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Recent Advances in Antenatal Factors Predisposing to Bronchopulmonary Dysplasia

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Abstract

Bronchopulmonary dysplasia (BPD) remains a major cause of late morbidities and death after preterm birth. BPD is characterized by an arrest of vascular and alveolar growth and high risk for pulmonary hypertension; yet mechanisms contributing to its pathogenesis and early strategies to prevent BPD are poorly understood. Strong epidemiologic studies have shown that the “new BPD” reflects the long-lasting impact of antenatal factors on lung development, partly due to placental dysfunction, as reflected in recent data from animal models. Improved understanding of mechanisms through which antenatal stress alters placental function and contributes to BPD may lead to preventive therapies.

Introduction

Despite striking improvements in perinatal care and diverse neonatal outcomes related to premature birth, preterm children remain at high risk for significant respiratory morbidities and mortality due to the development of bronchopulmonary dysplasia (BPD),¹ Figure 1. BPD is the chronic lung disease of prematurity that develops in infants who require respiratory support at birth due to immaturity of the preterm lung.² BPD is the most

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common sequel of prematurity, occurring in roughly 45% of infants born at or less than 29 weeks gestation with birth weights, with approximately 10 – 15,000 new cases of BPD in the USA alone each year.^{1,3,4} Importantly, the incidence of BPD has not changed over the past few decades, likely reflecting improved survival of extremely low gestational age newborns (ELGANS) who are at the highest risk for developing moderate and severe BPD.⁵ BPD is also associated with significant neonatal intensive care unit (NICU)-related complications, including the prolonged need for mechanical ventilation, respiratory support and oxygen therapy, longer duration of hospitalization and higher rates of non-respiratory co-morbidities, such as retinopathy of prematurity (ROP) and brain injury.^{5,6} Pathogenetic mechanisms linking lung, brain, retinal, renal and other systemic complications of preterm birth remain under intense investigation, but these diseases potentially share common origins related to the effects of adverse antenatal factors, as discussed below.

After NICU discharge, infants with BPD often require frequent hospital re-admissions and have high rates of emergency room or physician visits due to recurrent respiratory exacerbations, lower respiratory tract infections, reactive airways disease and pulmonary hypertension. Sustained abnormalities of lung function, poor exercise tolerance and the need for chronic respiratory medications throughout childhood and adolescence are also increased in former preterm infants.^{7,8} Past studies have shown that over 50% of preterm infants subsequently require re-hospitalizations or chronic respiratory medications after NICU discharge, including preterm infants without a formal diagnosis of BPD.⁸ Controversies persist regarding how to best define BPD and whether bearing this diagnosis at 36 weeks post-menstrual age (PMA) adequately reflects the late risk for lung disease during childhood and into adult life.^{9–11}

Although postnatal factors, such as hyperoxia, mechanical ventilation, prolonged patency of the ductus arteriosus, sepsis, inflammation and others, increase the risk for BPD, epidemiologic studies have further identified important roles for antenatal factors as well.^{12–19} Adverse antenatal factors, such as chorioamnionitis, preeclampsia (PE), pre-existing hypertensive disorders, gestational diabetes, maternal obesity, and others have been strongly associated with an increased risk for BPD.^{18–20}

An NHLBI-sponsored workshop discussed the importance of prenatal and early postnatal influences on lung growth and development on subsequent respiratory function and disease throughout childhood.¹¹ This workshop further highlighted major gaps in our understanding of how environmental and maternal factors can impact late respiratory outcomes during early childhood, and that the exact relationships between prenatal exposures and early postnatal events on the subsequent development of late respiratory disease during infancy, especially after preterm birth, remain uncertain. As studies have shown that preterm birth alone is associated with late respiratory disease in childhood, links between the diagnosis of BPD at 36 weeks corrected age and persistent chronic lung disease during infancy and beyond remains unclear. This issue of disease definition and identifying critical respiratory outcomes has become especially important in order to better understand the diverse physiology phenotypes of BPD, to enhance clinical research regarding disease pathogenesis, and to define study endpoints to enhance interventional clinical trials.²¹

Importantly, recent prospective cohort studies of very preterm infants have identified antenatal and early neonatal characteristics as strong predictors of both BPD and late respiratory disease during infancy and early childhood,^{22–27} suggesting that the fetal environment has a critical influence on the development of persistent lung disease in former preterm newborns. This review provides a brief overview on clinical, epidemiologic and laboratory-based data that support various mechanisms of perturbed lung and vascular development related to this environment, resulting in a neonatal lung with arrested development, altered vulnerability to postnatal injury, and an inadequate capacity for repair and regeneration.

Antenatal factors and BPD susceptibility: Epidemiologic Studies

Past studies have identified several characteristics that are associated with a higher incidence of BPD, including lower GA, male gender and white race. Postnatal events have long been associated with an increased risk for BPD and poor outcomes, including the severity of acute respiratory distress syndrome (RDS) at birth, prolonged exposure to high inspired oxygen tensions and mechanical ventilator support, lung inflammation, air leaks or pulmonary interstitial emphysema, pulmonary hypertension, systemic and pulmonary infections, prolonged exposure to a patent ductus arteriosus, and either specific or global nutritional deficits.

Although the pathogenesis of BPD and its severity is impacted by the adverse effects of these postnatal exposures, strong experimental and clinical data show that antenatal events are key contributors to BPD risk.^{9,11} In fact, prenatal insults may be sufficient to cause sustained disruption of lung development, leading to abnormal lung structure in the absence of additional postnatal stress. Alternatively, interactions between antenatal stress may alter susceptibility to critical postnatal factors, thereby impacting risk for BPD.

One of the strongest clinical markers reflecting the high importance of fetal events in the pathobiology of BPD is demonstrated by studies of the preterm infant with intrauterine growth restriction (IUGR).^{22–25} An observational study from the UK demonstrated a roughly 2-fold increase in early (28 days) and late mortality (36 weeks PMA) and the risk for BPD in small for GA (SGA) infants born at or below 32 weeks gestation. Perhaps even more important than the presence or absence of BPD at 36 weeks, preterm infants who were born with IUGR remain at high risk for late respiratory morbidities and lung function at school age.^{22–25} When studied at a mean age of 11 years, children who were born prematurely with IUGR had lower lung function, including forced expiratory volume in one second (FEV₁) and diffusion capacity for carbon monoxide (DLCO), suggesting abnormal airway function and decreased lung surface area, when compared with non-IUGR prematurely-born children. Cardio-respiratory abnormalities persisted despite recovery of somatic growth and the impact of IUGR was independent of BPD or prematurity alone.²⁴

The outcome of BPD at 36 weeks' PMA has been evaluated in several different cohorts in relationship to fetal growth in very preterm infants (as assessed by birth weight standardized for GA and analyzed by continuous or categorical measures of fetal growth restriction). The ELGAN investigators evaluated maternal, neonatal and placental characteristics, and

delivery indication, and showed that decreased fetal growth independently increased the odds of BPD.²² While lower GA remained an important predictor of BPD, pre-eclampsia lost its significance in this analysis, although “fetal indications” for delivery remained an independent predictor. After classifying preterm infants into similar categories by delivery indication (preterm labor versus vascular disease), Durrmeyer and colleagues evaluated associations between neonatal characteristics and severity of placental inflammation and BPD.²⁸ While lower GA was the only factor significantly associated with BPD in multivariate analysis among those infants in the preterm labor group, severe growth restriction was the only factor that remained significant among infants in the vascular disease group. Two other cohorts that analyzed the association of antenatal and birth characteristics and BPD found that lower GA was an important predictor of BPD, but decreasing birth weight z-score, a history of pre-eclampsia and clinical chorioamnionitis were variably associated with increased odds of BPD.^{18,27}

In a separate cohort of extremely low GA newborns < 29 weeks' GA at birth, Keller and colleagues demonstrated that IUGR (birth weight < 10th percentile) was associated with increased odds of persistent respiratory morbidity assessed at 1-year corrected age.²⁶ Interestingly, each of these studies used different fetal reference growth curves to standardize fetal growth, strengthening the epidemiological relationship between impaired growth due to an adverse fetal environment and poor respiratory outcomes, including BPD.

Two recent prospective multi-center cohort studies further examined the role of antenatal determinants and perinatal factors on the risk for not only developing BPD as defined at 36 weeks PMA but also examined factors associated with the development of late respiratory disease during early childhood.^{26,27} Importantly, these studies each noted that perinatal factors identified on the first day of life were strongly associated with BPD risk, especially maternal smoking, SGA status, degree of prematurity and others (Table 1; Figure 2). In addition, data modeling revealed that these antenatal determinants were at least as strong as the presence of BPD at 36 weeks in predicting late respiratory disease during infancy,^{26,27} and that the addition of BPD status to these models did not further strengthen this association.

Abnormal placental structure and function and the risk of BPD

Observations linking antenatal stress with poor respiratory outcomes in preterm infants implicate the critical role of altered placental structure and function in BPD pathobiology. Placental structural abnormalities related to IUGR and PE are strongly associated with fetal growth restriction and examination of placental tissue for vascular lesions after preterm birth may provide an additional approach to predict of the subsequent risk for BPD.²⁹ Preclinical data from experimental models of severe IUGR that markedly impact placental function and structure can decrease fetal lung airspace and vascular growth in the late gestation fetus,³⁰ which may persist throughout postnatal life. Recent experimental studies have demonstrated an impaired angiogenic and growth properties of endothelial cells derived from human IUGR placentas, which may relate to decreased aryl hydrocarbon receptor nuclear translocator (ARNT) expression.³¹

Additional studies have strongly linked histologic placental abnormalities that are consistent with patterns of “maternal under-perfusion” with preterm infants with IUGR and high risk for the development of BPD and BPD with pulmonary hypertension^{32,33} (Table 2). Cord blood biomarkers, including decreased vascular endothelial growth factor (VEGF) and soluble VEGF antagonist fms-like tyrosine kinase-1 (sFLT-1) levels, were strongly associated with IUGR and predictive of BPD in preterm infants,³⁴ suggesting that these circulating proteins may serve as effective biomarkers for predicting later neonatal morbidities associated with IUGR, including BPD. In addition, hypertensive disorders of pregnancy, especially PE, have been strongly associated with high risk for BPD after preterm birth.^{18,27} In a cohort study of 107 infants born < 32 weeks, the risk for BPD was dramatically increased in the presence of PE (OR, 18.7; 95% CI, 2.44 – 145; $p < 0.005$), even after accounting for IUGR.¹⁸

The Placenta and Neonatal Disease

The placenta is a major contributor to changes in the intrauterine environment that can lead to fetal and neonatal pathologies. The placenta may also serve as a direct source of early signaling for fetal disease in pregnancy, a concept that has been proposed with placental-derived signals circulating in the maternal serum such as cell free fetal DNA³⁵ and placental-shed extracellular vesicles.³⁶ This may be particularly true for the developing fetal lungs, which share some key aspects of structure and function with the placenta (Figure 3). Insights into placental development require extensive understanding of specific cell populations in the placenta that mediate intrauterine pathologies, and that these factors have the potential to directly or indirectly affect fetal lung development, especially in the setting of preterm birth. Key anatomical and pathophysiological similarities may exist between placenta and lung that reflect changes in the developing lung, and that the placenta could be a highly important adjunct organ for understanding neonatal lung biology. For example, cord blood biomarkers from preterm infants that reflect impaired angiogenesis, such as decreased VEGF signaling, are strongly linked with histologic findings of placental vascular lesions and are further associated with a high risk for BPD with pulmonary hypertension, as discussed further below.^{32–34}

Parallels between placental and fetal lung disease

The developing fetal lung has many similarities structurally and functionally with the placenta. As described above, the placenta is an organ consisting of budding epithelial structures with an underlying vascular system which creates a branching structure of increasingly smaller functional units which terminate in an exchange interface (Figure 3). This exchange interface consists of cells of epithelial lineage juxtaposed with endothelial cells interspersed with immune populations. This is a highly similar anatomical and physiologic environment to the developing fetal lung. Based on these similarities, the fetal lung and placenta may have similar responses to alterations in the intrauterine environment during pregnancy. This may be particularly true for responses to hypoxia.

Two reviews have approached this topic. First, van Patot et al proposed that studying hypoxic responses in organs such as the lung, intestine and kidney can inform studies of the

placenta, as these organs have some similar underlying vascular responses to hypoxia.³⁷ In addition, the “hypoxic placenta” may be associated with altered fetal physiology, as suggested by studies that infants from pre-eclamptic pregnancies at high altitude have elevated pulmonary artery pressures. In addition, Byrne suggested that therapies for pulmonary hypertension to lower placental vascular resistance could be trialed for treatments in PE, as based on molecular similarities in hypoxic responses between placental and pulmonary vascular networks.³⁸ However, neither review expressed the hypothesis that studies of the placenta may provide a novel adjunct research tool for understanding fetal lung disease. Thus, studies of placental physiology in normal and pathological pregnancies may define mechanisms that could lead to new insights into fetal lung disease and links between placenta and lung disease after birth.³⁹ This concept has been explored in several studies examining placental responses to hypoxia⁴⁰ and also summarized in a recent review highlighting parallels in the physiology of pulmonary hypertension and the placental vascular responses to PE.³⁸ At the molecular level, a vasoconstrictor response to hypoxia may be directed by oxygen sensing potassium channels in vascular smooth muscle cells.⁴¹ A variety of studies have demonstrated that in a hypoxic environment, oxygen sensing potassium channels have decreased activity leading to membrane depolarization, intracellular calcium influx and ultimately vasoconstriction.⁴² These channels have been well-characterized in pulmonary vasculature and more recently identified in placental vasculature as well.⁴³

There is additional evidence for similarities in the pulmonary and placental vascular networks with regard to endothelial cell responses to hypoxia. The endothelium in pulmonary and placental vascular networks have increased calcium influx in response to hypoxia.^{44,45} Increased calcium influx in endothelial cells can then lead to increased microvascular permeability with subsequent localized edema with the potential for altering the surrounding parenchyma.⁴⁶ While this response may reflect a systemic response of endothelium to hypoxia (rather than a unique aspect of these organs), it does suggest that the fetal lung and placenta may have additional similar physiological responses during pregnancy.

Thus, the combined study of placental and neonatal lung biology has many mutual benefits. First, the field of neonatal pulmonary research has many well-established *in vitro* and pre-clinical techniques, particularly with regard to the study of hypoxia, which could shed light into placental biology. Concurrently the human placenta is a uniquely accessible source of primary human tissue with still many unexplored aspects, particularly in regard to its influence on the developing fetal lung. We propose that the placenta could be a highly valuable organ in which to explore not only how its pathologies can affect fetal lung biology, but also as a novel adjunct model system for diagnostic and therapeutic targets for neonatal lung disease.

Potential Mechanisms of Placental Disease

Placental structural, cellular and humoral factors have been mechanistically implicated in neonatal lung disorders and postnatal growth, in cohort studies of preterm newborns. The mechanisms primarily implicated include 1) perturbations in vascular development and

angiogenesis, and 2) inflammation. The epidemiology of these two mechanisms as the etiology of preterm birth, and the association with adverse outcomes of preterm birth is discussed below. Placental structural and histological differences indicative of hypo-perfusion (maternal vascular under-perfusion, consisting of vascular and villous changes with necrosis and atherosclerosis, increased muscularization and mural hypertrophy, infarction, syncytial knots and villous hypoplasia) have been shown to be more common in extremely preterm infants with BPD compared to those without BPD.²⁹ Both vessel and villous changes were present more frequently in those infants with BPD complicated by pulmonary hypertension (PH, by echocardiography at 36 weeks' PMA), and villous vascularity was decreased in infants with this late PH, regardless of the diagnosis of BPD.^{29, 45}

Interestingly, resident villous endothelial cells from pregnancies characterized by abnormal placentation [fetal growth restriction, (FGR) resulting in preterm delivery], demonstrate decreased angiogenesis with impaired signaling in the VEGF pathway.³¹ As discussed above, there are parallels in development of the placenta and the lung. However, the direct relationship of placental developmental differences to fetal lung development has not been fully elucidated, although the broader effects on fetal and neonatal growth may be one factor.³⁰ Regardless, the observations regarding echocardiographic findings of late PH in preterm infants are particularly provocative, given the links between angiogenesis and alveolarization in the developing lung.^{46–48}

Additional cellular and humoral effects of this abnormal placentation should also be considered when evaluating these potential mechanisms. The placenta and umbilical cord blood contain, respectively, resident and circulating endothelial progenitor cells.⁴⁹ Both cell populations have been shown to have similar proliferative potential in term placentas, although the placental population had greater vasculogenic potential.⁴⁹ Decreased numbers of endothelial progenitor cells have been demonstrated in the cord blood of preterm newborns who develop BPD,^{50,51} cells which are also decreased in maternal diabetes and pre-eclampsia.^{52,53} Interestingly, cord blood from pregnancies with a placenta that demonstrated severe maternal vascular under-perfusion had lower levels of placental growth factor (PlGF), granulocyte-colony stimulating factor (G-CSF) and VEGF-A.³⁴ This pattern was consistent in cord blood of those infants who were later diagnosed with BPD complicated by echocardiographic findings of PH, but only the relationship with PlGF and G-CSF held up in a validation cohort. In contrast to these findings, increased placental VEGF levels were found in an analysis of protein expression from placental biopsies at birth from pregnancies affected by PE and extremely preterm delivery.⁵⁴ Additional protein expression patterns in the PE cluster (distinct from pregnancies affected by preterm labor or premature rupture of the membranes) include increased levels of P-selectin and transforming growth factor- β (TGF- β), further supporting placental vascular differences in these pregnancies.

Finally, regarding the vulnerability of the lung following pregnancies affected by placental vascular abnormalities and the lung's ability to repair following insult and injury during the neonatal hospitalization, the growth of cord blood endothelial progenitor cells from preterm pregnancies is inhibited by exposure to hyperoxia.^{51,55} Hyperoxia decreases nitric oxide (NO) production and endothelial nitric oxide synthase (eNOS) and VEGF receptor-2

(VEGFR-2) protein expression *ex vivo*, an effect that is mimicked by NOS inhibition.⁵⁵ The inhibitory growth effect of hyperoxia was mitigated by treatment with NO or VEGF (with increased eNOS expression), and antioxidant therapies.^{52,56} Fetal oxidative stress is inversely related to GA (assessed by cord 8-isoprostane levels at birth), resulting in additional vulnerability for the most preterm infants.⁵⁶ Later lung function data (3–33 months corrected age) from former preterm newborns without BPD demonstrate that alveolar volume and diffusing capacity are positively related to the pro-angiogenic potential of circulating stem cells from contemporaneous samples, supporting the long-term implications of these antenatal perturbations in angiogenesis and the consequences of neonatal care on these vulnerable newborns. Together, these data suggest that placental vascular abnormalities and the presence and function of endothelial precursor cells derived from the placenta influence both fetal lung development and infant lung and vascular growth during the neonatal hospitalization (manifested as increased susceptibility to BPD and PH), with potential for persistent impact on the dysplastic lungs as these children grow and develop.

Other factors further alter the fetal environment and impact lung development

Inflammation has long been considered key to the pathophysiology of BPD.^{1,2} However, antenatal infection and inflammation have been variably demonstrated to be a risk factor for BPD, using clinical chorioamnionitis as the marker for inflammation. Further investigations have evaluated the placenta for histologic chorioamnionitis, acute and chronic inflammation, and the fetal inflammatory response (FIR, assessed as neutrophil infiltration into fetal vessels), and have more convincingly argued that antenatal inflammation (defined by placental histology), plays a role in the later development of BPD.⁵⁷ Although placental signs of inflammation are associated with the development of BPD, investigations of early neonatal humoral inflammatory profiles fail to demonstrate consistent relationships with BPD.^{58,59} Cord blood levels of interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1) have been shown to be significantly elevated in very preterm infants who later developed BPD, although these and other relationships are influenced by the inverse correlation of these inflammatory markers with GA at birth.^{60–62} Interestingly, higher C-reactive protein levels were associated with decreased odds of BPD in former preterm newborns < 32 weeks' GA at birth.⁶² The co-occurrence of placental inflammation in the setting of maternal vascular under-perfusion also mitigates the strong anti-angiogenic relationships of abnormal placentation.^{29,34} Further, histologic chorioamnionitis is associated with lower rates of early lung disease (RDS), as some aspects of the inflammatory response may have maturational effects on the lung.⁵⁷ These variable effects of inflammation may explain the inconsistent findings regarding fetal humoral predictors of BPD in human cohort studies.

One factor closely associated with later adverse lung function in term newborns is maternal smoking, which is associated with increased levels of oxidative stress; the effects of *in utero* nicotine exposure may be mitigated by antenatal supplemental vitamin C, initiated at < 23 weeks' GA.^{63,64} In very preterm infants, maternal smoking during pregnancy is strongly

associated with both the development of BPD, and later respiratory morbidity (assessed at 1–2 years corrected age).^{26,27} In a small subset of these newborns, maternal smoking during pregnancy was associated with lower levels of Vitamin E isoforms over the first month of life, carrying increased vulnerability to pro-inflammatory and oxidant states.⁶⁵ With respect to other environmental influences on lung development, antenatal exposure to particulate matter and other environmental pollutants has been shown to have adverse effects on fetal growth and respiratory outcomes,^{66,67} preterm infants may be the most susceptible to the consequences of these exposures.⁶⁸

As suggested, the structural, cellular and humoral aspects of the placenta are closely tied to the primary underlying etiology of preterm birth, providing additional information toward understanding the antenatal underpinnings of BPD and its repercussions. The ELGAN investigators evaluated 8 proposed mutually-exclusive primary etiologies in singleton pregnancies among a prospective cohort of newborns delivered at < 28 weeks' gestation.⁶⁹ Through analysis of placental (histological and microbiological), demographic, clinical and neonatal characteristics, the investigators classified these 8 proposed etiologies of preterm birth into two distinct groups, one characterized by placental inflammation and infection and the second characterized by abnormal placentation and the consequences of those abnormalities (maternal PE, fetal growth restriction and other fetal indications). Thus, these preterm deliveries were grouped into either a “spontaneous” delivery, with an inflammatory pathophysiology (e.g., premature rupture of the membranes or preterm labor) or a distinct “indicated” delivery with a pathophysiology of placental dysfunction. Consistent with these findings, high grade maternal and fetal vascular obstructive lesions in the placenta were more likely to be associated with medically indicated preterm delivery and less likely to be associated with spontaneous preterm delivery, in a cohort study by Kelly and colleagues.⁷⁰ Similarly, Mestan and colleagues showed that the majority of pregnancies with placentas exhibiting maternal vascular underperfusion were accompanied by fetal growth failure, with 40% co-occurring with a diagnosis of pre-eclampsia.³⁴ Further data on protein expression from placental biopsies supports these relationships, with placentas from preterm pregnancies complicated by preterm labor or premature rupture of the membranes characterized by one of two inflammatory profiles, whereas those complicated by PE characterized by differences in angiogenic protein expression.⁵⁵ In addition, cord blood levels of VEGF were inversely correlated with birth weight standardized for GA in preterm newborns, while sFlt-1 had the opposite relationship.³³ Together, these data provide an important link between the epidemiology of preterm birth and respiratory outcomes among this high-risk population.

Antenatal Factors and BPD: Experimental Models

Experimentally, intra-amniotic exposure to sFlt-1, an endogenous VEGF inhibitor that is markedly elevated in the blood and amniotic fluid of women with PE, is sufficient to cause sustained abnormalities of lung structure in the offspring, including decreased alveolar and vascular growth and pulmonary hypertension, which persists throughout infancy^{71,72} (Figure 4). Importantly, antenatal sFlt-1 exposure was sufficient to impair lung development without additional postnatal injuries, such as exposure to hyperoxia or mechanical ventilation, and

may explain in part the sustained incidence of BPD despite marked improvements in respiratory therapies that minimize postnatal lung injury.⁷³

Very preterm birth is frequently associated with clinically silent fetal exposures to inflammation/infection as diagnosed by histopathology of the fetal membranes, culture, or pro inflammatory cytokines in amniotic fluid or cord blood. Other very preterm deliveries are associated with clinical chorioamnionitis, a non-specific diagnosis of limited clinical value. Inflammation associated chorioamnionitis seldom results in positive blood cultures or frank infection in the newborn, but indicators of lung inflammation prior to birth are frequent. While specific infections are seldom identified clinically, the very preterm infant can have lung abnormalities resulting from antenatal exposures that range from severe diffuse pneumonia (indistinguishable from severe RDS) to very mature lungs for GA.

Experimental studies demonstrate this extreme range of effects as well as modulation of fetal and postnatal immune responses. Thus, these antenatal exposures can promote early lung injury by decreasing lung function or decrease the risk of BPD by decreasing the severity of RDS. However, how fetal modulations of immune and inflammatory responses contribute to postnatal lung injury and the development of BPD are poorly understood. Antenatal exposure to endotoxin (e.g., *E. Coli* lipopolysaccharide, or LPS) is sufficient to cause BPD-type changes in infant rat lungs, even in the absence hyperoxia. mechanical ventilation or other postnatal injuries.^{73,74} This provides an additional model to dissect the mechanisms leading to human BPD and the potential for early, preventive interventions.

Early pulmonary vascular disease

Preclinical studies suggest that disruption of angiogenesis due to adverse antenatal factors, such as chorioamnionitis, PE or maternal smoking, and postnatal injury after preterm birth, can cause pulmonary vascular disease (PVD) that not only leads to pulmonary hypertension (PH) but can also impair distal lung growth.^{33,34} Laboratory studies have shown that the developing endothelial cell plays a key role in regulation and coordination of epithelial growth and distal airspace structure through the production of critical “angiocrines,” such as NO, hepatocyte growth factor, vitamin A, insulin growth factor-1 and others.^{11,33} As angiogenesis is necessary for normal alveolarization,³⁴ it has been suggested that protecting the developing pulmonary vasculature from early injury may not only lower pulmonary vascular resistance as one important goal but such strategies may enhance distal lung growth and improve gas exchange, exercise intolerance and other long-term outcomes.

As noted above, several studies have reported that altered cord blood biomarker levels, including various angiogenic factors and endothelial progenitor cells, are associated with the subsequent risk for BPD.³² More recently, clinical studies have shown that early echocardiographic findings of PVD after preterm birth are strongly associated with the development and severity of BPD and PH at 36 weeks corrected age.^{75–77} Interestingly, these findings were also associated with a worse respiratory course during the initial hospitalization, but also late respiratory outcomes, including respiratory exacerbations, hospitalizations and the need for asthma medications.⁷⁷ (Figure 5). Therapeutic strategies

that target enhanced endothelial survival, function and growth may provide novel approaches towards the prevention of BPD after early diagnosis of high risk within preterm populations.

The Need for Preventive Strategies:

Thus, the need for preventive strategies persists and remains a major challenge to better improve long-term respiratory outcomes after preterm birth. Despite these remarkable advances, many knowledge barriers and gaps towards enhancing late respiratory outcomes of premature infants continue. The current definition of BPD remains unsatisfying for several reasons, including the concept that BPD at 36 weeks is merely a surrogate of more concerning endpoints, related to late respiratory disease during childhood, such as risks for recurrent respiratory exacerbations, reactive airways disease, re-hospitalizations, exercise intolerance and other problems. In addition, there are several physiologic mechanisms underlying oxygen dependency, including variable contributions of large airways disease, impaired distal lung (airspace) development, pulmonary vascular disease, abnormal ventilator drive, chest wall mechanics and other factors, rendering the current definition imprecise.

An NHLBI workshop further emphasized the importance of preventive strategies, including the need to better understand mechanisms through which antenatal factors and placental dysfunction contribute to BPD risk.⁹ (Figure 6). This report highlighted the importance of developing effective disease predictors, perhaps through such methodologies such as genomics and proteomics in conjunction with clinical features, may help identify early pathologic pathways and therapeutic targets. More basic work is needed to better define interactions between genetic and epigenetic factors, antenatal stress, postnatal factors that contribute to disruption of lung development or alter the response to injury. Further studies using antenatal models of BPD may help better inform the field of novel interventions for disease prevention beyond the use of hyperoxia or mechanical ventilation alone.

Gaps in knowledge/future directions/conclusions

Since its original description, advances to reduce the incidence and severity of BPD have been surprisingly few, while the improved survival of extremely preterm babies has allowed the population of at-risk infants to grow substantially. Keller et al provide several new insights from the NIH-funded “Prematurity Respiratory Outcomes Program” (PROP), a large cohort of extremely preterm babies that were extensively phenotyped through the first year of life for perinatal, early postnatal and late respiratory outcomes. These data report that a perinatal model of risk factors identified on the first day of life - such as smoking in pregnancy, IUGR, public insurance, black race, and others- predicts chronic respiratory morbidity at 1 year, and that further inclusion of the diagnosis of BPD at 36 weeks PMA did not further enhance the strength of association beyond the perinatal model alone. These findings also tell us we need to better understand the importance of the prenatal environmental and other factors before birth in developing high risk for respiratory disease beyond postnatal care alone. Therapies in the neonatal intensive care unit are important but are not sufficient to overcome risk factors present before birth and in the home after discharge. Hopefully, the PROP data will enable better strategies for the early identification

of preterm infants at highest risk for late respiratory disease and the development of new strategies for disease prevention.

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Figure 1:

Pathogenetic mechanisms underlying the etiology of BPD and persistent late respiratory disease in childhood after preterm birth. In addition to extreme prematurity and postnatal factors that induce lung injury, experimental and clinical data have strongly linked antenatal stress as key determinants of chronic lung disease. (Modified from Abman SH, Bancalari E, Jobe AH. Am J Respir Crit Care Med, 2017)

Figure 2:

Antenatal factors are strongly associated with the risk of developing BPD. (from Morrow L et al. Am J Respir Crit Care Med, 2016)

Structural parallels between the fetal placenta and developing lung

Figure 3:

Parallel features of placental and lung development: A. Schematics of human placental villous and fetal alveolar networks throughout gestation. B. Histological cross sections of a term human placental villous and neonatal sheep lung alveolus. Boxes outline area of enlarged schematic. C. Exchange interface of maternal blood space with placental villous; alveolar air space with pulmonary blood vessels. MBS: maternal blood space, sTB: syncytiotrophoblast, cTB: cytotrophoblast, ALV: lung alveolus, EC: endothelial cell, BV: blood vessel, T1: type I pneumocyte, T2: type II pneumocyte. Histological images of human placenta and sheep lung courtesy of E. Taglauer and S. Abman, respectively.

Figure 4:

Antenatal exposure to sFlt-1, a VEGF receptor decoy, impairs lung alveolar (upper panels) and vascular growth (not shown) and causes lung endothelial cell apoptosis (lower left panel) and the development of pulmonary hypertension (lower right panel). Abbreviations: EC, endothelial cell; RV, right ventricle; BW, body weight). (from Wallace B et al. Am J Respir Crit Care Med, 2018).

Figure 5:

Echocardiogram evidence of pulmonary hypertension (PH) is strongly associated with subsequent late respiratory disease during early childhood. (from Mourani PM et al. Am J Respir Crit Care Med. 2017).

Antenatal Origins of BPD

Figure 6:

Schematic illustrating the hypothesis that antenatal stress may alter placental vascular growth and function through disruption of angiogenesis, leading to decreased angiogenic signaling in the fetus and subsequent complications of prematurity. (modified from Mandell E, Abman SH. *J Pediatrics*, 2017).

Table 1:

Perinatal factors at Day 1 of life and univariate associations with post-prematurity respiratory disease (from Keller RL *et al*, J Pediatr 2017²⁶)

Characteristic	Whole cohort n = 724	PRD n = 497	No PRD n = 227	P value
Gestational age (weeks)	26.7 ±1.4	26.6 ±1.4	26.9 ±1.3	0.009
Birth weight (g)	918 ± 234	899 ± 232	960 ± 233	0.003
Intrauterine growth restriction	36 (5%)	32 (6%)	4 (2%)	0.02
Multiple gestation	187 (26%)	111 (22%)	76 (3%)	0.006
Smoking during pregnancy	139/723 (19%)	111/496 (22%)	28/227 (12%)	0.004
Stabilization at birth: intubation	564 (78%)	405 (82%)	159 (70%)	0.003
Maternal education				0.007
High school	389 (54%)	283 (57%)	106 (47%)	
Some college	143 (20%)	100 (20%)	43 (19%)	
College graduate	192 (27%)	114 (23%)	78 (34%)	
Public insurance	470/721 (65%)	348/494 (70%)	122/227 (54%)	<0.001
Parent with asthma	173/712 (24%)	129/485 (27%)	44/227 (19%)	0.04

* by trend test

PRD, post-prematurity respiratory disease

Table 2:

Abnormal placental histopathology and high risk for bronchopulmonary dysplasia and pulmonary hypertension in preterm infants (from Mestan *et al*, Placenta 2014²⁹)

Placental characteristic	No BPD or PH n = 165	BPD only n = 84	BPD- associated PH n = 34	P value
Maternal vascular underperfusion (any)	56 (34%)	43 (51%) *	22 (65%) *	0.001
Severe MVU	6 (4%)	9 (11%)	6 (18%)	0.01
Vessel changes				
FN/AA	6 (4%)	8 (10%)	8 (24%) **	0.001
MBPA	16 (10%)	12 (14%)	10 (29%) *	0.01
MHMA	10 (6%)	9 (11%)	6 (18%)	0.07
Villous changes				
Infarcts	10 (6%)	14 (17%)	4 (12%)	0.02
Increased syncytial knots	53 (32%)	39 (46%)	20 (59%) *	0.01
Villous agglutination	4 (2%)	4 (5%)	2 (6%)	0.36
Increased perivillous fibrin	7 (4%)	2 (2%)	2 (6%)	0.67
DVH/STV	36 (22%)	36 (43%) *	18 (53%) **	< 0.001

PH determined by echocardiogram at 36 weeks' post-menstrual age

* P < 0.01 versus No BPD or PH

** P < 0.001 versus No BPD or PH

BPD, bronchopulmonary dysplasia; DVH/STV, distal villous hypoplasia/small terminal villi; FN/AA, fibrinoid necrosis/acute atherosclerosis; MBPA, muscularized basal plate arteries; MHMA, mural hypertrophy of membrane arteries; MVU, maternal vascular underperfusion; PH, pulmonary hypertension