

## Long-term respiratory outcome following preterm delivery

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While increasingly small and more immature infants are now surviving, the prevalence of pulmonary sequelae has not declined, as might have been expected, increasing the burden of respiratory illness for both health professionals and the families concerned.<sup>[1]</sup> As yet, the long-term consequences of preterm delivery in terms of lung function are not fully understood. True alveoli do not appear until approximately 30 weeks of gestation and therefore the lungs are extremely immature in infants delivered prior to 28 weeks. The early respiratory impact of preterm delivery is evidenced by an increased incidence and severity of wheezing, hospitalisation, apnoeas, bronchiolitis and SIDS in the first year of life. There is an extensive body of literature on the potential impact of preterm delivery on subsequent lung development. Within the literature there are various different methods of assessing lung function during early life, however, there is a general consensus that in infants with BPD there is:<sup>[2,3]</sup>

- reduced lung volume and reduced compliance in the early neonatal period
- reduced airway calibre as reflected by increased resistance and decreased flows
- reduced gas mixing efficacy
- alterations in the control of breathing.

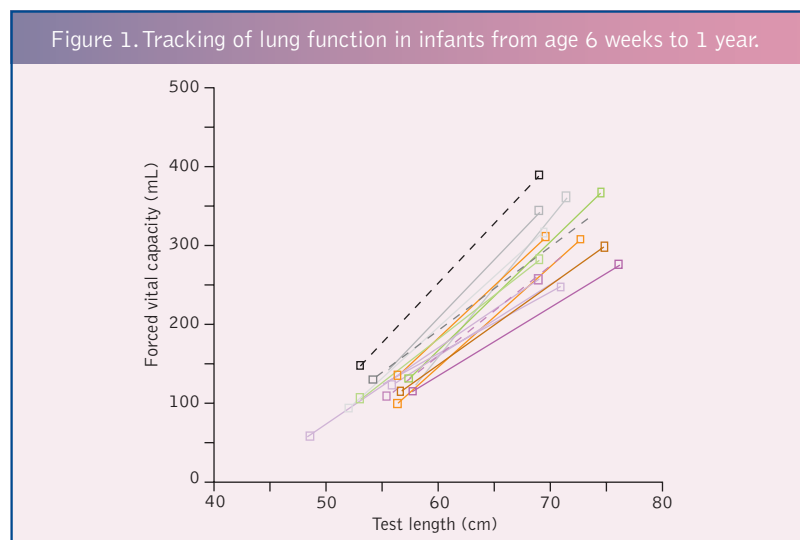
Preterm delivery results in alterations in alveolar and vascular development and airway growth. However, it is unclear whether these changes can be attributed to one specific factor or the culmination of a number of factors, such as those underlying PTL (i.e. maternal smoking, infection, IUGR), precipitous exposure to air breathing, neonatal lung disease and/or the effects of treatment, or a genetic susceptibility which may affect gene/environmental exposure and the way in which the infant responds to these factors.

### Longitudinal measures of lung function in resolving CLD

During the first year of life, although oxygen levels usually normalise there is persistent airflow obstruction with little evidence of 'catch up' growth. Furthermore, it is important to remember that these changes are not limited to preterm infants who have a challenging neonatal course and that diminished lung function can be present even in apparently healthy preterm infants who have had no resuscitation or ventilatory support.<sup>[4-8]</sup> It is therefore crucial to use appropriate control groups when investigating the effect of different neonatal treatment strategies because lung development is altered by preterm delivery *per se*.

There is remarkable tracking of lung function throughout childhood and significant evidence to suggest that the level of lung function in adulthood may be determined during fetal development and the first months of life. Data from a study that evaluated infant's lung function at 6 weeks then again at 1 year indicate that both infants with the highest lung function, according to body size, and those with reduced lung function during early life retained that position at 1 year of age (Figure 1).<sup>[5]</sup>

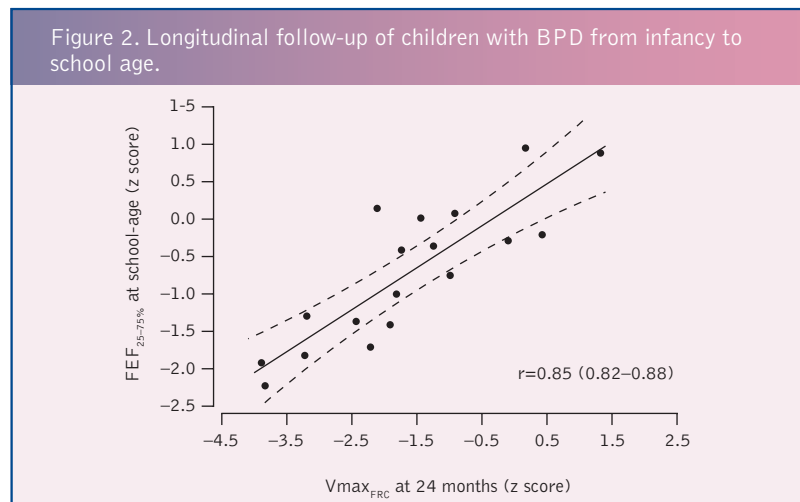
To date, there have been relatively few studies published on pre-school



children due to the inherent difficulties in measuring lung function in very young children with BPD (e.g. oral aversion, difficulty accepting face mask or mouth piece, lack of co-ordination or concentration or developmental delay) which means that many children are not evaluated until they are >5 years old.

An important longitudinal study, albeit in a small number of infants (n=18), evaluated lung function from birth (mean 28 weeks gestation and 930 g) until 9 years of age. The results demonstrated a strong correlation between FEF in early life and these measures at school-age (Figure 2).<sup>[9]</sup>

Data from a cohort of children born in 1991 to 1992 confirm that preterm infants are more likely to have reduced lung function when they are school-age than their healthy full-term counterparts.<sup>[10]</sup> Those infants that were <28 weeks gestation and <1000 g demonstrated highly significant reductions in all spirometric parameters (Table 1). In addition, those infants with BPD and those who developed asthma had significantly worse airflow and gas trapping at age 8 to 9 years than other preterms. Thus long-term abnormalities detected in children born preterm during the pre-surfactant era are still evident in the post-surfactant era, although survival for LBW infants has improved. Furthermore, in children aged 8 to 14 years, prematurity and BPD were associated with long-term airway obstruction, bronchial lability and increased bronchial responsiveness – this held true even for premature infants without BPD.<sup>[11]</sup>



| Table 1. Respiratory function in a cohort of preterm and healthy full-term children aged 8 to 9 years. <sup>[10]</sup> |                                |                                      |
|--|--------------------------------|--------------------------------------|
|  | <28 weeks GA/<1000g<br>(n=240) | Healthy full-term infants<br>(n=208) |
| FEV <sub>1</sub> (%)   | 85                             | 97                                   |
| FVC (%)  | 86                             | 95                                   |
| FEF <sub>25-75</sub> (%)   | 65                             | 86                                   |
| RV (%)   | 130                            | 112                                  |

81% and 79% follow-up for LBW and healthy full-term infants, respectively.

### Long-term respiratory follow-up to adulthood

There are very limited data on adult survivors, given that very few preterm individuals survived prior to the 1960s and the introduction of ventilatory support. It is also difficult to generate a clear picture from the literature because of differences within the populations being evaluated.

A recently published report on a Netherlands birth cohort of young adults demonstrated that preterm birth was associated with significant reductions in FEV<sub>1</sub> and gas transfer, elevated airways resistance, and reduced exercise capacity and anaerobic threshold (Table 2).<sup>[12]</sup>

While the results of this study are important, they should be interpreted with caution. By the time of the study, approximately 30% of the preterm cohort were smokers compared with only 15% of the full-term controls. Furthermore, the investigators concluded that there was no significant difference in lung function or exercise parameters between preterm individuals with or without BPD, but this was based on a post-hoc analysis of only 20 males (8 with and 12 without BPD). While mean lung function parameters appeared to be within the normal range, the prediction equations were not appropriate, as can be seen from the mean % predicted of 110% and 216% for FEV<sub>1</sub> and Raw in the fullterm controls.

Table 2. Lung function in a cohort of young adults born prematurely in the Netherlands.<sup>[12]</sup>

|                       | Preterm<br>(n=42) | Full-term<br>(n=48) |
|-----------------------|-------------------|---------------------|
| FEV <sub>1</sub> (%)  | 95                | 110                 |
| DL <sub>CO</sub> (%)  | 88                | 96                  |
| Raw (%)               | 82                | 60                  |
| Exercise capacity (%) | 185               | 216                 |
| AT (L/min)            | 1.55              | 1.84                |

This emphasizes the importance of including a prospective control group whenever possible in such studies, and developing more appropriate reference ranges for children. When translating the results of this study into clinical practice many very important subclinical changes will be missed. Real efforts must be made to gather more appropriate reference data, particularly between childhood and adulthood.

Evidence also indicates that the consequences of preterm birth may lessen over time; however, the consequences of SGA at preterm delivery appear to be long-lasting in terms of airflow obstruction and cardiovascular reprogramming (unpublished data). In LBW infants SGA but not AGA was associated with reduced cardiac output and gas transfer at rest which normalised on exercise.

Within this field there is a number of inherent problems when interpreting the literature including: respiratory follow-up time is usually limited to intact survivors who have sufficient maturity and coordination to undertake the tests, CLD is poorly categorised, heterogeneity of populations and methodologies, lung function tests are insensitive to acinar development, inappropriate use of reference data or controls and a lack of longitudinal studies measuring lung function from birth to school-age.

Available data indicate that long term respiratory problems may persist following preterm delivery. In preterm infants there is significant respiratory morbidity including increased frequency of cough and wheezing. Even in the absence of such symptoms there may be subclinical changes associated with airway obstruction, hyperinflation, airway reactivity and exercise limitation. These changes may improve with age in some individuals but are likely to persist in others. Adverse events are also observed in preterm children without significant neonatal disease, and IUGR may be of particular significance with respect to later outcomes – more so than has traditionally been recognised. Improved ongoing surveillance is essential if we are to understand the mechanisms and long term impact of early lung insults.

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