

## CLINICAL REVIEW

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# Long-term Pulmonary Outcomes Among Premature Infants With and Without a History of Bronchopulmonary Dysplasia: How Different are the Risks?

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### *Introduction*

Preterm delivery is the most common cause of abnormal lung development and is associated with reduced lung function, wheezing disorders, and frequent rehospitalizations.<sup>1-3</sup> Those born prematurely are at much greater risk of developing bronchopulmonary dysplasia (BPD) and other chronic lung disease (CLD) in childhood.<sup>1</sup> A history of premature birth and BPD/CLD is also a well-recognized risk factor for developing pulmonary morbidity later in life.<sup>4-6</sup> However, more recent evidence suggests that prematurity itself is a potentially under-recognized risk factor for pulmonary morbidity in adults, even among those who do not have a history of pulmonary disease earlier in life. Failing to attain optimal pulmonary function during development can manifest with obstructive symptoms in adults, who may be subsequently misdiagnosed as having asthma.<sup>3</sup> The purpose of this review is to summarize some of the recent data that supports the importance of prematurity as an independent risk factor for pulmonary disease, and help support timely diagnosis and treatment.

### *Prematurity and Altered Lung Development*

The third trimester is critical to lung maturation, including the full development of surfactant and antioxidant systems, lung volume, and surface area. Consequently, even birth at 33-34 weeks is associated with significant structural and functional pulmonary abnormalities.<sup>7</sup> One study of pre-term infants who were not ill or in need of supplemental oxygen found that, in comparison to their full-term counterparts, they had reduced lung compliance and gas-mixing efficiency. Differences in pulmonary function between the groups persisted when the premature birth group was retested at 39-41 weeks postmenstrual age. The authors concluded that exposure to the ex-utero environment prematurely could adversely affect alveolarization and the pulmonary elasticity.<sup>8</sup> Preterm delivery is also associated with changes in airway epithelium, although these data largely derive from studies done before the availability of surfactant.<sup>9</sup>

### *Early Prematurity and Pulmonary Disease*

A study of 811 infants born before 30 weeks gestational age (GA) with at least three years of follow-up found a similar risk for developing pulmonary conditions among those with and without a history of BPD (75% vs 60%; OR, 1.8; 95% CI, 1.27-2.54), although infants with previous BPD were more likely to

develop asthma. The authors noted significant differences in the care received between these groups, including the greater use of inhaled corticosteroids, referral to pulmonologists, and earlier referral to pulmonology among patients with a history of BPD. The authors concluded that failure to recognize prematurity as an independent risk factor for pulmonary disease may have resulted in undertreatment.<sup>10</sup>

### *Late Prematurity and Lung Disease*

Authors of a recently published prospective longitudinal study of newborns in Spain noted that while 84% of premature infants are between 32 and 36 weeks gestational age, their risk of developing respiratory morbidity later in life has not been well-characterized. They followed 232 infants from birth to 7-8 years of age. The incidence of bronchiolitis (56.9% versus 37.1%,  $p=0.002$ ) and recurrent wheezing (44.8% vs 31.0%,  $p=0.03$ ) were significantly higher in the preterm cohort in comparison to infants born at term. Moreover, the study showed that the risk factors for bronchiolitis and asthma differed between these groups. Among those with a family history of maternal asthma, the risk of developing bronchiolitis was significantly increased among full-term (OR = 8.3, CI 2.5-27.45), but not pre-term infants. Conversely, having older siblings increased the risk of developing asthma (OR=5.8, CI=1.11-2.08) among pre-term but not full-term infants. The authors concluded that differences in the clinical context in which symptoms present may differ between children with a history of prematurity, potentially delaying diagnosis.<sup>11</sup>

A cross-sectional population study in the United Kingdom compared outcomes between early (37-38 weeks) and full-term infants up to 10 years of age. The early-term cohort was more likely to be admitted to a neonatal intensive care unit (OR 1.7, 95% CI 1.2-2.5) and to a hospital in the first year of life (OR 1.6, 95% CI 1.2-2.1). Differences between the groups persisted into later childhood, with a higher incidence of a history of wheezing (OR, 1.4; 95% CI 1.05-1.8) and recent wheezing within the past year (OR 1.4, 95% CI 1.02-2.0) among early-term children older than 5 years of age.<sup>12</sup>

A separate longitudinal cohort study compared lung function and pulmonary morbidity among similarly defined early- and full-term subjects. The study demonstrated poorer adjusted spirometry measures at ages 8-9 years, but not at 14-17 years,

although the incidence of pulmonary symptoms and asthma did not differ. The authors of this study concluded that early delivery should be avoided due to the associated risk in morbidity later in life.<sup>13</sup>

### ***Prematurity With and Without a History of Bronchopulmonary Dysplasia***

The extent to which a history of premature birth and BPD increases the risk of pulmonary disease over that of premature birth alone is not clear. One cross-sectional study of adults ages 21-22 years in Canada born prematurely found that those with history of BPD were at greater risk of mild airflow obstruction and pulmonary gas trapping. This study was limited by a small sample size, including only 26 subjects in the preterm group that developed BPD.<sup>5</sup>

A prospective cohort study of extremely preterm infants, described as a gestational age  $\leq 26$  weeks at delivery, examined lung function at age 6.5 years. Compared to full-term controls, extremely preterm infants had lower forced vital capacity (FVC), forced expiratory volume (FEV<sub>1</sub>), and respiratory impedance. Amongst children born between 22 and 24 weeks gestational age, the prevalence of FVC and FEV<sub>1</sub> results below normal limits was 24% and 40% respectively. Differences in pulmonary function were not significantly affected by a history of BPD. However, as 90% of the extremely preterm infant group developed BPD, the study may have been underpowered to characterize differences in outcomes associated with this comorbidity.<sup>14</sup> Additional information may be derived from studies of very low birth weight infants, many of whom are also born prematurely. A study of adults ages 18-27 years with very low birth weight (VLBW, <1500 g, gestational age 29.2 +/- 2.2 weeks) found that both those with and without a history of BPD had reduced airflow, including FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and FEF<sub>25-75%</sub> compared to a similar aged cohort who were born at 37 weeks GA or later. These differences persisted after adjustment for age, gender, current height, BMI, parental education, maternal smoking during pregnancy, the subject's current daily smoking, obstructive airways disease, atopy, frequency of leisure time conditioning activity, and one or more sign of obstructive airways disease. Greater impairment in airflow was observed in the 18% of the VLBW cohort (n=29) with a history of BPD.<sup>15</sup>

A more recent study from Australia examined expiratory airflows among people aged 25 years who were born before 28 weeks GA or weighed less than 1000 g at birth with control subjects born contemporaneously and weighing more than 2499 g at birth. The aim of the study was to characterize differences in lung function in these groups following the introduction of surfactant, and showed significantly better spirometry results, including FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, and FEF<sub>25%-75%</sub> among control subjects. These differences were greatest between the control group and those with a history of BPD.<sup>16</sup> Authors of an accompanying editorial stressed the importance of recognizing the long-term influences of very preterm birth or very low birth weight on lung function as risk factors for pulmonary morbidity

in adults. and should consider adults who were born prematurely to be at high risk of lung function deficits.<sup>17</sup>

### ***Discussion***

Several lines of evidence support the importance of prematurity as an independent risk factor for lung disease, at least through young adulthood, possibly resulting from abnormal lung development.<sup>16</sup> The underlying mechanisms are unclear, with possibilities that include accelerated decline in lung function and/or lower resistance to noxious stimuli.<sup>3</sup> Recognition of the relevance of prematurity as a risk factor for pulmonary disease later in life is relevant to both diagnosis and management. Compared to those with a history of BPD or CLD of infancy, well-recognized risk factors for later development of asthma, pulmonary disease of prematurity may go undiagnosed or undertreated.<sup>10</sup> Frequently presenting with obstructive symptoms, pulmonary disease associated with prematurity is often only partially responsive to sympathomimetics.<sup>16</sup> Underappreciation of the relevance of pre-term birth to pulmonary disease in adults is even evident in reference material created by leading medical societies. Among risk factors for developing asthma as an adult, the American Lung Association lists "lung problems during infancy and childhood" but not prematurity itself.<sup>18</sup>

There are several obstacles to characterizing the impact of pre-term delivery on future respiratory outcomes. Some factors that affect fetal lung development may also increase the risk of premature birth, such as maternal smoking.<sup>14</sup> There are varying definitions of BPD in the literature, complicating efforts to clearly delineate the population of pre-term infants who do not have this condition. In addition, the treatment of prematurity changes over time, which may modify the association of pre-term delivery and subsequent adult disease. Ongoing study of prematurity and respiratory illness in the context of these changes may help to further elucidate some of the underlying mechanisms by which they are related.

### ***Conclusion***

Current literature demonstrates that the incidence of pulmonary disease among premature infants is high, and approaches that of infants who have BPD or other CLD. Failure to recognize prematurity as an independent risk factor for pulmonary disease may lead to delays in diagnosis and treatment.

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