Preterm Birth Enhances Ambient Pollution Toxicity: Oxidative Stress and Placental Function

Lung function tracks an individual percentile established early in life largely determining the level of maximal function reached as a young adult, which in turn affects cumulative risk of lung disease as we age (1). This understanding emphasizes the need to identify modifiable environmental risk factors and maximize early lung function. Lung development begins in utero and is characterized by a carefully choreographed series of events. Optimal coordinated functioning of many complex processes and their networks of interaction are necessary for normal lung development and the maintenance of respiratory health. We increasingly understand that lung function trajectories are largely established by in utero factors. Epidemiological studies implicate exposure to ambient air pollution, especially particulate matter (PM), with increased early childhood respiratory disease. Air pollution remains a major pediatric public health focus because of its ubiquity and projections that exposure patterns may increase over the coming years because of climate change.

In this issue of the Journal, Decrue and colleagues (pp. 99–107) add significantly to this literature underscoring that infants born preterm may be particularly vulnerable to in utero exposure to ambient air pollutant effects on respiratory outcomes (2). These authors leverage infants (254 preterm born ≤32 wk) followed prospectively in the BILD (Basel-Bern Infant Lung Development) study, an unsedated cohort of neonates, to examine associations between prenatal ambient air pollution exposure (PM ≤10 μm in aerodynamic diameter, NO₂) with postnatal lung function assessed using tidal breathing flow volume loops and fractional exhaled nitric oxide, a marker of airway inflammation and/or oxidative stress, at 44 weeks postconceptual age. The primary vulnerable window ultimately considered was the second trimester of pregnancy. Preterm birth was further classified as extremely early (<28 wk), very early (29–31 wk), or moderate to late preterm (32–37 wk gestation). The study found the strongest associations between PM ≤10 μm in aerodynamic diameter levels during the second trimester and increased Vf and fractional exhaled nitric oxide values in moderate to late term infants when compared with term infants; the latter remained significant after accounting for multiple comparison. Preterm birth, irrespective of whether babies require neonatal intensive care, is associated with lasting respiratory abnormalities compared with those born at term (3). Infants born at 30–34 weeks’ gestational age without clinical lung disease have altered lung function that persists throughout infancy. This knowledge led these authors to hypothesize that pollution-
induced disruption in normal lung function combined with consequences of prematurity will interact to compound risks for adverse respiratory outcomes. Although it is difficult to disentangle pollution effects on lung development and prematurity altogether, there are plausible pathways leading to this compounded risk.

Air pollutants can impact anatomy and/or physiological functioning of the developing lung and interrelated systems (4). Owing to developmental plasticity, exposure to pollutants during prenatal and/or early childhood development may alter the normal course of lung morphogenesis, resulting in changes that affect both structure and function of the respiratory system. Programming effects may result from pollutant-induced shifts in a host of molecular, cellular, and physiological states. Specific key regulatory systems susceptible to programming include both central and peripheral components of neuroendocrine pathways and autonomic nervous system functioning, which, in turn, influence the immune system. Although mechanisms involved in the toxicity of PM are complex, evolving epidemiological and biological evidence suggests PM exposure can trigger a cellular stress response and consequent oxidative damage. Specifically, increased susceptibility in these early critical periods is believed to result from an imbalance of activating and detoxifying enzymes, including antioxidant enzyme systems. (e.g., glutathione S-transferases and epoxide hydrolases). Moreover, xenobiotic metabolism and subcellular components, such as mitochondria, are targets of ambient air pollution and play a role in lung function programming. During pregnancy, mechanisms operating at the level of the placenta are particularly emphasized.

Oxidative stress (OS) resulting from an imbalance between reactive oxygen species and antioxidant defenses is increasingly believed to play a central role in lung pathogenesis. OS in the placenta may affect placentation function or somatic fetal growth, which has implications for lung development (5). Oxidative balance depends not only on cellular antioxidant systems but also on mitochondrial functioning and processes that are sensitive to external and internal environmental exposures and are targets and generators of OS. The human placenta has a defined lifespan, and placental aging and mitochondrial dysfunction are known to play a key role in pregnancy pathophysiology and fetal development. Premature aging of the placenta leads to placental dysfunction and consequent poor fetal development and premature birth (6). Particulate air pollution may contribute to placental aging. Mitochondrial function is critical to maintaining appropriate energy supply, cell functions/signaling, and fetal vitality (7). Particulate air pollution exposure has been associated with changes in placental mitochondrial DNA copy number suggesting disrupted mitochondrial placentation function (8). Biomarkers of mitochondrial dysfunction at the maternal–fetal interface that correlate with in utero environmental exposures can thus provide insight into the underlying involvement of mitochondrial bioenergetics in disease programming (9). Increasingly, studies also demonstrate associations between mitochondrial DNA copy number and/or mutations and lung-related outcomes, including lung function, allergic disease, and asthma.

Premature birth during this critical period may further enhance consequent alterations in lung function and physiology (3), as the pulmonary antioxidant system is believed to develop during the last 10–15% of gestation. Like many other proteins, detoxification activities are under strict developmental control (10). Phase I Cyp3A enzymes and enzymes catalyzing glucuronidation, sulfation, and glutathione conjugation are present in the human fetus. Among infants born full term, these enzymes have the capacity to catalyze most phase I biotransformation reactions; however, the rate of these reactions is generally slower than in adults, making young infants still vulnerable to ambient pollution. After 2 weeks of life in a full-term infant, phase I and phase II detoxification systems are produced more fully. Thus, in addition to physiological reprogramming of respiratory structure and function induced perinatally by PM exposure, those infants born prematurely would have further reduced capacity at birth to detoxify the air they are breathing compared with their term-born counterparts. Infants are also at greater risk for respiratory damage relative to older children and adults given a respiratory rate almost three times faster, a ventilation rate up to 66 times greater, and a smaller alveolar surface area. ■

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