Brief Review

Preterm Birth and Hypertension Risk

The Oxidative Stress Paradigm

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Preterm Birth

The majority of epidemiological studies in developmental programming have explored the influence of low birth weight (irrespective of gestational age) on long-term chronic disease in individuals born during the first half of the 20th century. Low birth weight neonates may represent infants born at term with intrauterine growth restriction (IUGR) or born preterm with or without IUGR. As such, there is emerging interest in the effects of preterm birth alone (beyond birth weight and IUGR) on specific aspects of human development and long-term health.

Approximately 10% of all births worldwide are preterm (before 37 completed weeks of gestation). Besides being of low birth weight, preterm neonates are suddenly and prematurely exposed to the extruterine environment at a time when organogenesis is incomplete. Exposure postnatally to factors such as high oxygen concentrations, medications (including glucocorticoids), and inadequate nutrition likely adversely influence postnatal growth and ongoing organ development. In addition to possible genetic and epigenetic factors that may contribute to hypertension risk (including hypertension-related complications of pregnancy), a multitude of aspects related to both intrauterine and extraterine growth, as well as the postnatal environment, may all play an important role in the programming of hypertension in individuals born preterm. In this review, we will highlight, in particular, the potential effect of oxidative stress associated with preterm birth on neonatal development and future disease risk.

Evidence From Epidemiological Studies: Preterm Birth and an Increased Risk of Developing Hypertension

The survival of neonates born at low and very low gestational ages is recent in the history of medicine and has increased remarkably over the last few decades. The first generations of survivors of very preterm birth are currently just reaching adulthood and as such are providing emerging evidence of chronic health conditions, such as hypertension. The link between preterm birth and hypertension risk (independent of birth weight) has been clearly demonstrated in a number of epidemiological studies. A significant inverse correlation between systolic blood pressure and gestational age at birth has been consistently observed from childhood to adulthood in preterm-born individuals; in particular, a recent meta-analysis demonstrated that systolic blood pressure in preterm-born children and young adults was an average of 2.5 mm Hg (95% confidence interval, 2.6–5.0 mm Hg) higher than those born at term. We have also recently shown in a population-based study in Quebec, Canada, that women born preterm, particularly if birth occurred <32 weeks gestation, had an increased risk (independent of birth weight) of pregnancy complications (including gestational diabetes mellitus, gestational hypertension, and preeclampsia), as well as chronic hypertension compared with women born at term.

It is to be noted, however, that many studies have not taken into account the effect of other confounding factors, such as chronic lung disease, that have effect on exercise capacity and thus cardiovascular health.

Possible Contributors to Increased Hypertension Risk in Neonates Born Preterm

The increased risk of hypertension evidenced in neonates born preterm is likely to be multifactorial in origin, with preterm birth resulting in alterations to cardiac, renal, and vascular development/function, as well as neural pathways.

Vascular

Preterm birth may disrupt or even prematurely arrest proper development of the vascular tree, resulting in stiffer arteries, a restricted vascular bed, and relatively narrowed blood vessels, all predisposing to endothelial dysfunction and arterial hypertension. Preterm birth often results from an abnormal pregnancy, with conditions such as preterm premature rupture of membranes, uteroplacental insufficiency, and preeclampsia being major causes of medically induced preterm birth. Therefore, it is to be noted that impairments to vascular system development may initially occur before preterm birth via IUGR and exposure to an inflammatory and antiangiogenic environment.

In humans, elastin synthesis in arterial walls peaks toward the end of gestation (near term) and then declines very rapidly after birth. Arterial distensibility and elasticity depend largely on the ratio of elastin to the more rigid collagen in...
arterial walls; therefore, a disruption to elastin synthesis at the end of gestation (such as in the event of preterm birth) may have long-term consequences. To date, studies have reported increased aortic stiffness in children as early as 7 to 14 years of age that were born moderately or very preterm. In addition, adolescents and young adults born preterm were found to have smaller aortic, carotid, and brachial artery luminal diameters compared with controls born at term, as aortic growth was shown to be impaired from the early neonatal period after preterm birth. Furthermore, in a sheep model of moderate preterm birth, evidence of vascular injury to the ascending aorta was observed in animals examined at 11 weeks postnatal age. Carotid intima-media thickness, an early marker of atherosclerosis and nonatherosclerotic remodeling, has also been shown to be increased in relation to lumen diameter.

The effect of preterm birth on microvascular development has also been highlighted by studies showing reduced retinal vascular caliber and density (independently of retinopathy of prematurity), as well as reduced cutaneous capillary density in children and young adults born very preterm. To date, studies assessing endothelial function have shown either no effect or diminished brachial artery flow-mediated dilatation in children and young adults born preterm; whether changes will be apparent later in adult life remain to be evaluated.

Cardiac

During maturation of the heart, fetal cardiomyocytes undergo both hyperplasia and hypertrophy; in humans, cardiomyocytes proliferate actively until 36-week gestation after which maturation, differentiation, and growth by hypertrophy take place. Although hypertension would not be caused by changes in cardiac structure and function after preterm birth per se, the heart of preterm-born neonates may be particularly susceptible to the effect of elevated blood pressure and associated risk factors for heart disease.

Preterm birth has been described to result in cardiac dysfunction that can be detected in infants at a very early age. In preterm infants, a progressive increase of left ventricular dimensions was reported in the first month of life, as well as discreet left ventricular systolic and diastolic dysfunction at the same age. Later in life, preterm-born children at 5 years of age exhibited increased interventricular septum thickness and smaller left ventricular cavity diameters compared with those born at term, which is indicative of premature cardiac hypertrophy. Altered cardiac shape, primarily characterized by increased left ventricular mass (with shorter left ventricles and smaller internal diameters), has also been observed in 20- to 39-year-old adults born preterm. These cardiac shape alterations were accompanied by impaired systolic and diastolic functions. A strong inverse correlation between gestational age and increased left ventricular mass was further observed in this study, suggesting causality. Findings relating preterm birth to altered heart development are supported by mechanistic studies in animal models. Bensley et al recently showed in a sheep model that moderate preterm birth resulted in cardiomyocyte hypertrophy and altered maturation (evidenced by an increased number of bi- and trinucleated cardiomyocytes and increased nuclear ploidy), as well as increased myocardial interstitial fibrosis by 11 weeks postnatal age.

Renal

Nephrogenesis (the formation of nephrons in the kidney) occurs largely in the second half of pregnancy. Although nephrogenesis continues postnatally after preterm birth, the process is likely disrupted. Nephron number is an important indicator of renal functional capacity, with impaired renal development (reduced nephron endowment), as well as later nephron loss, strongly correlated with the development of high blood pressure.

Whether preterm birth results in a reduced nephron endowment has to date only been investigated in animal models. In a mouse model of preterm birth (animals delivered at a relatively early stage of nephrogenesis), nephron number was significantly decreased. Additionally, these animals exhibited high blood pressure, low glomerular filtration rate, and albuminuria at 5 weeks of age. In comparison, Gubhaju et al showed that nephron number in preterm-born baboons (delivered at a timepoint equivalent to 27-week gestation in humans) was within normal range. However, nephron density was significantly reduced in the preterm kidneys, and a large proportion of newly formed glomeruli in the outer renal cortex was morphologically abnormal, with a shrunken glomerular capillary tuft. Importantly, these undervascularized (potentially atubular) glomeruli were also observed in human neonatal kidneys after preterm birth. In addition, the kidneys of human preterm neonates had a significantly reduced nephrogenic zone width, along with more generations of mature glomeruli compared with age-matched fetal controls; together, these findings suggest that renal maturation is accelerated postnatally and is possibly indicative of an early cessation to nephrogenesis. It is certainly conceivable that these alterations in the neonatal kidney (accelerated maturation and the potential early loss of abnormal glomeruli) would result in a diminished endowment of functional nephrons at the beginning of life.

Renin–Angiotensin System

Another critical regulator of systemic blood pressure is the renin–angiotensin system (RAS). The RAS is activated to increase glomerular filtration rate in the presence of oligonephria and contributes to the increase in, and maintenance of, high blood pressure. In genetic hypertension, RAS activity is a key factor underlying vascular dysfunction, vasoconstriction, and vascular rigidity; in the heart, myocardial hypertrophy, fibrosis, and inflammation also result from angiotensin II and its receptor type 1 activation. Importantly, alterations to the RAS have been evidenced in a number of animal models of hypertension programming. In preterm neonates, the urinary angiotensin-converting enzyme activity is increased compared with infants born at term, with a significant inverse association between angiotensin-converting enzyme activity and both gestational and postnatal age. However, very few studies have been conducted in this area, and further research is undoubtedly required to understand the potential role of the RAS in the programming of high blood pressure after preterm birth.
Sympathetic Nerve Activity

During the third trimester of gestation, the efferent sympathetic nervous system continues to mature.69 Sympathetic nerve activity contributes to blood pressure maintenance, to the elevation in blood pressure in situations of overactivation (or impaired counterregulatory mechanisms) in many forms of chronic hypertension, and after deleterious perinatal conditions (such as IUGR) in both humans and experimental models.61–63 Sympathetic nerve activity can also be activated by chronic inflammation (including through inflammatory cytokines secreted by adipose tissue) and increased expression of the RAS.64 In infants born preterm, the sympathetic system is overactivated, and parasympathetic nervous system tone is deficient.65 Although there is a probable role for sympathetic activation in the programming of hypertension in preterm-born children and adults, it has not yet been fully established.

The Oxidative Stress Paradigm

Important factors that may underlie the early life origin of hypertension susceptibility are hyperoxia exposure and oxidative stress. Infants are exposed upon birth to relatively high concentrations of oxygen (O2) compared with intrauterine life. Indeed, under physiological conditions, blood oxygen saturations (such as IUGR) in both humans and experimental models elicit a burst of free radicals, known as reactive oxygen species.68,69 The preterm infant is also exposed to a number of pro-oxidant molecules from parenteral nutrition, medications, plastic derivatives, and x-ray imaging, in addition to supplemental oxygen.70–72 However, neonates born preterm have an immature antioxidant defense system: virtually all research has demonstrated lower levels of antioxidant enzymes and reduced induction capacity thereof,73,74 as well as significantly increased indices of oxidative stress in preterm newborns.75–78 In the setting of organ development, significantly reduced cellular proliferation and increased apoptosis (via lipid peroxidation, protein aggregation, and DNA damage) because of the activity of reactive oxygen species may be particularly injurious.80

Besides an increase in reactive oxygen species, exposure to high oxygen concentrations after birth may also alter oxygen-sensing pathways in the preterm neonates. In the presence of oxygen, the transcription factor hypoxia-inducible factor 1 (HIF-1) is hydroxylated, which triggers its rapid proteosomal degradation. HIF-1 is known to regulate the expression of a multitude of genes involved in cellular proliferation, angiogenesis, and apoptosis.81 In HIF-1 knockout animal models, embryos are arrested mid development with significant cardiovascular defects.82 Therefore, it is possible that reduced HIF-1 expression after oxygen exposure may have adverse consequences for ongoing postnatal development in the preterm neonates. As such, it is undoubtedly important to determine the effect of early life exposure to hyperoxia and oxidative stress on organ and vascular development, which may contribute to vascular dysfunction and hypertension later in life.

Vascular Development and Rarefaction

Endothelial progenitor cells differentiate into endothelial cells during the process of vasculogenesis and also function to replace mature cells in the case of vascular injury.83 Preterm neonates have higher levels of endothelial progenitor cells than term infants, which is indicative of a greater capacity for vasculogenesis; however, the endothelial progenitor cells of preterm infants were found to have a heightened susceptibility to hyperoxia exposure, evidenced by reduced proliferation and increased cell death.84,85 In 1 animal study, neonatal mice exposed to 10 days of hyperoxia had lower endothelial progenitor cell numbers and decreased vessel density in the lung.86

In immature newborns, exposure to supplemental O2 halts microvessel growth, particularly in the lung and retina.4 This impaired microvascular development can be traced to significant reductions in vascular endothelial growth factor expression7; vascular endothelial growth factor expression is likely reduced because of lowered HIF-1 signaling of vascular endothelial growth factor transcription in the oxygen-rich extrauterine environment.81 In this regard, we have previously shown that neonatal hyperoxia exposure was associated with significantly reduced microvascular density (rarefaction) in the skeletal muscle of adult rats.88 In addition, animals exposed to hyperoxia as neonates exhibited increased vascular superoxide anion production and decreased NO production (linked to eNOS uncoupling), impaired endothelium-mediated vasodilation, and elevated blood pressure from 7 weeks of age.88,89 This finding of increased blood pressure subsequent to a hyperoxic insult during development is strongly indicative that high oxygen levels may play an important role in the programming of hypertension after preterm birth.

Renal and Cardiac Development

Findings from organ explant studies have indicated that low oxygen concentrations are required for correct renal90 and cardiac91 development. In addition, we have recently shown in a rat model that hyperoxic gas exposure (80% O2) in the early neonatal period (postnatal days 3–10, during the period of ongoing postnatal nephrogenesis in the rat) is associated with a 25% reduction in nephron number in adulthood.88 In contrast, however, exposure to 65% O2 from postnatal days 1 to 7 in a mouse model did not lead to any significant alterations in renal development or nephron number.92 A study on heart development found that in combination with maternal inflammation during gestation (commonly linked to preterm birth), postnatal hyperoxia exposure (85% O2 from postnatal days 1 to 14) was associated with both structural remodeling and dysfunction of the left ventricle.93 Certainly further studies are required to investigate completely the effect of hyperoxia exposure alone on renal and cardiac development.

Vascular Aging

In humans, as in animal models of developmental programming, individuals are not born with hypertension but undergo an age-dependant premature increase in blood pressure.88,94 Aging is a process characterized by the accumulation of oxidant-related damage,95 resulting in structural and
functional changes to the vasculature, including increased vascular stiffness (increased collagen and decreased elastin), reduced compliance, endothelial dysfunction, decreased NO bioavailability, increased reactive oxygen species production, increased vasoconstrictive tone,96 and impaired vascular repair capacity.97 As discussed above, preterm birth is associated with a number of these vascular consequences; therefore, it is possible that they are mediated by accelerated cellular aging triggered by an oxidative insult in early development.

Like other mitotic cells, vascular cells may undergo replicative senescence driven by telomere shortening or stress-induced premature senescence.98,99 Senescent vascular cells have decreased proliferative and angiogenic capacity. Importantly, oxidative stress has been linked to accelerated telomere shortening, DNA damage, senescence of endothelial and vascular smooth muscle cells, and atherosclerosis.99–101 Telomere length has been shown to be similar in low birth weight versus control infants assessed at birth102; however, another study demonstrated that telomere length was decreased in 5-year olds that were born with low birth weight,103 which together suggests accelerated attrition. To our knowledge, the effect of preterm birth on telomere shortening, however, has not been reported.

Inflammation

Preterm birth reflects intrauterine disturbances that are often inherently pro-oxidant and proinflammatory in nature, conditions such as preeclampsia, maternal diabetes mellitus, and obesity, infection, and preterm premature rupture of membranes all lead to increased inflammation markers in both mother and newborn, including those born preterm.104

Inflammatory and oxidative pathways are intimately associated, with reciprocal and synergistic activation in response to intrauterine or neonatal stress.104 Both human and animal studies have provided evidence that an oxidative insult in the fetal/neonatal period can have long-term consequences on redox equilibrium and inflammation. In particular, children (4–13 years of age) born IUGR or to mothers with diabetes mellitus were shown to have demonstrable increases in markers of oxidative stress, lipid peroxidation, and inflammation.106–108 In experimental studies, inflammatory challenges given periconception, midgestation and in the neonatal period led to increased visceral fat and metabolic syndrome in mice offspring in adulthood.44–46 Furthermore, adult guinea pigs that were administered parenteral nutrition (a contributor to oxidative stress) as pups exhibited dyslipidemia, glucose intolerance, and energy deficiency.70 In adult rats exposed to hyperoxic stress as neonates, increased vascular superoxide production has been observed.90 We have also shown that antioxidant supplementation in dams fed a low-protein diet prevents low glutathione levels, hypertension, and vascular dysfunction in the offspring.109 These observations are particularly important considering that an oxidized redox state, oxidative stress, and low-grade inflammation all contribute to the pathogenesis of chronic disorders, such as hypertension, cardiovascular and kidney diseases, and type 2 diabetes mellitus100,111; in this way, it is possible that these processes may enhance significantly the risk of chronic disease in neonates born preterm.

Conclusions

Emerging epidemiological and experimental findings have increasingly demonstrated that preterm birth is a key risk factor for the development of hypertension. Through the evidence reviewed here, we propose that underlying this risk may be exposure to hyperoxia and oxidative stress in the early neonatal period; at birth, all preterm neonates are prematurely exposed to oxygen concentrations markedly higher than those in the intrauterine environment, and this may have important consequences for ongoing postnatal development. Preterm infants are particularly susceptible to the damaging effect of oxidative stress because of an immature antioxidant system at birth. In a rodent model, we have shown that neonatal hyperoxia exposure leads to vascular dysfunction, hypertension, microvascular rarefaction, and reduced nephron number. To date, however, very few studies have been conducted to investigate the effects of oxygen exposure alone on cardiovascular development and hypertension risk. In the future, further research designed to delineate clearly the mechanisms involved and also to determine clinically which infants are at the highest risk for the later development of hypertension is essential. The overall goal of this research should be focused toward the future introduction of strategies to the clinical care of preterm neonates to prevent any adverse long-term consequences, such as through the enhancement of vasculogenesis and cardiac/renal development postnatally. In the meantime, there is also a need for increased awareness among pediatricians and general practitioners on the heightened risk of adult-onset cardiovascular disease in neonates born preterm.

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Disclosures

None.

References

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Y. Respective roles of preterm birth and fetal growth restriction in
IB, Cockcroft JR, Marlow N. Cardiovascular consequences of extreme
J Pathol
Berry CL, Look in pathogenesis of systemic hypertension.
and large conduit arteries during early development as an initiating event
Martyn
Pediatrics
Semin Perinatol
a focus on vascular factors.
2010;34:188–192.
Intapad S, Poplawski A, Simeoni U. Low
corticosteroids for preventing chronic lung disease in preterm infants.
Cochrane Database Syst Rev
Circulation
Risk of high blood pressure among young men increases with the degree
Hack M, Schluchter M, Cartar L, Rahman M. Blood pressure among very
Lawlor DA, Hildebrand A, Tynelius P, Leon DA, Smith GD, Rasmussen F
Associations of gestational age and intrauterine growth with systolic
blood pressure in a family-based study of 386,485 men in 331,089
Stevenson CJ, West CR, Pharoah PO. Dermatoglyphic patterns, very low
birth weight, and blood pressure in adolescence. Arch Dis Child Fetal
Johansson S, Iliadou A, Jokela M, Voutilainen S, Kivimäki M, Virtanen MJ,
Kistner A, Jacobson L, Jacobson SB, Svensson E, Hellstrom A. Low
Kozák-Báránky A, Jokinen E, Saraste M, Tuominen J, Välimäki I.
Development of left ventricular systolic and diastolic function in preterm
Zecca E, Romagnoli C, Vento G, De Carolis MP, De Rosa G, Tortorolo G.
nance reveals distinct differences in left ventricular mass, geometry, and
Bensley JG, Stacy VK, De Matteo R, Harding R, Black MJ. Cardiac remodeling as a result of preterm birth: implications for future cardio-
Hinchliffe SA, Sargent PH, Howard CV, Chan YF, van Velzen D. Human
intraterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. Lab Invest. 1991;64:777–784.
A quantitative study of normal nephrogenesis in the human fetus: its
Sutherland MR, Gubhaju L, Moore L, Kent AL, Dahlström JE, Horne HS, Hoy WE, Bertram JF, Black MA. Accelerated maturation and abnor-
Hoy WE, Bertram JF, Denton RD, Zimanji M, Samuel T, Hughson MD.
Apremacin in premature infants leads to reduction in nephron number, hypertension, and proteinuria. Transf Res. 2012;159:80–89.


63. Sutherland et al. Preterm Birth and Hypertension 17


84. Hoenig MR, Bianchi C, Rosenweig A, Sellke FW. Decreased vascular repair and neovascularization with ageing: mechanisms and clinical


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