Respiratory problems linked with extreme prematurity

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Abstract

Chronic respiratory morbidity is the common adverse outcome of extreme prematurity, particularly in infants who developed bronchopulmonary dysplasia (BPD). Affected infants can remain oxygen-dependent for many months, but not usually beyond two years of age. Troublesome respiratory symptoms requiring treatment and lung function abnormalities, particularly in those who developed BPD, can persist into adolescence and young adulthood. Rehospitalisations are common, particularly due to respiratory problems, but only in the first two years after birth. Many factors have been investigated with regard to a possible link to BPD development, one of those is chorioamnionitis which increases the risk of premature delivery. Early studies demonstrated that chorioamnionitis was associated with a reduction in the incidence of

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respiratory distress syndrome, but an increase in the incidence of BPD. However, in subsequent studies in which there had been gestational age adjustment in the analysis, no increased BPD risk has been highlighted in infants exposed to chorioamnionitis.

Keywords: bronchopulmonary dysplasia, rehospitalisation, lung function abnormalities, chorioamnionitis

Public declaration of interest

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INTRODUCTION

Infants born extremely prematurely can have significant developmental and motor delay in early childhood, and at school age they are more likely to have learning disabilities and behavioural problems than their classmates born at term [1]. Poor growth in early childhood is also common in those born extremely prematurely, particularly amongst those who had received postnatal steroids [2]. Chronic respiratory morbidity, however, is the common adverse outcome of very premature birth, particularly in infants who develop bronchopulmonary dysplasia (BPD). Approximately 40% of infants born either extremely low birth weight [3] or before 29 weeks of gestation [4] have been reported to develop BPD. The incidence of BPD is inversely related to gestational age and more common in boys rather than girls [5]. BPD is now diagnosed if infants require supplementary oxygen beyond 28 days after birth and then, in infants born at gestational ages of less than 32 weeks, its severity is graded according to level of respiratory support required at 36 weeks post-

menstrual age (PMA) [6]. The severity based definition of BPD compared to the definition of a requirement for supplementary oxygen at 36 weeks PMA classifies more infants with BPD, in one series the respective rates were 68% *versus* 42% [7]. A problem in comparing the incidence of BPD between neonatal units has been the lack of agreement regarding the criteria for starting and maintaining supplementary oxygen. A survey of the Vermont Oxford Network highlighted that only 41% of the respondents used the same criteria (<90%). Use of an oxygen reduction test [8] has helped to standardise the diagnosis of an ongoing need for supplementary oxygen.

Northway first described BPD in relatively mature infants who had severe respiratory failure in the neonatal period, they had been exposed neither to antenatal steroids nor postnatal surfactant [9]. At post-mortem, fibrosis and airway smooth muscle hypertrophy were prominent. Nowadays, BPD is frequently diagnosed in very prematurely born infants who may have had minimal or even no initial respiratory distress. This has been named « new » BPD and is mainly a developmental disorder in which the lungs fail to reach full structural complexity with a consequent reduction in the surface area for gas exchange [6]. The airways are spared and inflammation is less prominent than in the BPD Northway described [10]. Nevertheless, affected infants do suffer chronic respiratory morbidity.

This review focuses on the considerable, long-term, adverse respiratory outcomes of infants born extremely prematurely to emphasise the importance of identifying factors which might be manipulated to reduce that morbidity. There are many factors which have been investigated with regard to their possible role in the development of BPD, one of those is chorioamnionitis as it increases premature delivery. As a consequence, whether chorioamnionitis does increase BPD development and hence chronic respiratory morbidity is also discussed in this review.

I. RESPIRATORY PROBLEMS AT FOLLOW-UP

I.1. Supplementary oxygen at home (home oxygen)

Extremely prematurely born infants with BPD may require home oxygen for many months, but lung growth and remodelling results in progressive improvement in pulmonary function such that few infants

are oxygen dependent beyond two years of age [11]. Infants who require home oxygen compared to other BPD infants require twice the number of hospital readmissions in the first two years [11] and have more outpatient attendances and are more likely to wheeze and require an inhaler in the preschool years [12]. Even at school age, BPD infants who had home oxygen in the first two years after birth still had more respiratory- related outpatient attendances than those who did not need home oxygen [13].

I.2. Respiratory symptoms

Recurrent respiratory symptoms are common in extremely prematurely born children. In one study, 27% of infants born before 29 weeks of gestation were coughing and 20% wheezing at 6 and 12 months [14]. Respiratory symptoms remain common at preschool age with 28% of one BPD series coughing more than once a week and 7% wheezing more than once a week [12]. Even at school age and as young adults, prematurely born children, particularly if they had BPD, are more likely to be symptomatic. In one study it was demonstrated that 25% of 11 year olds who were prematurely born had a diagnosis of asthma which was twice the incidence seen in the matched controls [15]. Similar findings were also reported in 17 year olds; 56% of those born extremely prematurely had airway hyper-responsiveness compared to 26% of the controls [16]. In another, 27% of prematurely born young adults *versus* 8% of the controls reported excess of cough and wheeze [17].

I.3. Lung function abnormalities

Prematurely born infants have airways obstruction in the first two years after birth, the abnormalities being most marked in infants wheezing at follow-up [18]. The airway function abnormalities have been reported to deteriorate during infancy in extremely prematurely born infants [19]. Infants who had been supported by high frequency oscillation ventilation (HFOV) rather than conventional ventilation, however, had a smaller decline in small airway function between six and twelve months suggesting HFOV might have had a protective effect. To test that hypothesis, comprehensive respiratory assessment at follow-up is being undertaken of 12-year old children who were entered into a randomised trial comparing HFOV and conventional ventilation (UKOS) [4].

The lung function of prematurely born children does improve with age, but abnormalities are demonstrated in school age children, particularly in those with ongoing recurrent respiratory symptoms. Follow-up of babies from the EPICURE study at 11 years of age showed that 56% of the children who were all born before 25+6 weeks gestation, had abnormal baseline spirometry, the changes being most marked in those with prior BPD [15]. Airflow limitation has been reported in BPD survivors in late adolescence, worryingly with deterioration between 8 and 18 years [20]. Prematurely born school children [21] and young adults [22], have also been demonstrated to have reduced diffusing capacities compared to mature controls, which may relate to a decreased surface area for gas exchange because of a reduced number of alveoli, thickening of membranes due to fibrosis and/or ventilation perfusion mismatch. Those results are in keeping with the significant impairment in exercise capacity that has been reported in very prematurely born children [23]. The majority of the studies demonstrating lung function abnormalities in adolescents and young adults, however, report patients who had severe BPD.

I.4. Rehospitalisation

Readmission to hospital in the first two years after birth is common, in one series, 73% of infants with BPD required at least one readmission and 27% had three or more readmissions [24]. Readmissions are for respiratory disorders and particularly increased in infants who have a respiratory syncytial virus (RSV) lower respiratory tract infection [25]. In another series, BPD, younger gestation and lower birth weight significantly increased the risk of hospitalisation in infants with RSV infection [26]. Although, hospitalisation rates decline after the first two years in a case control study, a history of low birth weight was associated with greater risk of hospitalisation with respiratory disease in young adults between age of 18 and 27 years, with an odds ratio for hospitalization for respiratory illness of 1.83 [27].

II. BPD DEVELOPMENT

There are many factors which have been implicated in BPD development (Table 1). There has, however, been an increasing focus on whether antenatal inflammation/infection may have a role.

Table 1- Factors implicated in BPD development

Predisposed infant
Immaturity Family history RDS
Severe lung disease due to
Patent ductus arterious Pulmonary interstitial emphysema
Contributory factors
Infections Surfactant abnormalities Elastase/protease disturbance
High level of respiratory support
Oxygen toxicity Volutrauma

II.1. Chorioamnionitis – preclinical modes

To understand the role of *in utero* inflammation in fetal lung maturation, the impact of antenatal endotoxin on the structure and function of preterm sheep lungs has been examined [28]; a comparison group received betamethasone. Both treatments led to thinning of the alveolar walls and had similar effects on alveolarisation: the average alveolar volume increased by approximately 20% but the total alveolar number decreased by almost 30%. Alveolarisation begins with the appearance of secondary alveolar septa on the walls of existing airspaces [29], which may only be possible when the supporting primary septa are immature. If there is precocious differentiation of alveolar epithelial cells, they lose their ability to proliferate and form secondary alveolar septa [30]. The lack of effect of antenatal

glucorticoids on BPD development has been ascribed to increased survival of very immature infants, but an alternative hypothesis has been put forward and that is antenatal steroids are the first hit taken by the fetal lung, which primes the lung for more ventilation induced injury [31]. Antenatal glucorticoid treatment is given to women at risk of preterm delivery because it decreases the risk of death, RDS and intraventricular haemorrhage [32]. Preterm rupture of the membranes and histological chorioamnionitis are not contraindications to maternal glucorticoids [33, 34], but it has been suggested that in a subgroup maternal glucorticoids may increase lung inflammation promoting the subsequent development of BPD [35].

II.2. Chorioamnionitis – clinical studies

In early studies, antenatal infection and/or inflammation was shown to reduce the risk of surfactant deficiency and respiratory distress syndrome (RDS), but in one series chorioamnionitis was associated with an increased incidence of BPD [36]. The chorioamnionitis group, however, were of significantly lower gestational age and the data were not adjusted for that difference. In a case control study, in which the majority of infants were born prior to 29 weeks of gestation [37], histological chorioamnionitis was only associated with an increased BPD risk if the infant subsequently developed postnatal infection or required mechanical ventilation for more than seven days. The researchers [37] suggested that antenatal infection and/or inflammation is protective, unless there is postnatal sepsis or prolonged ventilation and proposed a multi hit model for BPD development. Subsequently, an increased incidence of BPD associated with chorioamnionitis has been reported in only six of 18 studies [38] and gestational age adjustment was only performed in one of the studies. In the remaining studies, multivariate adjustment generally showed no difference in the BPD risk. In addition, we reported not only no significant difference in BPD rates amongst infants who had and had not been exposed to chorioamnionitis, but also no significant differences in their lung function results either in the perinatal period or at 36 weeks PMA [39]. A possible explanation for the apparent lack of effect of chorioamnionitis on subsequent infant lung function may be the type of organisms known to cause chorioamnionitis in humans. These include *Ureaplasma urealyticum, Mycoplasma hominus and Gardnerella vaginali* which may be less injurious to the fetal lung than the endotoxin of *Escherichia coli.*

CONCLUSION

Extremely premature birth is associated with chronic respiratory morbidity even into adulthood, particularly in those who had developed BPD. Chorioamnionitis is associated with premature delivery, brain injury and adverse neurological outcome in prematurely born infants and hence it is important to minimize the effects of chorioamnionitis. In infants routinely exposed to antenatal steroids and postnatal surfactant, however, chorioamnionitis does not affect lung function in the perinatal period or at 36 weeks PMA or increase the incidence of BPD, thus reducing chorioamnionitis may not improve the respiratory outcome of very prematurely born infants.

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