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Journal

Proceedings of UCLA Health, 24(1)

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Publication Date

2021-01-11

CLINICAL REVIEW

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.[1-3] Those born prematurely are at much greater risk of developing bronchopulmonary dysplasia (BPD) and other chronic lung disease (CLD) in childhood.[1] A history of premature birth and BPD/CLD is also a well-recognized risk factor for developing pulmonary morbidity later in life.[4-6] 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.[3] 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.[7] 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.[8] Preterm delivery is also associated with changes in airway epithelium, although these data largely derive from studies done before the availability of surfactant.[9]

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.[10]

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.[11]

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.[12]

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.[13]

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.[5]

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 (FEV1), and respiratory impedance. Amongst children born between 22 and 24 weeks gestational age, the prevalence of FVC and FEV1 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.[14] 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 FEV1, FEV/FVC, and FEF 25-75% 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.[15]

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_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ among control subjects. These differences were greatest between the control group and those with a history of BPD.[16] 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.[17]

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.[16] The underlying mechanisms are unclear, with possibilities that include accelerated decline in lung function and/or lower resistance to noxious stimuli.[3] 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.[10] Frequently presenting with obstructive symptoms, pulmonary disease associated with prematurity is often only partially responsive to sympathomimetics.[16] 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.[18]

There are several obstacles to characterizing the impact of preterm delivery on future respiratory outcomes. Some factors that affect fetal lung development may also increase the risk of premature birth, such as maternal smoking.[14] 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 preterm 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.

REFERENCES

1. **Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, Sheikh A**. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med*. 2014 Jan 28;11(1):e1001596. doi: 10.1371/journal.pmed.1001596. PMID: 24492409; PMCID: PMC3904844.
2. **Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, Quigley MA**. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population

based cohort study. *BMJ*. 2012 Mar 1;344:e896. doi: 10.1136/bmj.e896. PMID: 22381676; PMCID: PMC3291750.
3. **Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L**. Lung consequences in adults born prematurely. *Thorax*. 2015 Jun;70(6):574-80. doi: 10.1136/thoraxjnl-2014-206590. Epub 2015 Mar 30. PMID: 25825005.
4. **Joshi S, Powell T, Watkins WJ, Drayton M, Williams EM, Kotecha S**. Exercise-induced bronchoconstriction in school-aged children who had chronic lung disease in infancy. *J Pediatr*. 2013 Apr;162(4):813-818.e1. doi: 10.1016/j.jpeds.2012.09.040. Epub 2012 Oct 27. Erratum in: J Pediatr. 2013 Jun;162(6):1298. PMID: 23110946.
5. **Landry JS, Tremblay GM, Li PZ, Wong C, Benedetti A, Taivassalo T**. Lung Function and Bronchial Hyperresponsiveness in Adults Born Prematurely. A Cohort Study. *Ann Am Thorac Soc*. 2016 Jan;13(1):17-24. doi: 10.1513/AnnalsATS.201508-553OC. PMID: 26523350.
6. **Davidson LM, Berkelhamer SK**. Bronchopulmonary Dysplasia: Chronic Lung Disease of Infancy and Long-Term Pulmonary Outcomes. *J Clin Med*. 2017 Jan 6;6(1):4. doi: 10.3390/jcm6010004. PMID: 28067830; PMCID: PMC5294957.
7. **Kotecha SJ, Dunstan FD, Kotecha S**. Long term respiratory outcomes of late preterm-born infants. *Semin Fetal Neonatal Med*. 2012 Apr;17(2):77-81. doi: 10.1016/j.siny.2012.01.004. Epub 2012 Jan 23. PMID: 22277112.
8. **Hjalmarson O, Sandberg K**. Abnormal lung function in healthy preterm infants. *Am J Respir Crit Care Med*. 2002 Jan 1;165(1):83-7. doi: 10.1164/ajrccm.165.1.2107093. PMID: 11779735.
9. **Looi K, Evans DJ, Garratt LW, Ang S, Hillas JK, Kicic A, Simpson SJ**. Preterm birth: Born too soon for the developing airway epithelium? *Paediatr Respir Rev*. 2019 Aug;31:82-88. doi: 10.1016/j.prrv.2018.11.003. Epub 2018 Dec 1. PMID: 31103368.
10. **Fierro JL, Passarella M, Lorch SA**. Prematurity as an Independent Risk Factor for the Development of Pulmonary Disease. *J Pediatr*. 2019 Oct;213:110-114. doi: 10.1016/j.jpeds.2019.05.066. Epub 2019 Jun 28. PMID: 31262531.
11. **Morata-Alba J, Romero-Rubio MT, Castillo-Corullón S, Escribano-Montaner A.** Respiratory morbidity, atopy and asthma at school age in preterm infants aged 32-35 weeks. *Eur J Pediatr*. 2019 Jul;178(7):973-982. doi: 10.1007/s00431-019-03372-1. Epub 2019 Apr 18. PMID: 31001655.
12. **Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S**. Early-term birth is a risk factor for wheezing in childhood: A cross-sectional population study. *J Allergy Clin Immunol*. 2015 Sep;136(3):581-587.e2. doi: 10.1016/j.jaci.2015.05.005. Epub 2015 Jun 24. PMID: 26115906.
13. **Kotecha SJ, Watkins WJ, Lowe J, Henderson AJ, Kotecha S**. Effect of early-term birth on respiratory symptoms and lung function in childhood and adolescence. *Pediatr Pulmonol*. 2016 Nov;51(11):1212-1221. doi: 10.1002/ppul.23448. Epub 2016 Apr 28. PMID: 27124554.
14. **Thunqvist P, Tufvesson E, Bjermer L, Winberg A, Fellman V, Domellöf M, Melén E, Norman M, Hallberg J**. Lung function after extremely preterm birth-A population-based cohort study (EXPRESS). *Pediatr Pulmonol*. 2018 Jan;53(1):64-72. doi: 10.1002/ppul.23919. Epub 2017 Nov 20. PMID: 29152899.
15. **Saarenpää HK, Tikanmäki M, Sipola-Leppänen M, Hovi P, Wehkalampi K, Siltanen M, Vääräsmäki M, Järvenpää AL, Eriksson JG, Andersson S, Kajantie E**. Lung Function in Very Low Birth Weight Adults. *Pediatrics*. 2015 Oct;136(4):642-50. doi: 10.1542/peds.2014-2651. Epub 2015 Sep 7. PMID: 26347433.
16. **Doyle LW, Irving L, Haikerwal A, Lee K, Ranganathan S, Cheong J.** Airway obstruction in young adults born extremely preterm or extremely low birth weight in the postsurfactant era. *Thorax*. 2019 Dec;74(12):1147-1153. doi: 10.1136/thoraxjnl-2019-213757. Epub 2019 Sep 26. PMID: 31558625.
17. **Dharmage SC, Bui DS, Perret JL, Lodge CJ**. Lung function deficits of adults born very preterm and with very low birthweight. *Lancet Respir Med*. 2019 Aug;7(8):643-645. doi: 10.1016/S2213-2600(19)30042-6. Epub 2019 May 8. PMID: 31078499.
18. Recognition is important. Even guidelines don't: https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/asthma-symptoms-causes-risk-factors/asthma-risk-factors.html. Accessed 9/21/20.