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Perinatal Factors in Neonatal and Pediatric Lung Diseases

Rodney D. Britt Jr.[1], **Arij Faksh**[3], **Elizabeth Vogel**[1], **Richard J. Martin**[4], **Christina M. Pabelick**[1,2], and **Y.S. Prakash**[1,2]

[1]Department of Physiology, Mayo Clinic, Rochester, MN

[2]Department of Biomedical Engineering, Anesthesiology, Mayo Clinic, Rochester, MN

[3]Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN

[4]Department of Pediatrics, Division of Neonatology, Rainbow and Babies Children's Hospital, Cleveland, OH

Abstract

Wheezing and asthma are significant clinical problems for infants and young children, particularly following premature birth. Recurrent wheezing in infants can progress to persistent asthma. As in adults, altered airway structure (remodeling) and function (increased bronchoconstriction) are also important in neonatal and pediatric airway diseases. Accumulating evidence suggests that airway disease in children is influenced by perinatal factors including perturbations in normal fetal lung development, postnatal interventions in the intensive care unit, and environmental and other insults in the neonatal period. Here, in addition to genetics, maternal health, environmental processes, innate immunity, and impaired lung development/function can all influence pathogenesis of airway disease in children. We summarize current understanding of how prenatal and postnatal factors can contribute to development of airway diseases in neonates and children. Understanding these mechanisms will help identify and develop novel therapies for childhood airway diseases.

Keywords

Infant; Child; Perinatal; Asthma; Wheezing; Remodeling; Bronchoconstriction

Introduction

Diseases such as bronchopulmonary dysplasia (BPD), recurrent wheezing and asthma are significant causes of pulmonary morbidity in infants and young children worldwide, and adversely impact childhood quality of life, education and physical activity [1]. Asthma is particularly prevalent and is characterized by airway obstruction and hyperreactivity resulting from inflammation, structural changes (airway remodeling) involving enhanced epithelial and smooth muscle cell proliferation, increased airway smooth muscle (ASM) cell contractility, and impaired relaxation [2,3]. Innate and adaptive immune responses facilitate

Corresponding Author: Y.S. Prakash, MD, PhD, Professor of Anesthesiology and Physiology, 4-184 W Jos SMH, Mayo Clinic, 200 First St SW, Rochester, MN 55905, 507 255 7481, 507 255 7300 (fax), Prakash.ys@mayo.edu.

chronic inflammation characteristic of asthma and regulate airway remodeling [4]. Severity of airway disease is highly variable and there are a variety of factors that contribute to asthma pathogenesis in children [3]. Similarly, the long-term sequelae of BPD involve wheezing and asthma as well as failure to thrive, resulting in significant morbidity. Such mechanistic complexity, due to the variety of factors, make it important to identify preventable or modifiable factors to develop targeted and effective therapies for infants at risk of developing lung diseases.

While a number of genetic and environmental factors can contribute to lung diseases at different time points in a child's life, the perinatal period (5 months antepartum to 2 months postnatal) is a critical time window during which lung development and growth are substantially influenced. A number of maternal, fetal, neonatal, environmental, and iatrogenic factors influence the subsequent course of diseases in infancy and childhood (Table 1). Our goal is to highlight some of these important contributing perinatal factors, and their potential mechanisms of action that can result in lung diseases, particularly in the conducting airways. Furthermore, no single review can comprehensively integrate the myriad of likely extrinsic vs. innate factors, including the important influence of genetics. The intent here is to establish the link between perinatal events and subsequent progression of lung diseases, thus stimulating further bench and clinical investigations.

A particularly important contributory factor to neonatal/pediatric lung disease is preterm birth. While approximately 12% of infants in the United States are born prematurely [5], the healthcare and financial burden imposed by this small fraction is disproportionately large (approximately $25 billion/year in United States) [6]. Preterm infants are at higher risk of developing lung diseases including bronchopulmonary dysplasia, recurrent wheeze, and asthma compared to term infants [7]. This risk is further modulated by multiple maternal factors that uniquely affect preterm infants such as chorioamnionitis, systemic infections, and metabolic disease that are all linked to development of airway disease [8]. Maternal behaviors, including diet and smoking, as well as environmental factors such as pollution and tobacco smoke may also be important contributors and modulators [9].

Prematurity and subsequent pulmonary immaturity often require respiratory support in the neonatal intensive care unit (ICU) placing the neonate at high risk for ongoing respiratory problems due to effects of mechanical ventilation and supplemental oxygen. Early preterm infants (24–28 weeks) are at highest risk of developing BPD [10]. Preterm infants have immature alveolar structure resulting in reduced airway tethering, airway collapse, and/or increased airway resistance which increases the respiratory load on a highly compliant chest wall [11]. Thus, altered alveolarization and airway architecture can contribute to airway dysfunction and may explain why preterm infants with BPD develop airway reactivity. Although late preterm infants (born at 33–36 weeks gestation) are less likely to develop BPD, they are still at risk of developing recurrent wheezing and asthma [12,13]. Given these important considerations, this review attempts to highlight factors that not only contribute to prematurity but also influence subsequent lung development and diseases.

Beyond prematurity, many innate and extrinsic factors can influence the development of lung disease during the perinatal period. Genetic and innate immune responses are likely

important in initial sensitization to environmental factors such as allergens, while the exacerbating effects of allergens, pollution, and tobacco smoke in asthma are recognized [14]. Additional factors such as deficits in growth and nutrition, recurrent infections (particularly respiratory viruses), and impaired lung function due to other causes may also play an important role [15]. These postnatal factors are also discussed in this review. While detailed discussion of genetics and innate immunity is beyond the scope of this review, the reader is referred to other reviews on these subjects [8,9,15].

Prenatal Factors

Chorioamnionitis

Chorioamnionitis is a common source of *in utero* inflammation defined as the presence of inflammation within fetal membranes. Clinically, chorioamnionitis is diagnosed by the presence of maternal fever greater than 38°C, maternal tachycardia, fetal tachycardia, uterine tenderness, purulent or malodorous amniotic fluid, and/or maternal leukocytosis [16]. Inflammation in this condition is a result of bacterial or viral infection of the amniotic fluid, fetal membranes, placenta, and/or uterus. Chorioamnionitis is a leading cause of preterm labor, and is highly associated with preterm birth [8]. Neonates born to mothers with chorioamnionitis are at increased risk of mortality and of developing significant lung morbidities including acute respiratory distress syndrome, BPD, and reactive airway disorders [8]. Recent studies indicate that chorioamnionitis is correlated with an increase in risk of preterm infants for developing asthma, even after correction for confounding factors [8,17,18].

An important, yet unanswered, question is regarding the relative importance of microbes that cause chorioamnionitis vs. microbial products vs. host (maternal)-derived inflammatory mediators that cross the placenta. These issues are difficult to resolve given that all three processes occur concurrently. Nonetheless, the fetal lung is a major target of the inflammatory mediators induced by *in utero* infection (Figure 1). Chorioamnionitis-induced pro-inflammatory mediators primarily reach the lung through fetal breathing and swallowing of amniotic fluid. Fetal inflammatory response, as measured by proteins identified in the blood of neonates exposed to chorioamnionitis, is characterized by an upregulation of cytokines, chemokines, adhesion molecules, matrix metalloproteinases (MMPs), and angiogenic factors.

Animal models of intrauterine inflammation and infection suggest that chorioamnionitis substantially dysregulates lung development by arresting alveolarization and vascular development. For example, lipopolysaccharide (LPS) exposure in mice, with concomitant postnatal hyperoxia (simulating oxygen supplementation in the neonatal ICU of the premature newborn of a chorioamnionitis mother) arrests alveolarization, enhances fibrosis, and impairs pulmonary function, resulting in pathophysiology similar to human BPD [19]. Moreover, intra-amniotic injection of LPS in fetal mice during the saccular period of lung development causes dilation of airways and inhibition of airway branching resulting in altered lung structure [20]. This is a particularly devastating insult since airway branching is fixed by the time of birth, unlike the continued postnatal development of alveoli.

While the mechanisms underlying chorioamnionitis-induced lung injury are still under investigation, one important target may be fibroblast growth factors (FGF) which are vital for synchronized epithelial-mesenchymal branching morphogenesis and alveolarization [21]. In a study examining fetal rat lung explants, endotoxin exposure during the pseudoglandular period was found to alter lung morphogenesis with accompanying decreases in FGF9, FGF-10, and FGF-2R [20]. Another investigation suggested that nuclear factor-κB (NF-κB) activation is responsible for inhibiting the expression of FGF10 [22]. One study in mice found that chorioamnionitis increases angiogenesis during the saccular stage, which may be mediated in part by chemokines, ultimately contributing to altered vascularization, impaired gas exchange, and respiratory disease [23].

Given the known inflammatory response of both mother and fetus to chorioamnionitis, it is somewhat surprising that studies have found that chorioamnionitis may actually enhance lung maturation. The maturation response involves increases in surfactant, improved pulmonary compliance and gas exchange, and thinning of the lung mesenchyme. Surfactant serves an essential purpose of decreasing alveolar surface tension to reduce the work of breathing and prevent alveolar collapse at exhalation. A study in sheep showed that intra-amniotic injections of *E. coli* endotoxin administered prior to a preterm delivery cause increases in lung compliance, lung gas volumes, and alveolar phosphatidylcholine independent of cortisol [24]. Likewise, a prospective clinical study by Watterberg *et al*. first reported that chorioamnionitis decreases incidence of respiratory distress syndrome in preterm infants; however the incidence of chronic lung injury, noted by the manifestation of BPD is increased [25]. In preterm sheep, injection of bacterial LPS into the amniotic fluid results in increased surfactant production and lung growth [26].

The published clinical studies examining the effects of antenatal inflammation on neonatal respiratory outcomes differ considerably, and there is no clear consensus on how mechanistically intrauterine inflammation impacts neonatal pulmonary outcomes, especially given the opposing effects of increased inflammation and enhanced lung maturation. Furthermore, given the fact that many lung development mechanisms common to several different cell types are likely affected in antenatal inflammation, it is difficult to justify clinical interventions when there is lack of knowledge regarding the actual mechanisms by which inflammation affects the lung. From a mechanistic perspective, pro-inflammatory mediators that are released following exposure to antenatal inflammation likely contribute to lung maturation. *E. coli* LPS increases the number of alveolar type II cells in fetal mouse lungs, potentially explaining the increased surfactant production [27]. A study that exposed fetal sheep to intrauterine inflammation demonstrated higher prostaglandin (PG)E_2 concentration [28]. PGE_2 increases surfactant secretion in rat alveolar type 2 cells [29]. Thus, inflammatory mediators, such as LPS, can stimulate lung maturation through upregulation of the PGE_2 signaling pathway resulting in increased surfactant production by alveolar type II cells.

While these animal data provide clues to enhanced surfactant production and improved lung maturation, mechanisms detrimental to the lung that result in chorioamnionitis leading to increased risk for postnatal lung diseases, particularly reactive airway disease, are largely unknown. Airway remodeling through altered cell proliferation and migration is a key

feature of diseases such as asthma. In fetuses exposed to chorioamnionitis, there is increased apoptosis of distal airway epithelial cells as well as increased endothelial and smooth muscle cell proliferation [30]. Additionally, intra-amniotic LPS reduces expression of the plasma membrane protein caveolin-1 [31], which can have substantial implications for cell proliferation and intracellular signaling. For example, we have previously shown that human fetal airway smooth muscle cells express caveolin-1 [32] and exposure to LPS results in reduced caveolin-1 but increased cell proliferation, and altered extracellular matrix (ECM) production, which should lead to increased airway stiffness. In this regard, chorioamnionitis also increases expression of mediators that regulate alveolar and airway ECM. Elevated MMP-8 and MMP-9 levels have been reported in bronchoalveolar lavage fluid from premature infants exposed to chorioamnionitis [33]. Conversely, no significant differences in levels of tissue inhibitors of metalloproteinases (TIMP)-1 have been noted between preterm infants exposed to chorioamnionitis compared to preterm infants without chorioamnionitis exposure [33]. Intra-amniotic LPS increases phosphorylation of signaling proteins such as Smad2/3, Stat-1, and Stat-3 in the lung suggesting activation of the TGFβ signaling pathways which regulate ECM composition [31]. Overall, these data suggest that chorioamnionitis activates a number of pathways that can contribute to airway remodeling with functional consequences of stiffer, fibrotic airways and hyperreactivity resulting from greater smooth muscle mass.

While prevention, early recognition, and treatment of chorioamnionitis are obviously preferable, in the event of preterm labor acceleration of lung maturation is beneficial. In this regard, it is interesting that the commonly used corticosteroid, Betamethasone, increases lung maturation, but does not inhibit inflammation in the presence of LPS [34]. This raises the intriguing question: In the presence of chorioamnionitis, are steroids more effective in enhancing lung maturation? And could this influence the long-term consequences to lung function? Along a similar line, hyperoxia (80% O2) following exposure to intra-amniotic LPS actually results in enhanced postnatal alveolar and vascular development [35]. This has implications for exposure to supplemental oxygen in the neonatal ICU following premature birth under conditions of chorioamnionitis. However, the mechanisms of interactions between infection/inflammation and oxygen, and the long-term consequences of hyperoxia with inflammation on the airway or lung are not known.

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) is a complication of pregnancy observed in both preterm and full-term births, with an incidence of 5–12% depending on the stringency of its definition. Given that IUGR also occurs in full-term babies, it becomes important to distinguish the effects of IUGR *per se* on lung development and subsequent disease from that resulting from prematurity alone. Fetal growth restriction has been linked to the inability of the placenta to meet the needs of the fetus for oxygen and metabolic substrates, and this environment may have an additional impact on the fetal lung. Studies have demonstrated an association between growth-restricted neonates and increased likelihood of developing cardiovascular disease, diabetes mellitus, metabolic syndrome, and asthma later in life [36]. Recent studies have identified an association between altered fetal growth and

the development of wheezing at 3 years of age [37]. This association appears to be independent of gestational age at birth.

Processes related to IUGR limit fetal lung growth and maturation, making the lung more vulnerable to postnatal insults. Studies have shown that premature, small for gestational age infants are at higher risk for developing chronic lung disease compared with premature infants that are at appropriate weight for gestational age [38], again highlighting the distinction between IUGR and prematurity. In animal studies, mice with fetal growth restriction had decreased expression of mRNA for surfactant proteins [39]. In ewes, growth restricted offspring demonstrated decreased pulmonary vascularization and alveolarization [40]. A second study in ewes evaluated the impact of IUGR during late gestation on fetal pulmonary structure. Evaluation was performed near term as well as 8 weeks postnatally demonstrating decreased alveolar number and increased septal thickness, with these structural changes being more notable 8 weeks post-delivery [41]. These structural pulmonary changes could certainly cause impaired gas exchange and lung function. In fact, another study examining growth-restricted neonatal ewes identified a reduction in pulmonary diffusion capacity, hypoxemia, increases in metabolic rate, and ventilation relative to body weight in comparison to non-growth restricted ewes [42]. Further studies are needed to elucidate the mechanisms that contribute to IUGR-induced deficits in lung development and function.

Maternal Infection

Maternal infections during pregnancy can increase the risk of childhood asthma. Prior studies have shown that childhood asthma is observed at higher frequency in mothers who experienced respiratory tract infections, febrile infectious diseases, urinary tract infections, or vaginitis during pregnancy [43]. A Finnish prospective study observed a trend that a febrile infection early during pregnancy makes the risk of childhood asthma even higher [44].

The mechanisms by which maternal infections result in increased risk of childhood asthma are currently under investigation. One hypothesis is that allergic sensitization starts *in utero* and the asthma phenotype is programmed prior to birth such that postnatal challenges can result in asthma *per se*. Indeed, epidemiological effects of protective factors observed under the ‘hygiene hypothesis’ are thought to be due to the effects of endotoxin and other microbial exposure via the innate immune system. For example, the PARSIFAL study previously found that prenatal exposure to environmental factors in the farming sector is associated with increased expression of innate immune receptors such as the TLRs and with decreased incidence of atopic sensitization [45]. Failure of such tolerance mechanisms may occur in the setting of maternal infection, leading to enhanced sensitization of the fetus and newborn.

Interestingly, the mechanisms underlying the correlation between maternal infections and asthma in the progeny can be potentially gleaned from information on maternal periodontal disease. While obviously not a hugely prevalent problem, the association between maternal periodontitis, preterm birth, and adverse perinatal outcomes [46] may provide mechanistic insight. Studies have shown that chronic inflammation from periodontitis results in elevated

systemic levels of cytokines such as TNF-α, IL-8 and IL-1β. These cytokines subsequently promote release of uterine stimulating factors such as PGE_2 which impact placental function, onset of labor, contractions, and fetal outcomes [47]. Although no studies have specifically examined the correlation between maternal periodontal disease and development of neonatal lung disease, the observed increase in cytokines, in addition to the various inflammatory mediators associated with periodontitis could certainly have an impact on fetal lung development and postnatal pulmonary function. Other studies focusing on different etiologies of maternal inflammation have indicated that exposure to chronic inflammation *in utero* can impact fetal organ development. In utero exposures to cytokines such as TNF-α, IL-8, and IL-1β, have all been implicated in disruptions of fetal lung development. Furthermore, as with chorioamnionitis, it is important to consider the roles of microbes causing periodontal disease vs. their products such as LPS and/or maternal factors such as cytokines.

Maternal Smoking

Tobacco abuse continues to be a major prenatal problem with 10–12% of women admitting to tobacco use during pregnancy [48]. Moreover, approximately half of women smokers continue to do so early during pregnancy despite substantial evidence of the deleterious impact of *in utero* tobacco exposure on fetal development [48]. Additionally, maternal exposure to second-hand smoke due to paternal or grandparental smoking has been associated with increased risk of neonatal development of asthma and airway disease [49,50]. Mechanistically, nicotine in tobacco products results in elevated placental vascular resistance, leading to decreased uterine blood flow, increased carboxyhemoglobin, fetal hypoxia, and impaired fetal development [51]. Nicotine, fat soluble, and additive components of tobacco can cross the placenta, be detected in amniotic fluid, and have an adverse impact on fetal lung development [52]. Certainly, given the multitude of detrimental compounds present in cigarette smoke, several other mechanisms may also be at play, but have not been systematically elucidated.

Studies have shown that both maternal smoking during pregnancy and maternal exposure to tobacco results in abnormal lung function in the offspring. These abnormalities in pulmonary function can be detected in the neonatal period, continuing into childhood, and persisting throughout adult life [53]. In terms of asthma and respiratory morbidity, *in utero* exposure to tobacco smoke is known to impair lung function and increase airway hyperreactivity, potentially forming the underlying basis for the known association between maternal smoking during pregnancy and asthma. Indeed, maternal smoking increases neonatal Th2 cytokine responses to antigen (representing asthma pathophysiology), decreases production of the anti-inflammatory interferon gamma, and impairs TLR-mediated responses. These smoking related effects on lung structure, airway function and immune function are likely to have both short term and long term effects in the context of asthma.

Maternal smoking, before and during pregnancy, increases airway reactivity and thickening in pups exposed to house dust mite [54]. These findings are attributed at least in part to alterations in Wnt signaling, and lower expression of genes involved in the Wnt signaling

pathway in newborn mouse offspring from mothers exposed to cigarette smoke during pregnancy [55]. The Wnt-β signaling pathway regulates expression of multiple genes that are critical for mediating lung development [55]. In rats, maternal smoking in pregnancy results in increased alveolar size and decreased number of alveoli in rat offspring [56]. *In utero* nicotine exposure has been shown to increase IL-13 and TGF-β in the neonatal lung (Figure 1) [57]. Additionally, *in utero* nicotine exposure increases responsiveness to methacholine and smooth muscle layer thickness and collagen III deposition around the airways in mouse offspring [58]. *In utero* nicotine exposure has been shown to increase procollagen type I and III mRNA expression in neonatal monkeys [59]. These data suggests that nicotine can lead to increased collagen deposition, resulting in increased airway wall dimension in the fetal lung, thereby influencing lung mechanics postnatally [59]. Furthermore, studies have demonstrated that *in utero* exposure to smoke alters alveolar-airway attachments, leading to abnormal airway function due to reduced forces that can counteract airway narrowing [60], akin to adult COPD. Overall, these data highlight the detrimental effects of cigarette smoke exposure in fetal and neonatal lung development, and only emphasize the need for greater efforts to curb or eliminate maternal smoking.

Maternal Diet

Studies suggest that development of asthma and wheezing is influenced by the maternal nutritional status and antenatal environmental conditions. Epidemiologic and immunologic studies also indicate that maternal diet may affect the development of neonatal allergic diseases [61]. There are a number of studies exploring the relationship between maternal nutritional status, specifically the presence or absence of particular nutrients and dietary supplements and childhood asthma.

The biologically active form of vitamin D, 1-α-hydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$), is a critical nutrient which regulates numerous physiologic functions including calcium metabolism, skeletal integrity, and immune responses [62]. Vitamin D signaling occurs predominantly through binding to the Vitamin D receptor, VDR. Serum levels of <20 ng/mL of the precursor to Vitamin D, 25(OH)D, corresponds to Vitamin D deficiency [63]. In clinical studies, low maternal Vitamin D levels have been associated with increased occurrence in wheezing in 5 year-old children [64]. Conversely, another study found that higher antepartum maternal consumption of Vitamin D was associated with a lower risk of recurrent wheeze in children at 3 years of age [65]. However, these results are not universal, with another study showing no significant associations between maternal late-pregnancy serum 25-hydroxyvitamin D levels and risk of asthma, or for transient or persistent wheeze at 1, 3, or 6 years of age [66]. Furthermore, there is one human study suggesting that vitamin D supplementation in the first year of life may actually increase asthma [67].

There has been considerable interest in understanding the mechanisms by which Vitamin D can influence airway structure and function, particularly in adult asthma. In the adult airway, proposed mechanisms include: ability of vitamin D to increase differentiation and recruitment of macrophages, enhance responsiveness to corticosteroids, and downregulate atopy [62]. In mouse models of asthma, notably higher expression of TNF-α in the lungs of vitamin D deficient mice have been noted, corresponding to a role for vitamin D deficiency

in increasing airway inflammation [68]. Additionally, Vitamin D has also been shown to mediate airway smooth muscle cell proliferation and cytokine-induced chemokine expression [69,70]. There is currently a paucity of information on the potential mechanisms by which Vitamin D could influence the developing airway; however, it is hypothesized that mechanisms similar to the adult airway may be involved. For example, in ongoing studies, we have found that in human fetal airway smooth muscle cells, Vitamin D can reverse inflammation-induced changes in ECM deposition and agonist induced Ca^{2+} responses.

A number of studies have shown that omega-3 polyunsaturated fatty acids (PUFAs) have anti-inflammatory properties and function as immunomodulators [71]. There have been investigations examining the protective role of fish consumption in the development of asthma [72]. One study demonstrated decrease in persistent wheeze with increased fish intake in non-breastfed children [73]. A recent study suggests that increased omega-3 PUFA lung tissue concentration reduces ovalbumin (OVA)-induced airway inflammation and hyperresponsiveness [74]. In a murine model, maternal docosahexaenoic acid (DHA) supplementation enhances alveolarization and reduces inflammation in newborn pups exposed to hyperoxia [75]. These data overall suggest that maternal omega-3 PUFA supplementation may be useful in preventing the development of airway disease in infants.

Maternal Metabolic Syndrome

Metabolic syndrome in pregnant women encompasses a spectrum of conditions including obesity and insulin resistance which increases their risk of preterm delivery [76,77]. More than two-thirds of North American women of childbearing age are overweight (BMI 25–30) or obese (>=30) [76]. Metabolic syndrome results in elevated levels of pro-inflammatory mediators, such as IL-6 and C-reactive protein, in the circulation and placenta (Figure 1) [78,79]. Pregnant mothers with metabolic syndrome are at higher risk of having infants who develop wheezing and asthma, regardless of gestation at birth [80,81]. This leads to the question whether maternal metabolic syndrome has an impact on development of postnatal neonatal lung diseases. Here it is also important to distinguish between the topic of maternal issues of obesity vs. excessive weight gain of the child which can be influenced by several factors. Given the substantial rise in maternal obesity and excessive gestational weight gain, the prevention of pediatric obesity through prenatal interventions during pregnancy represents a novel area for future research [82]. However, this aspect is beyond the scope of this review.

Children of obese mothers have an increased risk of recurrent wheezing [83]. A large population based study of children born in United States cities from 1998–2000 followed after delivery showed that maternal obesity correlated with a 52% chance of asthma in the offspring by age 3 [84]. A Norwegian study identified a linear rise in the risk of wheezing at up to 18 months of age with increased maternal BMI [80]. Moreover, a Danish National Cohort Study found that maternal BMI greater than or equal to 35 was associated with severe asthma diagnosis by age 7 years [85]. With all of these studies, it is important to differentiate between obesity during pregnancy vs. continued post-partum obesity: another area that is not well studied.

There is also an association between maternal type 2 diabetes and development of neonatal airway disease [81]. Diabetes during pregnancy is classified by the White's system which takes into account maternal age at onset of diabetes, duration of diabetes diagnosis, and the severity of the diabetes. The White's classification distinguishes between gestational diabetes (type A) and pre-gestational diabetes. Diabetes in pregnancy can increase the risk of abnormal fetal organogenesis. One proposed mechanism by which diabetes induces embryonic anomalies is through increased oxidative stress [86]. In newborn rats exposed to intrauterine hyperglycemia, examination of their postnatal lung development revealed diminished alveolarization [87]. *In vivo* and *in vitro* experiments established that hyperglycemia and the resulting fetal hyperinsulinism resulted in delayed fetal lung maturation [88]. Moreover, exposure to intrauterine maternal hyperglycemia results in upregulation of genes coding for pro-collagen Iα and IIIα, as well as an upregulation of MMP-14, suggesting that intrauterine environmental factors apart from inflammatory conditions may also impact pulmonary development [89]. Although these studies suggest that obesity and diabetes influence neonatal airway disease, future clinical studies are needed to determine how these complications contribute to the development of airway disease. Furthermore, additional studies in animal models will help to identify mechanisms by which maternal obesity and diabetes alter lung development and airway reactivity.

Environment

Maternal exposure to deleterious environmental factors negatively impacts the developing fetus, potentially altering immune and respiratory system maturation, subsequently influencing the risk of acquiring chronic lung diseases postnatally [61]. Traffic or motor vehicle related air pollution is common especially in urban areas, and typically includes: carbon monoxide, particulate matter, nitrogen oxides, and ozone. Recent studies have revealed that ozone exposure in asthmatic individuals tends to increase the risk of airway injury and further enhance inflammation [90]. Although, there is concern that environmental factors such as air pollution may be associated with increasing prevalence of asthma the pathophysiologic processes involved in pollutant-mediated effects remain undefined.

Recent studies suggest that maternal exposures can influence development of airway disease in offspring. Maternal inhalation of diesel exhaust increases pro-inflammatory markers in fetal mouse lungs [91]. An animal study using OVA exposure showed that neonates of mothers exposed to titanium dioxide and diesel exhaust particles developed airway hyperresponsiveness and allergic inflammation [92]. In another murine model, maternal exposure to an urban particulate matter increased placental TNF-α, IL-6, and keratinocyte-derived cytokine levels [93]. Postnatal ozone exposure increased pro-inflammatory cytokine levels in whole lung compared with postnatal air exposed groups [93]. Interestingly, ozone exposure increased airway reactivity but had no effect on alveolar volume or surface density [93]. The mechanisms by which maternal exposure to air pollutants influences postnatal pulmonary structure and function are not well elucidated. A proposed explanation is that the organic components of diesel exhaust particles contain polycyclic aromatic hydrocarbons resulting in a greater production of Th2 cytokines which are known to mediate allergic and asthmatic disease (Figure 1) [93]. It is possible that maternal Th2 cytokines can potentially traverse the placental barrier and affect the developing fetus [94]. These data suggest that

pregnancy exposure to either “inert” particles or known toxic substances such as diesel exhaust particles can exacerbate pulmonary inflammation and asthma in offspring.

Postnatal Factors

Respiratory Support

Immaturity of the lung and respiratory system accompanying premature birth frequently necessitates administration of supplemental oxygen (hyperoxia) with or without additional mechanical ventilation. Studies show that hyperoxia and ventilation are pro-inflammatory, and detrimental to alveolar development and airway structure and function. Prolonged respiratory support leads to alveolar simplification and impaired lung function in preterm infants [10]. Similar pathologies are observed in animal models of neonatal lung disease involving hyperoxia or mechanical ventilation and represent the “new BPD” in the post-surfactant era [95,96].

Airway dysfunction in preterm infants is due to changes in airway function and structure and over and above alveolar or vascular dysmorphogenesis. Preterm infants who developed BPD show persistent airflow obstruction [97] and increased bronchial hyperresponsiveness to methacholine [98]. Although late preterm infants do not develop severe deficits in alveolar structure/function they are still vulnerable to developing airway dysfunction [99]. Early studies showed that hyperoxia increases airway reactivity in rodents [100]. This phenotype attributed to increased thickness of the airway wall, a characteristic of remodeling. Ventilation of the neonatal lung further increases airway reactivity in newborn mice [101]. The combination of hyperoxia and ventilation can synergistically worsen airway function, although the extent of such interactions are likely to vary considerably depending on the level of prematurity, and intensity/duration of oxygen and ventilation.

The extracellular matrix (ECM) is a key component of both alveolar and airway structure. Elasticity and stiffness of the parenchyma is impacted by the composition of structural proteins, such as collagen and elastin, within the ECM. Transforming growth factor-β (TGF-β) is a key mediator of ECM composition and is highly expressed during lung development [102,103]. Dysregulation of TGF-β signaling results in abnormal alveolar development [104]. Preterm infants who develop BPD show altered TGF-β levels in bronchoalveolar lavage [105]. Histology from preterm infants with BPD demonstrates increased collagen expression and deposition in the parenchyma [106]. Expression of MMP-2 MMP-8, MMP-9, and TIMP-2 are all increased in preterm infants who developed BPD [107]. However, these changes may also be influenced by gestational age [108]. Overall, ECM remodeling in preterm infants mostly likely varies, but could contribute to altered alveolar and airway structure resulting in airway dysfunction.

Hyperoxia increases TGF-β (Figure 2) and bone morphogenetic protein (BMP) expression and signaling in newborn mice [102]. Additionally, hyperoxia increases expression of ECM proteins including collagen I, MMPs, and TIMP [96,102] as well as non-structural ECM proteins such as periostin [109]. These data suggest that hyperoxia-induced changes to ECM composition are consistent with the observed changes in lung structure of preterm infants.

The mechanisms by which hyperoxia mediates its effects on airway contraction, relaxation, and remodeling are still under investigation. Electric field stimulation induced tracheal relaxation is reduced by hyperoxia, and is attributable to lower levels of PGE_2 and cAMP [110]. Newborn rats exposed to >95% O2 for 7 days have increased tracheal contractility in response to acetylcholine [111] while airway smooth muscle from newborn rats show increased contraction following 14 days of exposure to 60% O2 [112]. Expression of the neurotrophic factor, brain-derived neurotrophic factor (BDNF), and its receptor, tyrosine kinase B receptor (TrkB), is increased in newborn rats exposed to >95% O_2 [113]. BDNF can increase airway smooth muscle cell proliferation and contractility [114,115], thus contributing to hyperoxia induced enhancement of airway tone (Figure 2). Separately, mechanical ventilation can also influence airway structure and function. For example, in fetal ovine lungs, mechanical ventilation increases collagen deposition and airway smooth muscle thickness [116]. Separately, mechanical ventilation increases contractility of tracheal rings isolated from newborn rats [117]. What is not known is whether parameters such as tidal volume and respiratory frequency, mechanical stretch on the developing airway, and superimposed hyperoxia influence the effects of mechanical ventilation.

Enhanced ASM proliferation is a key aspect of remodeling (Figure 2). ASM responds to cytokines and growth factors which may be enhanced by hyperoxia. Recent studies have suggested that fetal ASM cells proliferate in response to changes in redox balance [118]. Our recent study showed that moderate levels of hyperoxia (30–50% O_2) increase proliferation of human fetal ASM, while higher oxygen concentrations induce apoptotic pathways [32], indicating that hyperoxia can detrimental to the developing airway regardless of concentration.

Inflammation is a typical response to hyperoxia or mechanical ventilation. Inflammation has been extensively studied in preterm infants, particularly those at risk of developing BPD. Preterm infants have elevated levels of pro-inflammatory mediators in tracheal aspirates and whole blood, suggesting systemic inflammatory responses [119]. Infants with BPD may also have increased mast cells and eosinophils [120,121] contributing to enhanced airway reactivity, as suggested by studies in the newborn rat lung [122,123]. However, not all studies show that inflammation contributes to airway dysfunction in preterm infants. Preschool children with prior BPD show hyperresponsiveness to methacholine but not adenosine monophosphate, which stimulates release of bronchoconstrictors by inflammatory cells [124]. Thus, wheezing in some former preterm infants with BPD may not be mediated by chronic inflammation. Additionally, late preterm infants who develop recurrent wheeze likely experience less inflammation than infants at risk of developing BPD. Thus the development of airway disease in preterm infants may be due to deficits in the parenchymal and airway structural network [124]. Further studies are needed to determine if airway dysfunction in this cohort is mediated by inflammation.

Children with airflow obstruction and severe asthma have increased oxidation in the airway [125]. Oxidative stress is a consequence of pro-inflammatory processes. The fraction of expired nitric oxide (FE_{NO}) is a marker of lung inflammation and increased in asthma. Recently, FE_{NO} has been identified as a potential marker for infants that will develop

childhood asthma [126]. Monitoring the progression of airway inflammation may help with implementation of therapeutic strategies [127].

Lung Structure and Function

Clinical data show that preterm infants have impaired lung function, including airway obstruction [11,128]. Assessment of lung function and hyperresponsiveness may be useful tool to identify infants that are at risk of developing asthmatic symptoms later in life. Indeed, children with persistent asthmatic symptoms show lower lung function and airway hyperresponsiveness as infants [129,130]. Lower lung function in infants born at term is associated with development of wheezing between 1–3 years old [37], while one month old term infants with increased airway reactivity are at higher risk of developing airway disease and have lower forced expiratory volume (FEV_1) and functional vital capacity (FVC) at age 6 [131]. Infants with lower lung function and airflow obstruction were more likely to develop asthma by adolescence [132,133]. These clinical data underline the need to understand the short-term and long-term influences of prematurity and other factors on the developing airway. Airway inflammation and remodeling are present in children with early wheeze and asthma [134,135]. Biopsies from children with asthma revealed thickening of the reticular basement membrane, epithelial injury, and inflammatory cells. Interestingly, these symptoms were found in children with atopy but without asthmatic symptoms [135]. Altered airway structure and inflammation correlates with lower FEV_1 in children with difficult asthma [136]. In contrast to older children, infants with recurrent wheeze and reversible airflow obstruction do not present with reticular membrane thickening and increased eosinophils [137].

Postnatal Infection

Infants infected with rhinovirus or respiratory syncytial virus (RSV), are at an increased risk of developing asthma [138,139]. Rhinovirus, more than RSV, results in higher risk of developing asthma [139]. Viral infection alters immune responses and can interact with atopy to instigate asthmatic symptoms [138,140]. Although influenza A also presents in infants, it has not been linked to development of asthma. However, recent studies suggest that influenza be a factor for specific patient populations [141]. Preterm infants are at risk of hospitalization during infancy and acquiring viral infections, particularly RSV [142]. A recent trial suggests that infection with RSV during the first year of life, may contribute to development of recurrent wheezing in former preterm infants [143]. Thus former preterm infants with RSV infection could be particularly vulnerable to instigation of airway disease. Further investigation is needed to determine to what degree infections heighten the risk of developing recurrent wheeze and asthma.

Recent studies have investigated the impact of viral and bacterial infection on the developing lung and immune system. RSV infection increases airway inflammation in the developing lung of neonatal mice [144], which is exacerbated by OVA challenge and persists into adulthood [145]. The adverse effects of RSV on the airway may be mediated by Th2 responses (Figure 2) [146] since inhibition of Th2 responses reduces OVA-induced airway inflammation [147]. Bacterial pathogens also affect allergen-induced airway inflammation. In a murine model, Influenza A infection during the neonatal period

exacerbates immune responses and airway hyperresponsiveness to house dust mite allergens [148]. Airway dysfunction persisted in these mice to adulthood [148]. A similar phenotype was reported in mice challenged with *Chlamydophila pneumoniae* as neonates and OVA as young adults [149]. These investigations suggest that infection during the neonatal period alters innate immune responses and can negatively impact airway inflammation and function. Modulation of Th2 responses in infants with pulmonary infection may reduce airway inflammation and susceptibility to developing airway disease. However, there is currently no information on the modulatory factors such as hyperoxia or mechanical ventilation that is often implemented upon re-admission to the NICU or the accompanying inflammation.

Allergens

Sensitization to allergens is a key component for pathogenesis of asthma and may develop early during fetal development and continues into infancy [14]. While innate immune responses as well as genetics play substantial roles in the progression towards asthma, exposures to indoor allergen such as house dust mite, cockroach, mold, and dander from animals early in life may induce sensitization, setting the stage for further disease, and increasing the risk of developing asthma [150]. Following sensitization, subsequent allergen exposures can trigger asthmatic symptoms [151]. Primary prevention studies show that reduced exposure to allergens early in life reduces sensitization and may influence the development of asthma [152,153]. Although these studies suggest that allergen exposure contributes to development of wheezing and asthma, it is unclear to what extent sensitization causes asthma [154].

From a pathophysiological perspective, allergen sensitization perpetuates chronic inflammation due, in part, to increased Th2-mediated responses that facilitate airway remodeling and hypercontractility (Figure 2) [155]. In adults, cytokines such as IL-4 and IL-13 stimulate changes in the airway that lead to an asthmatic phenotype including mucus secretion and ASM proliferation [2]. Children with asthmatic symptoms have inflammation that may be mediated by eosinophils [134] and T cells [135,136]. Data that provides insight into the mechanisms by which sensitization and subsequent allergen challenge could mediate airway inflammation and hyperresponsiveness infants, particularly preterm infants, remain limited. Future studies will be needed to elucidate early mechanisms that contribute to the pathophysiology of recurrent wheeze and asthma in young children.

Recent studies from animal models have begun to characterize the effects of allergen sensitization on the developing lung and adaptive immune response. Sensitization and challenge with allergens such as OVA or house dust mite induce robust inflammatory responses and airway hyperresponsiveness in newborn mice [156,157]. Following challenge, these mice develop increased eosinophil and T lymphocyte infiltration as well as airway remodeling that is characterized by increased collagen deposition and mucus production. Expression of Th2 cytokines, IL-4, IL-5, and IL-13, are increased in allergen challenged mice [156,157]. Allergen sensitization also alters ECM composition in the airway. Rhesus monkeys develop airway remodeling and increased collagen deposition following house dust mite sensitization [158].

Environmental Tobacco Smoke and Pollution

The effects of prenatal vs. postnatal environmental tobacco smoke (ETS) exposure are difficult to separate since mothers often smoke during and after pregnancy. In addition to the association between prenatal ETS exposure and wheezing and/or asthma in the offspring, evidence suggests a similar but less robust association in postnatal ETS exposure, with effects lasting into adolescence. Such effects of ETS (even that of *in utero* exposure) wane as the child reaches adulthood. Genetic polymorphisms for nicotine metabolizing genes such as glutathione S-transferase (GST) and pathways such as TGF-β and IL-1R may be important. Other immunological or epigenetic changes induced by ETS may also predispose to asthma. However, further systematic studies in these areas are required.

Postnatal exposure to pollutants has been attributed to development of airway disease in children. Children who live close to busy motorways show reduced lung function [159]. Young children who reside in high pollution areas have increased risk of developing asthma [160,161]. Exposure to diesel exhaust particles have been shown to instigate asthma in mice [162]. In 6 week old mice, inhalation of diesel exhaust particles has been shown to enhance allergic airway inflammation, hyperresponsiveness, and goblet cell hyperplasia [162]. Particulate matter induces epithelial-mesenchymal transition in airway epithelial cells in neonatal mice [163]. Persistent free radicals in the environment increase oxidation within the lung and increase airway responsiveness to methacholine [164]. Here, reduced antioxidant capacity may make neonatal animals more susceptible to particulate matter contributing to airway dysfunction [165,166]. Distal airway structure is also altered by particulate matter changing airway diameter and length [167].

Expert Commentary

The path of the fetus to a healthy extrauterine life is fraught with several obstacles, not all of which are due to genetic or physiological abnormalities. Maternal and societal behaviors and environmental insults clearly play a role, as reviewed above. Many of these factors interact substantially at different time points during lung development resulting in a variety of phenotypes. Furthermore, the contribution of the myriad of factors does not end with parturition but can frequently endanger the newborn, especially under conditions of prematurity. In this regard, the developing fetal and early postnatal lung is likely very susceptible to these insults for a number of reasons: 1) *in utero* where it is not required for oxygenation and ventilation, the lung is undergoing a period of very rapid growth and increasing complexity in terms of branching and alveolar genesis. Accordingly, factors that impair airway branching or induce alveolar and vascular dysmorphogenesis manifest their devastating effects postnatally when the baby (especially in prematurity) is born with the now-reduced adult number of airway branches and a simplified lung morphology leading to lifelong impairment of function; 2) in humans alveolar formation continues postnatally for a number of years. Accordingly, insults in the perinatal period can produce long-term effects in terms of lung structure and function; 3) even in the airways, exacerbated structural and functional changes induced by factors such as inflammation, infection or even oxygen can impair respiratory efforts, particularly in the setting of a premature respiratory control system and a highly compliant chest wall; 4) during early childhood the lung continues to

remain one of the main initial exposure points for environmental and infectious factors, and can thus continue to suffer structural and functional changes that result in diseases such as asthma and wheezing.

Overall, these issues underline the importance of understanding the mechanisms by which various factors influence prenatal and postnatal lung development (Table 1), and the potential roles of timing and interactions between contributory factors. In this regard, a primary problem is premature birth. While identifying factors that induce premature birth is key to therapy, there is a considerable knowledge gap regarding controllable vs. non-controllable factors. In the prenatal period, factors such as chorioamnionitis and maternal infections may be preventable, but not entirely avoidable. Nonetheless, given the substantial detriment induced in the lung by these conditions, there is a clear need to identify at risk mothers with early antibiotic therapies. Similarly, early identification of IUGR and correction of factors such as placental insufficiency become essential. This only underlines the need for a well developed and implemented prenatal care plan. Within this realm is the need to allow for maximal *in utero* lung maturation prior to delivery, i.e. minimizing the extent of prematurity.

Compared to infectious causes, a number of factors that contribute to impaired lung development arise due to causes that are highly preventable, often by maternal efforts. Certainly tobacco abuse is one such factor that is the focus of much research as well as community outreach and education. While such campaigns have substantially reduced maternal smoking, the fact that more than 10% of women and 50% of smokers smoke during pregnancy, and also post-partum, suggests the need to better highlight the deleterious impact of both *in utero* and postnatal tobacco smoke exposure. Indeed, emerging studies in both animal models and human suggest that the combination of prematurity, hyperoxia with or without mechanical ventilation in the ICU, and subsequent exposure to tobacco smoke following discharge to home can be even more devastating than any of these factors individually. Similarly, a more nutritious, low-fat maternal diet with proper weight control and avoidance of gestational diabetes may be beneficial not only to maternal health but the general growth and well-being of the neonate and its developing lungs.

While prenatal factors can be controlled to a certain extent, premature birth does occur. Even with maternal corticosteroid therapy and the availability of surfactant, ICU management of the immature lung is difficult. Here, as reviewed above, factors such as supplemental oxygen and mechanical ventilation could potentially enhance the burden of premature birth placed on the developing lung. Furthermore, the issue of hyperoxia with or without mechanical ventilation is also relevant to term babies with respiratory insufficiency due to abnormal lung structure/function, infection or other causes. While it is unlikely that hyperoxia *per se* can be avoided, the limited data in both animal models and humans suggest that more oxygen is not necessarily good. Indeed, clinical protocols increasingly involve moderate levels of hyperoxia of limited duration, although even moderate hyperoxia may be detrimental to the developing lung as suggested by emerging studies. Nonetheless, one major “improvement” in the management of premature infants is the move away from endotracheal intubation and mechanical ventilation, replaced by equally effective nasal CPAP strategies. Whether the latter non-invasive approach also produces longer-term

detrimental changes to the airway such as increased thickening or hyperreactivity, and impairs alveolar growth remains to be established. Along these lines, pharmacological interventions would be excellent adjuncts. However, the promise of inhaled nitric oxide has not been fulfilled, and new approaches are being sought. Here, phosphodiesterase inhibition as well as targeting of emerging signaling targets such as growth factors (BDNF, TGF-β, VEGF) are of interest. Assuming the survival of the premature infant and its discharge from the NICU, further detriment to the lung could be avoided through measures targeting cessation of maternal smoking, minimization of environmental tobacco smoke and pollutant exposures, and infections.

Five Year View

Both pre-clinical and clinical studies have identified a number of prenatal and postnatal factors that can have detrimental effects on the developing lung. Given that a number of such factors are controllable, clinical and research efforts should be geared towards understanding the mechanisms that underlie the effects of these factors on the developing lung (both short-term and long-term), and importantly public education of the importance of limiting such factors. From a clinical perspective, improved understanding of the effects of oxygen and ventilator strategies (including CPAP) will greatly enhance the adoption of intelligent approaches to balancing the need for sufficient oxygenation and ventilation against the harmful effects of these interventions. From a research standpoint, identification of novel signaling targets leading to altered airway structure and function will allow for pharmacological or other adjunct therapies to limit the development of asthma and other airway disorders as well as alveolar simplification and fibrosis. Overall, these complementary approaches will greatly assist in improving the pulmonary outcomes of premature infants and limit the short-term and long-term pulmonary morbidity in children.

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Key Issues

- Development of lung disease in children and even in adults is influenced by both prenatal and postnatal factors
- Prenatal factors such as infection and chorioamnionitis and maternal factors including smoking, obesity and diabetes can substantially impair normal fetal lung development. The mechanisms underlying changes to lung structure and function induced by these factors are under investigation, and should lead to novel therapies for limiting their detrimental effects
- Postnatal factors that contribute to short-term and long-term pulmonary morbidity include treatments and procedures in the NICU necessitated by premature birth or perinatal respiratory problems. In this regard, maternal health, environmental processes, immune responses of the child, and impaired lung development and function can all influence the pathogenesis of lung disease in children. Understanding of the targets and effects of such factors on development of recurrent wheeze and asthma will help identify and develop novel therapies for children with airway diseases.

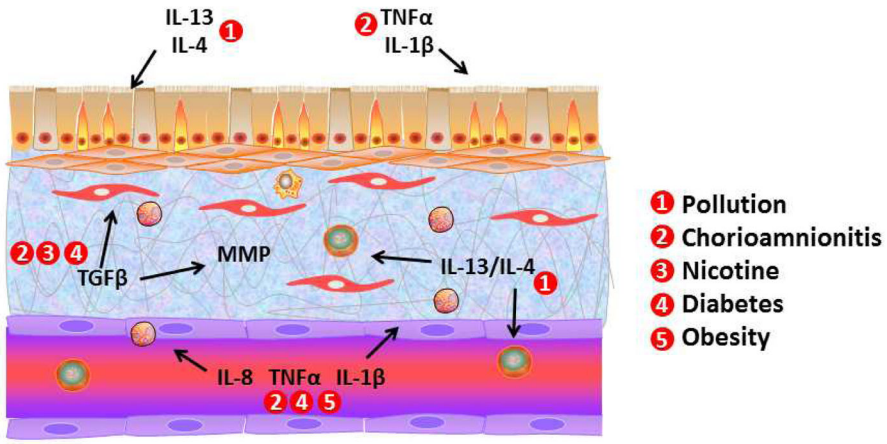

Figure 1.

Prenatal factors and underlying mechanisms in lung development. Environmental insults such as pollution and environmental tobacco smoke exposure can have substantial influence on the inflammatory milieu and production of pro-fibrotic factors such as TGF-β and matrix metalloproteinases during critical periods of *in utero* lung development. Infectious and inflammatory insults, particularly chorioamnionitis can substantially lung development via cytokines such as TNFα and IL1β which target not only the developing airways but the pulmonary vasculature as well. Such factors can pre-dispose the newborn to premature birth and subsequent bronchopulmonary dysplasia, especially in the setting of supplemental oxygen and mechanical ventilation in the intensive care unit. Maternal factors such as diabetes and obesity can also influence *in utero* lung development, with a potential role of chronic inflammation that overlaps with other factors such as infections which are more likely to occur in mothers with these chronic diseases.

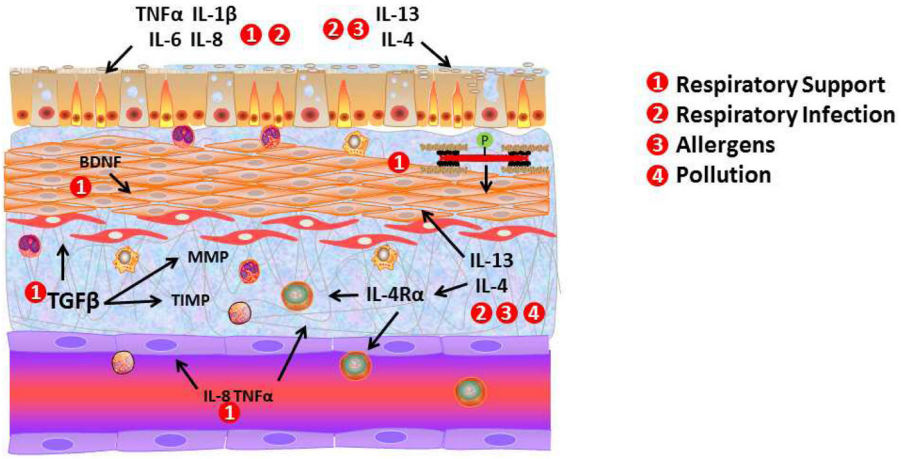

Figure 2.

Postnatal factors and underlying mechanisms in lung development. Although prenatal factors already predispose the newborn lung to diseases such as BPD, asthma and wheezing, both environmental and iatrogenic factors in early postnatal life can be either exacerbating or causative insults. For example, in premature infants, supplemental oxygen with or without mechanical ventilation in the neonatal intensive care unit enhances the inflammatory and pro-fibrotic environment in both airways and pulmonary vasculature contributing to BPD and asthma. Isolated or superimposed respiratory infections (particular RSV) can also activate common inflammatory and pro-fibrotic mechanisms that contribute to wheezing and asthma later in life. What is less clear is the factors that sustain these detrimental changes following the neonatal period. Here, growth factors such as BDNF may be contributory. Certainly, ongoing environmental insults such as pollution, allergens and environmental tobacco smoke exposure particularly by parents can continue to have detrimental effects on postnatal lung development leading to chronic airway diseases.

Table 1

Key Effects of Detrimental Prenatal and Postnatal Factors in Lung Development

Data derived from multiple references. See text for details and individual references from bibliography.

	Model	Key Findings	Mechanisms
Prenatal Factors	Intra-amniotic,-uterine, - peritoneal endotoxin	• ↓ Alveolarization • ↑ Surfactant • ↓ Gas exchange • Altered angiogenesis	• ↑ TNF-α, IL-1β, and IL-8 • ↓ Caveolin-1 expression • ↑ TGF-β expression and signaling • ↑ MMP expression • Altered FGF signaling
	Intrauterine growth restriction	• ↓ Alveolarization and vascularization • ↓ Surfactant • ↓ Gas exchange • Altered ECM composition	• ↓ Surfactant protein mRNA • ↓ Vascular endothelial growth factor • (VEGF) and VEGFR expression
	Maternal smoking	• ↓ Alveolarization • ↑ AHR • ↑ ASM thickness	• ↑ TGF-β • ↑ Procollagen I and III mRNA expression • ↑ Th2 cytokine responses • Altered Wnt signaling
	Maternal Diabetes	• ↓ Alveolar type II cell differentiation • ↓ Surfactant	• ↑ Oxidative stress • ↑ Collagen I and III expression • ↑ MMP expression • ↓ Phosphatidylcholine levels
	Pollution	• ↑ Airway inflammation • ↑ AHR • ↑ Mucus secretion	• ↑ TNF-α, IL-1β, KC, MCP-1 • ↑ Th2 cytokine responses
Postnatal Factors	Respiratory Support	• ↓ Alveolarization • ↑ AHR • ↑ ASM thickness • ↑ ASM proliferation	• ↑ TNF-α, IL-1β, IL-6, and IL-8 • ↑ TGF-β expression and activity • ↑ MMP/TIMP expression • ↑ BDNF expression

	Model	Key Findings	Mechanisms
		• ↑ ECM remodeling • ↓ Airway relaxation	• ↑ Myosin regulatory light chain • phosphorylation • ↓ cAMP and PGE_2 levels
	Respiratory Infection	• ↑ Airway inflammation • ↑ Mucus secretion • ↑ AHR	• ↑ IL-13 and TNF-α • ↑ Th2 responses mediated by IL-4Rα
	Allergens	• ↑ AHR • ↑ ECM remodeling	• ↑ IL-4/IL-13 expression • ↑ Mucus production
	Pollution	• ↑ AHR • ↑ Epithelial-mesenchymal transition of airway epithelial cells • Altered distal airway structure	• ↑ Oxidative stress • ↓ Activity of glutathione-dependent detoxifying enzyme