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Why Do Former Preterm Infants Wheeze?

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We are all beginning to accept that wheezing disorders in infancy, childhood, adolescence, and possibly beyond are problematic consequences of preterm birth. Whether this wheezing phenotype is synonymous with asthma is a matter of definition and subject to debate among the pediatric pulmonary community. Meanwhile, there is a lively discourse among adult pulmonologists and physiologists as to whether change in airway smooth muscle phenotype is the dominant contributor to asthma.¹ It is interesting how much we do not know in spite of substantial research on asthma pathophysiology! This knowledge gap is all the more stark in the developing respiratory system.

There is no doubt that very low birth weight infants are at greater risk of later wheezing disorders, and that this is aggravated by the presence of bronchopulmonary dysplasia (BPD).² This is not surprising, given the potential functional and structural injury that these infants' immature lungs sustain in the Neonatal Intensive Care Unit (NICU). What is surprising is that wheezing is the dominant later symptom in these infants in whom alveolar simplification and impaired vasculogenesis are the dominant early pathobiologic processes contributing to their lung injury.³ The question arises whether early interventions such as exposure to supplemental oxygen in the NICU have long-term effects on the immature conducting airways beyond their role in the development of BPD. For example, we recently found that the immature human airway smooth muscle is highly sensitive to even short durations of hyperoxia, demonstrating increased proliferation at clinically moderate levels of oxygen (<60%), but apoptosis at higher levels,⁴ with either effect being detrimental to the structure and function of the developing airway. Whether insults such as brief periods of mechanical ventilation, or even continuous positive airway pressure, influence the airway during a critical growth period is currently unknown.

What do we know about respiratory morbidity in the late (or near late) preterm infant? Available data largely indicate that these infants are also predisposed to wheezing in infancy and early childhood.⁵⁻⁷ This is not a cohort at risk for exposure to excessive supplemental oxygen or ventilatory support, and unlikely to develop BPD. There we must look beyond sustained lung or airway injury for etiology. Early birth and ex-utero lung development itself likely account for a large part of the developmental differences that contribute to wheezing

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in this population. For example, in the late preterm infant exposure to 21% oxygen represents premature exposure to a hyperoxic environment compared with that in utero. Other postnatal developmental perturbations may also play a role. A variety of risk factors have recently been shown to be associated with asthma. These include prenatal exposure to chorioamnionitis, intrauterine growth restriction, accelerated postnatal growth, antibiotic exposure, and postnatal exposure to viral infection (notably respiratory syncytial virus or rhinovirus).⁸⁻¹⁴ The proposed mechanisms underpinning the observed associations between chorioamnionitis, altered colonization, or postnatal infections, and later wheezing, hinge on alterations of the immune system as well as of the pulmonary system. In addition to changes in alveolar and airway architecture, alterations in immune and inflammatory responses, lung innervation, and even metabolic status have the potential to contribute to the asthma-like phenotype in children born preterm. Furthermore, the emerging field of developmental immunotoxicology suggests that certain medications may trigger life-long changes leading to asthma-like phenotypes,¹⁵ and preterm infants may be even more vulnerable due to their relative immaturity.

In this issue of *The Journal*, McEvoy et al evaluated respiratory function in a group of healthy, late preterm infants in Portland, Oregon.¹⁶ Their data were collected using sophisticated pulmonary function assessment at 40 weeks' post-menstrual age for both a late preterm and a term control group. Although they did observe a higher tidal volume and lower compliance in the late preterms, their most striking finding was a 33% higher respiratory resistance in the preterm group at comparable weights. Unfortunately, we can only speculate what the underlying pathophysiologic mechanism might be. Furthermore, it would be interesting to determine whether the changes observed early in life have long-lasting structural and functional impact. From the preclinical perspective, this will include the continuing development of survivable animal models, such as rodent pups undergoing mild and brief hyperoxic exposure simulating the NICU experience of late preterm infants of the type examined by McEvoy et al. From the clinical side, wouldn't it be nice to perform sequential imaging and functional studies of such infants, employing future technologies that could resolve individual conducting airways? Across the research spectrum, we also need a better understanding of how the pulmonary and extrapulmonary contributors to wheezing illnesses interact.

We do know that in term infants, reduced lung function at birth is associated with childhood asthma.^{17,18} We can only assume that the late preterm cohort is already at considerable risk, all the more reason to avoid aggravating the problem with adverse postnatal environmental exposures.

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Glossary

BPD	Bronchopulmonary dysplasia
NICU	Neonatal intensive care unit