Lung consequences in adults born prematurely

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ABSTRACT

Although survival has improved significantly in recent years, prematurity remains a major cause of infant and childhood mortality and morbidity. Preterm births (<37 weeks of gestation) account for 8% of live births representing >50 000 live births each year in the UK. Preterm birth, irrespective of whether babies require neonatal intensive care, is associated with increased respiratory symptoms, partially reversible airflow obstruction and abnormal thoracic imaging in childhood and in young adulthood compared with those born at term. Having failed to reach their optimal peak lung function in early adulthood, there are as yet unsubstantiated concerns of accelerated lung function decline especially if exposed to noxious substances leading to chronic respiratory illness; even if the rate of decline in lung function is normal, the threshold for respiratory symptoms will be crossed early. Few adult respiratory physicians enquire about the neonatal period. The management of these subjects in adulthood is largely evidence free. They are often labelled as asthmatic although the underlying mechanisms are likely to be very different. Smoking cessation, maintaining physical fitness, annual influenza immunisation and a general healthy lifestyle should be endorsed irrespective of any symptoms. There are a number of clinical and research priorities to maximise the quality of life and lung health in the longer term not least understanding the underlying mechanisms and optimising treatment, rather than extrapolating from other airway diseases.

Preterm delivery (<37 weeks of gestation) accounts for 8% of UK births, and the proportion is increasing in many countries. Although survival of these infants has improved significantly with advances in obstetric and neonatal care, prematurity remains a major cause of infant and childhood mortality and morbidity. There is now a large population of adults who were born preterm, with current impairment in spirometry and increased susceptibility to respiratory infection, who constitute a significant public health and financial burden in terms of National Health Service healthcare provision.6,7

However, despite the numerical importance of the problem, it does not apparently impinge on the current practice of most adult chest physicians.9 The purpose of this article is to try to address this by highlighting how prematurity and its treatment impact long-term lung function and respiratory health; to discuss the implications for the treatment of obstructive airway disease in survivors of prematurity; and to highlight the gaps in knowledge that should be addressed by future research.

METHODS

We conducted PubMed and MEDLINE searches using the terms ‘bronchopulmonary dysplasia’ or ‘premature’ or ‘prematurity’ or ‘preterm’ AND ‘<follow up’ AND ‘lung’ or ‘pulmonary’ or ‘airway’ or ‘respiratory’ >AND <37 weeks gestational age’ or ‘preterm: <37 weeks gestational age’ or ‘early term: 37–38 weeks gestational age’.3

Terminology

- Extremely preterm: ≤28 weeks gestational age
- Very preterm: ≤32 weeks gestational age
- Late preterm: 33–36 weeks gestational age
- Preterm: <37 weeks gestational age
- Early term: 37–38 weeks gestational age

NORMAL LUNG DEVELOPMENT

It is impossible to understand the developmental consequences of prematurity and its treatment and how this results in long-term disease without understanding normal lung development. Antenatal lung development has been reviewed in detail elsewhere. Briefly, in the embryonic phase (0–6 weeks) the lung bud starts to differentiate from the primitive foregut and the main pulmonary arteries appear. In the pseudoglandular phase (7–16 weeks), the complete airway branching pattern is laid down, together with the pre-acinar vessels. The canalicular stage (16–26 weeks) is characterised by marked capillary multiplication, which establishes a loose three-dimensional network in the mesenchyme. There is flattening of the cuboidal cell layer and the first development of a thin air-blood barrier, with differentiation of type 1 and type 2 pneumocytes and the first appearance of surfactant. The saccular phase (27 weeks term) is followed by phase of alveolar development. These traditional anatomical stages have been shown to have accompanying gene expression patterns.10

Postnatally, the pattern of airway physiological development is best characterised by the global lung initiative (http://www.lungfunction.org/). The FVC and FEV1 increase throughout childhood to a plateau at 20–25 years. Meanwhile, the ratio (FEV1/FVC) decreases. Thereafter, there is a decline in both FEV1 and FVC into old age (figure 1). As a general rule, lung function is thought to track...
Throughout life, although under some circumstances there is potential for catch-up. The threshold for pathological airway obstruction may be crossed prematurely by any combination of (1) airway obstruction at birth, (2) failure to achieve normal airway growth in childhood and (3) accelerated decline in lung function.

Traditionally, alveolar numbers have been thought to be largely complete at age 2 years, thereafter with alveoli increasing in size. Recent in vivo studies using hyperpolarised 3-helium MRI suggest that alveolar numbers increase throughout the period of somatic growth, confirmed by direct histological measurements in rhesus monkeys. Hyperpolarised 3-helium MRI studies suggest that alveolar volume increases with ageing, particularly in the apices and mid-zones.

**PRETERM BIRTH AND LIKELY NEONATAL SCENARIOS**

Until recently most focus has been on preterm infants born at 32 weeks’ gestation or less, especially if these infants required respiratory support with mechanical ventilation and increased ambient oxygen in the neonatal period due to neonatal respiratory distress syndrome (RDS). RDS results from failure to adequately expand the lungs after birth due to surfactant deficiency, which is especially relevant to preterm infants. Many of these infants progressed to prolonged supplemental oxygen dependency especially due to ventilator-induced and hyperoxic-induced acute lung injury of the fragile newborn lung. In 1967, Northway and colleagues first described the evolving clinical condition and associated pathological correlates of this lung injury and in the process coined the term broncho-pulmonary dysplasia (BPD, often also called chronic lung disease of prematurity). Infants were more mature than the current preterm infant typically gestational ages of between 33 and 34 weeks and those who died from BPD had markedly enlarged alveoli rather than the fibrotic processes previously observed. The term ‘new’ BPD is often used to describe these changes. Thus, the effects of prematurity and its treatment have changed over time, and may change again in the future; it should not be assumed that follow-up studies of young ex-preterm adults are necessarily relevant to the preterm delivery of today. There have been various attempts to define BPD but of most prognostic value is supplemental oxygen dependency at and beyond 36 weeks’ postconceptional age.

More recently there have been attempts to define the severity of BPD on the basis of duration of oxygen dependency and any additional need for respiratory support. Admittedly, all these terms are crude, and more precise definitions of respiratory disease arising from prematurity are needed, preferably which predict outcome, but this is outwith the scope of this review.

There are several factors that may cause a premature birth and additionally likely to affect fetal lung development and adult outcomes; however, it is impossible to separate the causes from the neonatal consequences of prematurity. These include maternal smoking and chorioamnionitis. It is also becoming increasingly clear that even late preterm and early term delivery is associated with significant long-term morbidity. Another factor that can enhance airway obstruction is fetal growth restriction, which may be associated with preterm birth.

**FETAL PROGRAMMING**

The hypothesis that in utero events can reprogramme an individual for immediate adaptation to gestational disturbances but with deleterious consequences for later responses to adverse events, known as the Developmental Origins of Health and Disease hypothesis, has been studied in animal models in respiratory diseases. For example, in utero smoke exposure leads to enhanced responses to postnatal allergen and fungal exposure. In murine models, neonatal hyperoxia may affect adult cardiovascular function and lifespan and alter pulmonary oxidative stress and immune responses. The mechanism may be epigenetic, through DNA methylation. The most intriguing human data have come from a study of the responses to high-altitude hypoxia of adult survivors of persistent pulmonary hypertension of the newborn. Compared with 10 matched controls, the mean increase in pulmonary artery pressure at altitude measured by echocardiography at high altitude was significantly greater. There was no difference in the fall in arterial oxygen saturation. The relevance of this or any other effect of fetal programming and perinatal treatment in human survivors of prematurity is an important subject for future research. Whether similar abnormalities of the pulmonary arterial circulation persist in adult survivors of preterm birth is unknown, and it is speculative whether, if present, they may increase the risk of pulmonary hypertension if there is a second insult, for example, alveolar hypoxia at altitude.

**PRETERM BIRTH AND CHILDHOOD LUNG HEALTH**

In summary, the evidence below suggests that childhood survivors of preterm birth, irrespective of whether they require neonatal intensive care, have (a) increased respiratory symptoms; (b) at least partially reversible airflow obstruction, but with little evidence of eosinophilic inflammation; and (c) abnormal thoracic imaging.

**Respiratory symptoms**

Children who survive preterm birth have frequent respiratory symptoms and hospitalisation for respiratory reasons, especially...
in the first decade of life. Even late preterm infants have increased respiratory symptoms and greater likelihood of being given a diagnosis of asthma, although the exact cause for the symptoms is unclear (see below).

Pulmonary function
Obstructive spirometry with some acute bronchodilator reversibility is common after premature birth, including in late preterm delivery. The Avon Longitudinal Study of Parents and Children reported that children born at 33–34 weeks’ gestation had impaired childhood lung function compared to children born 25–32 weeks and who required mechanical ventilation. This is particularly important because babies born slightly prematurely often are born very prematurely.

Early studies suggested that in the first year of life, far from airway function catching up, it actually worsened over time. This airway disease is likely different from conventionally understood childhood asthma; there is evidence of increased airway oxidative stress, and there is no evidence of eosinophilic airway inflammation. Abnormal parenchymal development may lead to airflow obstruction, as may airway wall thickening. Space precludes a detailed review of all the literature in this area.

Even, early term delivery (37–38 weeks) has been associated with increased wheezing, although lung function and airway inflammation were not measured, so the relationship to conventionally understood childhood asthma is also unclear in this group.

Imaging
Lung parenchymal abnormalities are common in preterm survivors, especially in those with prolonged oxygen dependency. It is likely these will be non-progressive, but the extent and severity of some of these changes is concerning.

PRETERM BIRTH AND YOUNG ADULT LUNG HEALTH
The most persuasive evidence suggests respiratory symptoms are increased and that clinically relevant lung function impairment exists into early adulthood. However, most of these studies were undertaken in subjects at an age where lung growth was still ongoing and some of the findings contrast those reported elsewhere, which have provided some evidence for a more optimistic perspective. Ultimately the existing literature in adult survivors of preterm birth has been difficult to interpret for reasons that include small sample size and the lack of suitable control groups. These factors may contribute to a clinician ‘blind spot’.

Symptoms and quality of life
Increased respiratory symptoms have been shown to persist into early adulthood. Wong and colleagues reported significantly increased respiratory symptoms in a young adult population born at a time prior to the routine use of surfactant and who had all survived moderate to severe BPD. In a longitudinal evaluation of 21-year-old adults born prematurely, Narang and colleagues identified more respiratory symptoms in the preterm group compared with term controls. More recently, Gough et al. reported that adult survivors of BPD had significantly more symptoms, more likely to have an asthma diagnosis, be prescribed asthma medication than term controls and also have worse quality of life.

Lung function
The question whether this tracks through life such that they generally fail to reach peak predicted lung function by adulthood has been debated. It has been suggested that a degree of ‘catch-up’ or improvement in lung function may occur in survivors of BPD as they reach adolescence. However, this was not evident in a recent cohort study that reported a significant decline in lung function between the ages of 8 and 18 years. A short report of ex-BPD survivors also suggested a steeper decline. A study of adult survivors of BPD in their third and fourth decade of life confirmed substantial and clinically important airflow obstruction compared with preterm and term controls. In 57% of these BPD subjects, airflow obstruction was fixed or only partially reversible (Caskey PhD, QUB, unpublished data). It is uncertain whether impaired lung function is a consequence solely of prematurity or whether BPD is a specific factor. Halvorsen et al. reported lung function abnormalities increased with increasing BPD severity. Gibson et al. recently reported results of a lung function follow-up study of very low birthweight (VLBW) infants both with and without BPD at age 25 years. Adults with VLBW, most of whom were born preterm, had, as expected, more airflow obstruction than terms, but among the VLBW cohort, survivors of BPD had greater reductions in airflow compared with the non-BPD group. Bronchial hyper-responsiveness (BHR) has been reported in preterm survivors; in asthmatics, BHR is associated with a more rapid decline in lung function. Whether this is the case in survivors of prematurity is unclear.

There is some evidence for optimism in that, despite the survival of increasingly more premature infants, the FEV1% predicted in those who developed lung problems has actually improved over the last three decades. This may be due to improved medical care including routine use of surfactant, antenatal steroids and gentler mechanical ventilation strategies. There remains concern whether young adults born preterm, having failed to reach optimal lung function, will decline during adulthood with a steeper trajectory than those born at term and whether external factors including the irritant effects of pollution, infection and smoking will have a further detrimental effect on this. The study of Vollsæter et al. would suggest tracking, but this needs to be demonstrated in a larger cohort. With respect to other lung physiology, there are few studies. Narang et al. demonstrated impaired gas transfer in those born preterm compared with term controls. This normalised during exercise.

Structural lung changes
It is not clear if early preterm lung injury is associated with structural damage to surrounding lung tissue. What evidence there is suggests an association between the extent of radiological abnormality on high-resolution CT (HRCT) scans and the severity of lung function impairment. Wong and colleagues reported a high prevalence of emphysema in 21 adult survivors of moderate and severe BPD and found the extent of emphysema was inversely related to the FEV1 z-scores. Aquino et al. reported evidence of air trapping and reticular opacities on HRCT scans in the majority of BPD survivors and reported abnormal lung function significantly correlated with air trapping on expiratory scanning. However, these studies lacked a suitable control group. A recent study of adult BPD survivors demonstrated that all had radiological abnormalities on HRCT scans. Significantly more structural lung abnormalities were evident in the adult BPD compared with those preterm non-BPD controls.
Exercise capacity

To date, studies undertaken to characterise exercise capacity in adults born preterm have been relatively small with conflicting findings.47 55 67 A population-based national cohort study of male army conscripts reported preterm birth as an independent predictor of reduced exercise capacity.67 Narang and colleagues reported no significant difference in exercise capacity between those born preterm and term controls.53 Interestingly, those born small for gestational age but not those appropriate for gestational age had reduced cardiac output and carbon monoxide transfer at rest, but these normalised at maximal exercise, suggesting reprogramming of cardiac output rather than heart or lung disease. In contrast, Vrijlandt et al47 reported significantly lower diffusing capacity of the lung for carbon monoxide at rest and 15% lower workloads in ex preterms compared with term controls. Significant differences in activity levels between groups may have accounted for the lower exercise performance in ex preterms. Clemm and colleagues reported only modest differences in activity levels between those born preterm and term controls, which they attributed to baseline physical activity rather than neonatal factors.68 However, all preterm subjects had FEV1 measurements in the normal range, suggesting potential selection bias towards a milder population. Lowering et al66 reported more exercise limitation in ex-preterm adults than terms, which they attributed not only to ventilatory constraints but greater intolerance of dyspnoea and leg discomfort. In a recent study, BPD subjects had significantly lower exercise capacity than non-BPD and term controls despite similar weekly activity levels. Interestingly, <15% of the BPD adults were ventilatory limited.70

As the number of infants born prematurely has increased globally in the last 30 years, the longitudinal follow-up of larger cohorts of these infants throughout adulthood is required to improve understanding and raise awareness of long-term lung sequelae.71

CLINICAL PRESENTATIONS

There are likely two different groups to consider: those presenting to clinic with respiratory symptoms and those with no symptoms who may have significant lung impairment; this latter group would likely be detected at routine medical screening or at consultation for an intercurrent unrelated illness. Such patients should have their airway function evaluated in detail as above; correct management may reveal to the patient that in fact they were more symptomatic than previously realised. Key is questioning about early life.

APPROPRIATE QUESTIONING IN CLINICS IN THOSE PRESENTING WITH RESPIRATORY SYMPTOMS

In addition to a full ‘adult’ clinical respiratory history, specific questions that are relevant in adults who may be presenting with lung disease in part attributable to early-life events include

- birth weight
- gestational age
- time course on a neonatal unit
- the presence of respiratory distress at birth and/or the need for mechanical ventilation or oxygen
- maternal antenatal or postnatal smoking.

However, this in itself poses challenges in that unless the adult is accompanied by their parents they are unlikely to know some of these details. However, they usually know at least if they were very premature, if from no other source than family discussions. While paediatricians are more attuned to ask, have

the ‘red book’ and parents to inform, a more systematic method for recording neonatal data in adult patient records is required. Linked electronic datasets and patient records should address this issue in the future.

Worryingly, our recent British Thoracic Society survey highlighted that few adult respiratory physicians routinely consider early-life factors during patient assessment.8 Raising awareness across primary and secondary care will be imperative through structured education opportunities and is one of the purposes of this review.5

Diagnostic labels acquired in childhood should always be reconsidered in the adult Chest Clinic, together with reports of impaired physical fitness judged against peers and susceptibility to respiratory infection throughout childhood.

INVESTIGATIONS

Core pulmonary function tests would include pre-bronchodilator and post-bronchodilator spirometry including flow volume loop. Reversible airflow obstruction may exist without an eosinophilic inflammatory process, which expired nitric oxide (FeNO) measurement may help differentiate. Although pragmatically determining the presence or absence of eosinophilia is a challenge as part of a routine clinical assessment, it would seem justified in these young adults to measure FeNO or induced sputum eosinophils (if available) before committing them to an expensive inhaled corticosteroid therapy with risk of adverse effects.

Through expert consenus, we advocate a low threshold for more detailed physiological testing (total lung volume, gas transfer) when the clinical picture in an adult born premature presents with symptoms and clinical findings atypical for major prevalent respiratory diseases, particularly asthma and COPD. This may also require cross-sectional imaging with CT scanning. However, both approaches require validation before being able to make firm recommendations.

DIFFERENTIAL DIAGNOSES

Given that the major spirometric manifestation of a preterm birth and BPD in adults appears to be airflow obstruction, the differential diagnosis is primarily that of asthma and COPD, or an ‘Asthma COPD Overlap Syndrome’. Ascertaining where airflow obstruction is likely due to preterm birth is important given the potential for misdiagnosis and therefore undertreatment and overtreatment. A diagnosis of COPD generally considered as fixed or partially reversible airflow obstruction following sufficient exposure to noxious particles or gases (in particular, cigarette smoke) may need to be reconsidered in the young adult with little smoking history but fixed airflow obstruction. Likewise, although asthma, at least in its mildest forms, should typically be associated with a significant degree of bronchodilator reversibility, it may not be the correct diagnosis in a preterm-born young adult with exertional wheeze and dyspnoea. Characterising airways disease in adult survivors of preterm birth in terms of extent and nature of airflow obstruction, pattern of any inflammation and presence of airway reactivity is key.

Consideration of other neonatal interventions (eg, subglottic stenosis from repeated intubation or tracheomalacia or bronchomalacia secondary to prolonged mechanical ventilation) that may lead to later symptoms and impaired lung function is fundamental. One study reported that 7/13 adults who had undergone surgery for a patent arterial duct had a left recurrent laryngeal nerve palsy; misdiagnosis as asthma was common, but laryngoscopy correctly diagnosed the abnormality.73 This thankfully remains rare.

MANAGEMENT
There is no evidence-based or consensus-based guidelines. What is clearly essential is to eschew labels such as ‘asthma’ and ‘COPD’ in the preterm survivor; rather the individual components of any lung disease (fixed or variable airflow obstruction, airway inflammation (if any) and hypoxaemia) should be identified and treated on their merits, without extrapolating uncritically from evidence-based management of commoner airway diseases. The standard chronic respiratory disease principles of smoking cessation, annual influenza immunisation, maintaining physical fitness and a general healthy lifestyle should be adhered to. Although individuals born preterm are often risk-averse,74 physical activity likely underestimated.82 83

It is possible that postnatal respiratory infections, and the impact on future hospital admissions is underestimated.81 There are no evidence-based guidelines for treatment.90 There is no current evidence to advocate widespread use of bronchodilators or inhaled corticosteroids, although a component of variable airflow obstruction may be present. Additional evidence for optimal treatment is required.74 They should be introduced on the basis of an individual therapeutic trial and should be discontinued unless there is documented objective improvement. A lack of improvement should not lead to stepwise increases in doses of bronchodilators or particularly inhaled corticosteroids. The failure to correctly diagnose respiratory disease in adults born preterm raises concerns regarding under-appropriate, over-appropriate or inappropriate prescribing. Typically, airflow obstruction, when present, is not associated with asthma-type airway inflammation,43 which may or may not respond to asthma therapy.79 Therefore, an asthma misdiagnosis in a symptomatic individual is likely to lead to inappropriate stepwise increases in high-dose inhaled and/or oral corticosteroids with the associated deleterious effects of cumulative therapy: bone mineral loss,80 increased respiratory infection31 and cost. Whether long-term monitoring for (accelerated) decline of lung function is required is uncertain.

TRANSITION OF CARE FROM PAEDIATRICS TO ADULT
The survivors of preterm birth will reach adult life with airflow obstruction but possibly other comorbidities, including neurodevelopmental with secondary musculoskeletal issues such as joint contractures, visual impairment and possibly pulmonary hypertension, poor growth, bone disease and systemic hypertension.

In childhood, an integrated schools and community therapeutic team will have monitored and treated many of these children; when the child leaves school, none of this is available. Given the lungs continue to develop during childhood, the respiratory issues are unlikely to be majorly symptomatic, often merge with the array of normal childhood respiratory infections and may therefore be overlooked—a ‘forgotten generation’.

LIKELY IMPACT ON ADULT SERVICES
It remains unknown whether all young adults born preterm should have lung function and symptoms assessed. Since introduction into Quality and Outcomes Framework, spirometry has become integrated into primary care for the confirmation of COPD and therefore readily available. However, we currently do not know whether this is the optimal method to determine lung disease of prematurity from other physiological tests. Children and adults born preterm have increased risk of respiratory infections, and the impact on future hospital admissions is likely underestimated.82 83

RESEARCH PRIORITIES
There are large gaps in our understanding of lung disease associated with prematurity that now must be addressed through extensive research (box 1). A real likelihood of longstanding structural and functional limitation into adulthood for those born prematurely highlights the dearth of evidence for identifying and treating this condition. Further, the majority of research in young adults born prematurely that is currently available, by nature, is based on subjects born 20+ years ago where neonatal care and the size of babies was very different from today; and likely, in 20 years’ time, practice will have changed again.

Take home bullet points
- Increasing numbers of preterm newborns are surviving into adult life.
- They have a unique respiratory disease, comprising airflow obstruction without eosinophilic inflammation, failure of normal lung development, and lung parenchymal destruction.
- Additionally, they may have significant extrapulmonary comorbidities, including neurodevelopmental handicap, retinopathy and bone disease.
- Changing neonatal practices and the survival of ever smaller and more preterm babies mean that the nature of lung disease in survivors may change over time.
- There are no evidence-based guidelines for treatment. Survivors must not be labelled uncritically as ‘asthma’ or ‘COPD’ and treated accordingly. Rather it is essential to dissect out in the individual the components of any lung disease, such as fixed airflow obstruction, variable airflow obstruction, airway inflammation (if any) and hypoxaemia, and treat each on its merits.

Box 1 Research priorities
- Need to identify scale of the lung disease, at-risk populations and the moving goalpost effect of ever-better neonatal intensive care.
- We do not fully know the long-term consequences of prematurity, and particularly whether during adulthood there is an accelerated trajectory of decline in symptoms and function.
- Whether there is an active process continuing or whether the lung impairment relates solely to structural/developmental disruption during the neonatal period.
- Whether screening those born prematurely (or very preterm) allows a window of opportunity to intervene to optimise health status and prevent deterioration.
- Which investigations are optimal for clinically meaningful impaired lung health in those symptomatic.
- Impact on quality of life.
- The potential synergistic adverse effects of other factors such as infections, environmental pollution and smoking.
- Smoking cessation interventions specific for this population.
- Role of pharmacological therapy through well-designed randomised controlled trials.
- Whether annual monitoring is required.

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- Changing neonatal practices and the survival of ever smaller and more preterm babies mean that the nature of lung disease in survivors may change over time.
- There are no evidence-based guidelines for treatment. Survivors must not be labelled uncritically as ‘asthma’ or ‘COPD’ and treated accordingly. Rather it is essential to dissect out in the individual the components of any lung disease, such as fixed airflow obstruction, variable airflow obstruction, airway inflammation (if any) and hypoxaemia, and treat each on its merits.
However, the most important priorities remain the prevention of preterm delivery (and in this regard, the effects of tobacco legislation have been salutary)66, the optimisation of lung health throughout childhood, and above all, ensuring that adult physicians realise the ongoing burden of respiratory disease and comorbidities in this population. The goalsposts are not so much moving as disappearing over the horizon as neonatal intensive care salvages ever smaller babies, and uses ever more innovative treatments, which may, however, cause the baby to pay a heavy price in the long term; and this is the chief future challenge for the next generation of adult chest physicians.

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