programming of disease. Birth weight is influenced by maternal nutrition and protein intake.⁵ In fact, a 70% reduction of caloric intake in a mother's diet can induce a 35% decrease in birth weight as demonstrated in animal studies.⁶ In comparison, human gestation demonstrates remarkable adaptive capacity and protection of the fetus. In the Dutch Hunger Winter,⁷ mothers exposed to low food rations (approximately 500 kcal/day) during their third trimester had offspring that were only approximately 300 g lighter than their siblings born outside of this time period.

Caloric restriction has been shown to have adverse effects on the developing pancreas and kidney, and also leads to glucose intolerance and insulin resistance in the peripheral tissues. In rat models with total caloric restriction during gestation, their offspring are hyperphagic, hyperinsulinemic, develop hypertension, and become obese as they mature into adulthood.⁸ Interestingly, maternal overnutrition creates a predisposition to metabolic syndrome as well.⁹ Offspring of overnourished mothers have altered neuronal development, increased adiposity, and also exhibit hypertension, impaired cardiac function, and become hyperglycemic and hyperinsulinemic in adulthood.¹⁰ Similar studies in rats have also demonstrated that mothers with a specifically high fat diet prior to conception and throughout pregnancy produce offspring with a similar metabolic syndrome phenotype in adulthood.¹¹ These studies highlight the importance of maternal diet in the

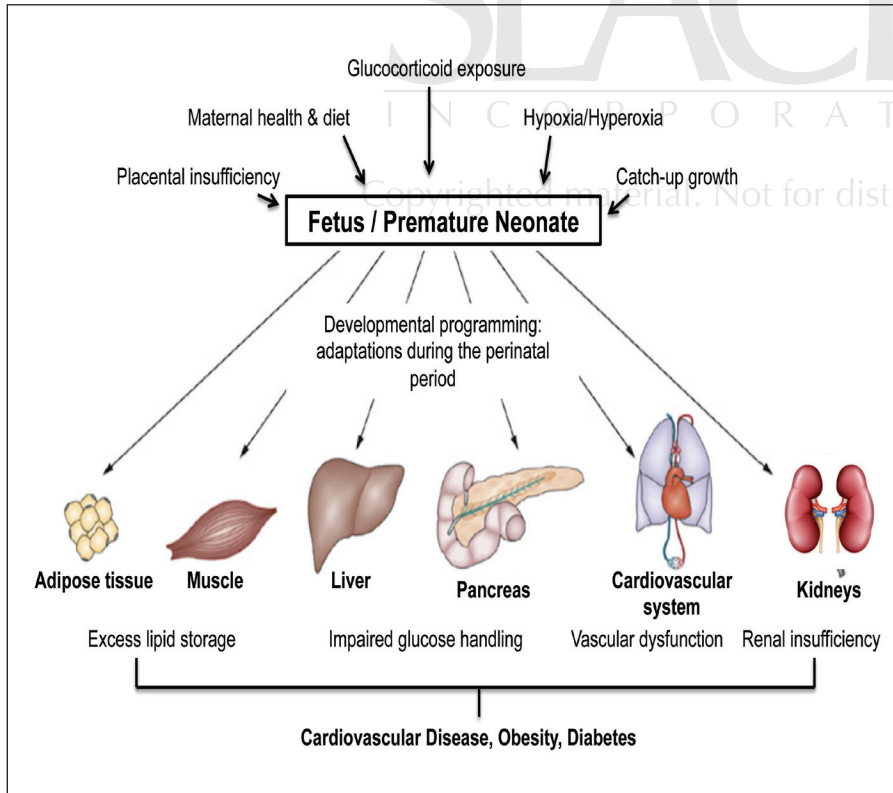


Figure 1. A schematic diagram of perinatal exposures leading to physiologic adaptation and developmental programming of adult disease in premature infants. Modified with permission from Macmillan Publishers Ltd.³¹

developing fetus and on the long-term health of both mother and neonate.

Placental Insufficiency

The placenta is a key organ at the maternal-fetal interface, regulating nutrient transport, hormone synthesis, and blood flow. Intrauterine growth restriction (IUGR) can be caused by placental insufficiency, which results in hypoxia, altered hormone levels, and poor nutrient provision to the fetus. In some cases of placental insufficiency, increased resistance to blood flow in the placenta leads to fetal hypertension and increased pulsatility, which have been shown to cause vascular changes and remodeling. A study done by Dodson et al.¹² used a sheep model to demonstrate that IUGR is associated with decreases in vascular compliance, specifically in the carotid and umbilical arteries. They correlated these changes with alterations

in the composition and structure of the extracellular matrix in blood vessels by demonstrating histologic changes such as increased collagen, elastin, and glycosaminoglycan deposition.

Another proposed mechanism of the development of hypertension centers around impaired endothelial vasodilation. IUGR and preeclampsia have been associated with low levels of nitric oxide (NO). NO is a pleiotropic cellular-signaling molecule that can act as a potent vasodilator. NO is usually released by endothelial cells as a response to mechanical forces and neurohumoral mediators to regulate vascular tone. Several studies in humans have demonstrated evidence of impaired vasodilation by various measures of endothelial dysfunction.¹³ Impaired vasodilation is considered an early marker of hypertension. In animal models of IUGR resulting

from placental insufficiency, impaired vasodilation was also seen. Although the mechanism of how underlying placental insufficiency/IUGR leads to decreased vasodilatory capacity is still unknown, a reduction in nitric oxide synthase expression or bioactivity has been suggested.

Lastly, prematurity and IUGR both adversely affect renal development, causing a premature cessation in nephron endowment. Studies have demonstrated associations with low birth weight and end-stage renal disease (ESRD). In fact, in neonates below the 10th percentile in weight, the relative risk of ESRD is 1.7—compared to their appropriate for gestational age birth weight counterparts.¹⁴ Furthermore, other studies demonstrate that with every 1 kg of weight increase, there is a corresponding increase of 2.6 to 7 mL/min in the glomerular filtration rate.¹⁵ In addition to the structural alterations seen, development of endothelial dysfunction contributing to small artery resistance can also be explained by alteration of the renin-angiotension (RAS) pathway. Increased production of reactive oxygen species (ROS) via reduced vascular nicotinamide-adenine dinucleotide phosphate occurs in hypoxic conditions such as that seen with placental insufficiency, and can lead to reprogramming of the RAS pathway. Viridis et al.¹⁶ demonstrated that chronic angiotensin II infusion induces endothelial dysfunction in small mesenteric arteries via reduced availability of NO secondary to increased ROS production. This stiffening and dysfunction of the arterial walls leads to decreased compliance and increased tone of blood vessels and thus hypertension. Taken together, these studies demonstrate complicated cross-talk between various organ systems, all of which may be altered by the relatively hypoxic and nutrient

deficient in-utero environment resulting from placental insufficiency and contributing to vascular dysfunction later in life.

Glucocorticoids

One proposed mechanism for risk of hypertension and CVD is fetal exposure to excess glucocorticoids. This can occur as increased exposure in-utero or as synthetic glucocorticoids such as those used in the neonatal intensive care unit. Glucocorticoids are important regulators of fetal growth, and several studies have linked glucocorticoid exposure to altered development of the growing human fetus. In addition, elevated glucocorticoid levels have been associated with increased blood pressure.¹⁷ In rat studies, it has been shown that the administration of dexamethasone in-utero not only resulted in decreased fetal weight, but was also associated with the development of elevated blood pressure and glucose intolerance in adulthood. These studies were validated in a sheep model years later.¹⁸

This effect is best explained by permanent changes in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis after birth. The increased intrauterine exposure to glucocorticoids leads to a decrease in the number of cortisol receptors formed during the development of the hypothalamus. This decrease in receptor number impairs the negative feedback loop and therefore leads to an increase in serum level of cortisol later in life. This increased state of cortisol contributes to the increases in blood pressure and glucose intolerance observed in adulthood.¹⁹

In studies of the placenta, infants of mothers with lower placental 11beta-hydroxysteroid dehydrogenase type II (11beta HSD-2)—an enzyme that contributes to inactivation of cortisol in the placenta—also demonstrated an increase in glucose intolerance

and increased blood pressure in adulthood.¹⁹ A possible explanation for the aforementioned decrease in placental 11beta HSD-2 is maternal dietary restriction. With maternal malnutrition and a fasting state, there is an increase in glucocorticoid secretion

Elevated glucocorticoid levels have been associated with increased blood pressure.

and decrease in placental 11beta HSD-2. This decrease in enzyme occurs as a means of conserving as much cortisol as possible. In this, the fetal HPA axis function is affected and similarly contributes to the down-regulation of fetal cortisol receptors in the developing hypothalamus.

One notable use of glucocorticoids during pregnancy is the administration of betamethasone. During pregnancy, if a mother is at risk for delivering prematurely, a course of betamethasone may be administered to assist in fetal lung maturation. This course should not be withheld as the effect of such a dose has not been shown to contribute to an increase in blood pressure, decrease in birth weight, or affect plasma cortisol levels.²⁰ Although the effects of this short course of steroids in adult life have not been well studied, the benefits betamethasone provides to the maturing fetal lung far outweigh the detriments of a single course and its possible contribution to adult disease.

POSTNATAL FACTORS

Hyperoxia and Hypoxia in Premature Infants with Chronic Lung Disease

There is a relative paucity of data on the long-term effects of postnatal

environmental exposures in premature infants on long-term health outcomes. However, it is well known that premature infants are at high risk for exposure to frequent hypoxic and hyperoxic events via several different mechanisms. First, they have immature lungs and surfactant deficiency, leading to subsequent respiratory distress and the development of chronic lung disease. The premature delivery of a fetus during the late canalicular or saccular stages of lung development also leads to immature alveolar structures that function poorly in gas exchange. Second, fetal oxygen supply can be greatly influenced by multiple factors including maternal oxygen supply, uterine blood flow, and placental sufficiency.²¹ These maternal factors can include conditions like obstructive sleep apnea, tobacco use, or diabetes, all of which decrease maternal oxygen supply or prevent effective vascularization of the uterus or placenta. This can create an abnormal hypoxic environment for the fetus, which can contribute to compromise of the alveolar, airway, or pulmonary vascular development. Lastly, infants born prematurely are at risk for apnea of prematurity, which results in hypoxic events postnatally. The administration of increased supplemental oxygen to treat hypoxic episodes often times results in intermittent alternating hyperoxia.

Several groups have demonstrated that recurrent postnatal hypoxia affects cardiovascular regulation, and those disruptions in normal calcium channel functioning, the renin-angiotensin system, and the generation of ROS may be mechanistically involved in the development of cardiovascular disease.^{22,23} A study²⁴ using a mouse model of postnatal chronic intermittent hypoxia demonstrated persistent elevated systolic blood pressure, impaired baroreflex, decreased heart

rate variability in association with increased generation of ROS, alteration of the renin-angiotensin system, and changes in DNA methylation of key enzymes acting in the RAS.²⁴ These studies suggest that for a premature infant, postnatal exposures may be as important as prenatal environment for the programming of cardiovascular disease. There is a desperate need for more research in this area to identify modifiable exposures in neonatal intensive care to optimize long-term outcomes in these patients.

Postnatal Growth

Postnatal nutrition and early growth patterns are known to affect risk for adult-onset hypertension in ex-premature infants.²⁵ For example, breast-fed preterm infants compared to formula-fed infants demonstrate lower blood pressures in adolescence.²⁶ There is a contradictory body of evidence as to how postnatal growth attrition affects risk of hypertension. Bonamy et al.³ found an association between lower blood pressure at age 2.5 years and normalization of postnatal weight in ex-premature infants, whereas Vohr et al.²⁵ reported that higher weight gain in the first 3 years of life predicted higher blood pressure at age 16 years. These findings suggest that there is a delicate balance between the benefits of postnatal growth on the developing brain, and the risks of too-rapid weight accumulation. It is likely that in ex-premature infants, rapid weight gain in infancy that exceeds relative growth in length may be disadvantageous and increase risk of cardiovascular disease.²⁷

Epigenetic Modification

Although these studies^{3,13-15,25,26} seem to conclusively demonstrate that premature infants are at increased risk for cardiovascular disease, and present a number of plausible possibilities

of systems that may be involved in the developmental programming of disease, the mechanisms underlying how perinatal exposures lead to later disease are still unclear. Epigenetic modification is understood to be the

Breast-fed preterm infants compared to formula-fed infants demonstrate lower blood pressures in adolescence.

molecular basis for developmental programming, and explains how gene expression can be modified in a heritable manner, outside of altering the genetic code. Epigenetic modification is achieved by various mechanisms, including DNA methylation, histone modification, and via noncoding microRNAs. Over the lifetime, epigenetic DNA imprinting activity is most active during the perinatal period, implying that exposures in the fetal environment and postnatal period potentially have huge effects on gene expression. Several studies have demonstrated evidence of epigenetic modification in important metabolic, renal, endocrine, and vascular pathways in response to altered fetal and postnatal environment. It is essential to continue to uncover the epigenetic regulation of these pathways because it may unveil biomarkers for disease as well as therapeutic targets to reduce the burden of cardiovascular disease seen in ex-premature infants.^{28,29}

CONCLUSIONS

Premature infants are at increased risk for the development of hypertension and cardiovascular

disease in adulthood. There are several organ systems and physiologic pathways involved in the developmental programming of cardiovascular disease, including the vascular system, the kidney, and the neuroendocrine system. Although premature delivery in and of itself abruptly disrupts the normal development of these systems, there are also several prenatal factors that may lead to alterations of these systems, including maternal nutrition status, placental insufficiency, or exposure to glucocorticoids. For a premature infant, there is evidence to suggest that postnatal exposures such as chronic intermittent hypoxia/hyperoxia and steroid exposure may also contribute to the developmental programming of disease. The study of epigenetics is critical in this field, as it serves as a mechanism by which humans can adapt to adverse environmental exposures in the perinatal period, but can be unmasked as disease later in life. As prematurity affects up to 12% of births in the United States, ex-premature infants represent a significant portion of the population. Whereas the short-term costs of caring for premature infants is enormous, estimated at over \$26 billion in 2005, the long-term costs related to increased risk for adult disease is unknown and likely substantially larger. As the direct and indirect costs of hypertension and heart disease in the US in 2011 were reported to be over \$250 billion, and projected to increase over the next 15 years, ex-premature infants who may represent up to 10% of this adult population likely contribute significantly to these costs.³⁰ Therefore, the study of and development of intervention strategies to mitigate the risk for cardiovascular disease in ex-premature infants are of paramount importance, not only for an individual patient, but also from a public health perspective.

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