Review

Neonatology
formerly Biology of the Neonate

Neonatology 2010;97:388–394
DOI: 10.1159/000297771

Published online: June 10, 2010

Pulmonary and Neurological Follow-Up of Extremely Preterm Infants

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Key Words
Extremely preterm infants · Pulmonary function · Cerebral palsy · Cognitive function

Abstract
The long-term consequences of extreme prematurity assume more importance as survival rates increase. Pulmonary problems are common immediately after birth and most extremely preterm (EP) infants (<28 weeks' gestation) require respiratory support. Many survivors develop bronchopulmonary dysplasia and some have long-term oxygen dependency, occasionally for years. Their brain has to respond to an environment very different to that of the uterus, and cerebroventricular haemorrhage and white matter injury occur much more frequently than in term infants. Compared with children born at term, EP survivors have higher rates of wheezing and hospital readmission for respiratory illnesses in the first few years after the primary hospitalisation. As they grow older they have reduced pulmonary function, particularly airway obstruction, and lower exercise tolerance. Larger proportions of EP children have significant developmental and motor delay in early childhood. At school age other cognitive impairments including learning disabilities and behavioural problems occur more frequently. Despite these difficulties, most EP survivors escape without major long-term pulmonary or neurological problems.

Introduction

Prior to the 1970s, long-term survival rates for extremely preterm (EP) infants (<28 weeks' gestational age) were very low, usually <10%. However, with the advent of modern neonatal intensive care, notably the ability to support ventilation, long-term survival rates for EP infants began to rise to approximately 1-in-4 for those of birth weight 500–999 g (extremely low birth weight; ELBW) on a regional basis in the late 1970s [1]. Following the introduction of prenatal corticosteroids, exogenous surfactant after birth, and an increased willingness to offer treatment, survival rates for EP infants were almost 3-in-4 by the late 1990s in population-based cohorts [2].

Despite prenatal corticosteroids and exogenous surfactant after birth, respiratory problems remain the major cause of mortality in EP infants in the surfactant era [3]. For those who survive the neonatal period, some develop bronchopulmonary dysplasia (BPD) [4, 5] with prolonged oxygen dependency, occasionally for years. Although most EP survivors have no ongoing oxygen dependency in early childhood, their respiratory health later in life remains to be determined.

EP infants are subject to much stress and many noxious stimuli in the newborn nursery to which they would not be exposed if they remained in the uterus. Compared with term infants, cerebroventricular haemorrhage [6] and white matter injury [7] occur more frequently, both of which contribute to the higher rates of substantial long-term neurological problems in EP survivors.

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1661–7800/10/0974–0388$26.00/0

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The purpose of this article is to review respiratory and neurological outcomes after discharge for EP infants, topics that have been recently reviewed elsewhere [8–11]. These reviews will be updated where possible, focusing on data on respiratory ill health and pulmonary function in later life, as well as cerebral palsy and other motor dysfunction, and developmental and cognitive delay. If data by gestational age are not available, data by birth weight will be considered as a substitute; outcomes for infants <1,000 g birth weight [1] generally mirror those for EP infants [2].

Pulmonary Outcomes

Readmissions to Hospital for Respiratory Illness

Rates of rehospitalisation of EP infants occur severalfold more than in term controls, and rates of hospital readmission have risen as survival rates of more EP infants have increased over time [12]. Overall, respiratory illnesses are the most common cause of rehospitalisation in these early years [13, 14], and occur more frequently in those preterm survivors who had BPD [13]. However, as the rate of hospital readmission declines later in childhood, those who had BPD are no more likely to be readmitted to hospital, for respiratory or other reasons [15].

Respiratory Health Problems

EP children have more ill health than term children over the first few years of life in most areas, but particularly in upper and lower respiratory illnesses [12, 16], and particularly in those who had BPD [12, 17–19]. Asthma is more prevalent in children who were very tiny or preterm infants at birth compared with those not born preterm or very tiny in some [20, 21], but this was not found in all studies [15, 22]. Those who had BPD sometimes have even higher rates of asthma [23].

Pulmonary Function

There are no long-term studies reporting pulmonary function tests in cohorts of EP survivors alone, partly because reports from preterm subjects born prior to the 1990s have predominantly selected subjects by birth weight, and those that have been reported include many subjects with gestational ages >27 weeks. Several studies have reported respiratory function data in preterm subjects compared with controls in the second and third decades of life [20, 24–27]. Two studies [24, 25] have reported outcomes for survivors who had ‘old' BPD [4]; subjects had required assisted ventilation, were oxygen-dependent at 28 days of life, and had scarring or cystic changes on chest X-ray. Northway et al. [24] described the respiratory function, at a mean age of 18.3 years, of 26 subjects born between 1964 and 1973 compared with 26 age-matched controls of similar birth weight and gestational age who had not been ventilated as infants, and 53 age-matched normal subjects who were not born preterm. Those with BPD had reductions in variables reflecting airflow and increased gas trapping compared with both the preterm controls and the normal controls. Very few of the subjects of this study would have been EP, as the mean gestational ages were 33.2 and 34.5 weeks for the two preterm groups, respectively. In a study of 147 survivors of birth weight <1,501 g born between 1977 and 1982 in the Royal Women's Hospital, Melbourne, who had respiratory function tests at a mean age of 18.9 (SD 1.1) years, the 33 (22%) who had BPD had substantial reductions in respiratory function variables reflecting airflow and more had reductions in airflow in clinically important ranges compared with the 114 preterm survivors without BPD [25]. Compared with normal birth weight term controls, the preterm subjects without BPD also had substantially reduced variables reflecting flow. In this study, 40 of the 147 subjects were EP; as expected, more EP subjects had BPD (41%) than the preterm subjects who were not EP (8%). The EP group had reductions in airflow compared with the remainder of the preterm cohort (e.g. forced expired volume in 1 s [FEV_1]; % predicted mean difference –5.8, 95% confidence interval [CI] –11.2 to –0.4), but little evidence of air trapping (e.g. residual volume/total lung capacity ratio; % mean difference 0.9, 95% CI –1.6 to 3.4).

Halvorsen et al. [20] reported the pulmonary outcomes for 46 subjects of birth weight <1,001 g or gestational ages <29 weeks at a mean age of 17.7 years from a geographically-based cohort of births between 1982 and 1985 in western Norway. Twelve (26%) of the subjects had moderate or severe BPD (oxygen requirement at 36 weeks' postmenstrual age), 24 (52%) had mild BPD (oxygen requirement at 28 days but not 36 weeks), and 10 (22%) had no BPD. Results were compared with 46 term controls. The preterm group had reductions in variables reflecting flow, and these were lower with increasing severity of BPD. Anand et al. [28] measured respiratory function with a portable spirometer at 15 years of age in a cohort of 128 children born weighing <1,500 g in 1980–1981 from the region around Liverpool, England, and compared the results with age-, sex-, and school-matched controls who were not <1,500 g birth weight (lowest birth weight 2,098 g) and again found reductions in some variables reflecting airflow in the preterm group.

In contrast with the preceding studies, in one study of 60 preterm subjects (median gestational age 31.5 weeks) born in the pre-surfactant era, compared with 50 healthy term controls there were no significant differences in measured pulmonary function at 21 years of age [27].

Only one study has reported changes from early school age up to late adolescence/early adulthood [25]. In this study, data at 8 and 18–22 years of age in 129 subjects of birth weight <1,501 g were described; 29 of the 129 subjects had BPD. Compared with respiratory function variables measured at 8 years, the only variable with a statistically significant difference over time in BPD subjects was a larger fall in the FEV_1/forced vital capacity ratio between 8 and 18 years of age compared with non-BPD preterm subjects (mean reduction 3.4, 95% CI 0.2–6.7%).

The effect of surfactant administered soon after birth on respiratory function of small numbers of children enrolled in clinical trials has been reported to be minimal [29], or possibly beneficial [30]. Moreover, the nature of BPD has also changed in recent times, with the advent of the 'new BPD' [5], which is characterised more by alveolar arrest rather than by pulmonary fibrosis and cyst formation typical of BPD in earlier times. The effect of BPD in the surfactant era on respiratory function has been reported to be similar to that before surfactant was available in several studies [31, 32]. In one study the 34 BPD cases had lower FEV_1 at 7–8 years of age than 34 VLBW children without oxygen dependency and 34 term controls [31]. In a geographic study of children born in the state of Victoria, Australia, respiratory function was measured in 81% (240/298) ELBW/EP children at a mean age of 8.7 years, and in 79% (208/262) NBW controls at a mean age of 8.9 years [32]. Most of the 89 ELBW/EP children with BPD had respiratory function within the expected range. However, some variables reflecting airflow were reduced in children with BPD, compared with both ELBW/EP children without BPD, as well as with NBW controls, but the differences were not as marked as in the pre-surfactant era.

Exercise Tolerance

Cardiopulmonary limitations may not be evident at rest using standard respiratory function measurements but only become apparent when the respiratory and cardiac systems are put under stress during an exercise test. In one study of 10-year-old children born in 1992–1994 weighing <1,000 g and before 32 weeks' gestation, the exercise capacity of the preterm group was approximately half that of term controls [33]. Compared with controls, some other studies [34–36], but not all [26, 37, 38], have also reported diminished peak oxygen consumption with exercise testing in preterm children. None of these studies was limited just to EP subjects, although one studied only infants with <801 g birth weight [36], another selected subjects with <32 weeks' gestational age or <1,500 g birth weight [26], and the remainder studied just those with BPD, and not complete cohorts of preterm children.

Neurological Outcomes

Cerebral Palsy and Other Motor Dysfunction

Cerebral palsy occurs more frequently in very preterm survivors compared with children born at term, and rates increase inversely with diminishing gestational age [39, 40]. In Victoria, 9.8% (16/163) of EP survivors born in 2005 had cerebral palsy at age 2 years compared with 0% of term controls [41]. Rates of cerebral palsy in EP cohorts born in earlier eras in Victoria were slightly higher at 11.0% for 1991–1992, and 12.1% in 1997. Rates of cerebral palsy may have fallen in the 2005 cohort because most survivors would have received caffeine, which reduces cerebral palsy rates [42], in 2005, but not in the 1990s, and also because the rate of prescribing early postnatal corticosteroids, also known to cause cerebral palsy [43, 44], fell substantially after the early 2000s compared with the 1990s. Rates of cerebral palsy in EP children have fallen over time in some other regional studies [45], but in others the rate has risen [46].

Apart from cerebral palsy, EP children have higher rates of other motor dysfunction than term children. Developmental coordination disorder occurred in 9.5% of EP survivors born in Victoria in 1991–1992 compared with 2.0% in term controls, [47] rates that were lower than in most other studies reported up to that time. Since that report, several other groups have described higher rates of motor impairment in preterm infants. Wocadlo and Rieger [48] reported that 31.3% of infants <30 weeks' gestation had suspect motor development at 8 years of age. In another study, 30% of EP children had developmental coordination disorder at 8 years whereas no classroom controls did [49].

Sensory Deficits – Blindness and Deafness

Rates of bilateral blindness after the introduction of cryotherapy and laser treatment to prevent retinal detachment are <3% in most reported studies of EP survivors, although higher in those <26 weeks' gestation [50]. Rates of bilateral blindness at 2 years of age in EP survivors in Victoria were 2.3% for the 1991–1992 birth cohort, 2.7% for the 1997 birth cohort, and then fell to 0% for the 2005 birth cohort [41], probably by chance as there were no changes in the techniques for diagnosis or treatment of severe retinopathy of prematurity over those years. Rates of deafness requiring amplification or worse also range between 3 and 5% in EP survivors [50]. Rates of deafness at 2 years of age in EP survivors in Victoria have been stable over time, at 0.9% for the 1991–1992 birth cohort, 1.3% for the 1997 birth cohort, and 2.5% for the 2005 birth cohort [41].

Developmental Delay

Developmental delay is more prevalent than cerebral palsy, blindness or deafness in EP survivors if defined as a developmental quotient (DQ) more than 1 SD below the mean and SD for contemporaneous controls; in the 2005 Victorian study, 48% of EP survivors had some developmental delay at 2 years of age compared with 21% of term controls [41]. The rates of developmental delay at 2 years of age for the 1991–1992 and 1997 birth cohorts in Victoria were 42 and 46%, respectively. Severe developmental delay (DQ > 3 SD below mean for controls), on the other hand, fell substantially over time in Victoria, from 14.8% for the 1997 birth cohort to 3.7% for the 2005 birth cohort [41].

Major Neurological Disability in Early Childhood

Rates of major disability in early childhood reported from regional cohort studies ranged between 21 and 35% for EP survivors born in the 1990s in a recent review [50]. For the state of Victoria, the rate of major neurological disability (DQ > 2 SD below term controls, moderate or severe cerebral palsy, blindness, or deafness) was 21% in 1991–1992, increased to 28% in 1997, and decreased to 20% in 2005. In particular, rates of severe disability (DQ > 3 SD below term controls, severe cerebral palsy, or legal blindness) were 8% in 1991–1992, increased to 15% in 1997, and decreased significantly to 4% in 2005 [41].

Survival and Quality-Adjusted Survival Rates

Long-term neurological outcomes cannot be interpreted fully without knowledge of the competing risk of mortality. Survival rates from geographically-determined cohorts born predominantly in the 1990s at 22 weeks' gestation were very low, but then increased quickly with increasing gestational age; up to 40% survival at 23 weeks, 40–60% at 24 weeks, 60–80% at 25 weeks, and 70–80% at 26 [50]. For births in the 2000s from regional cohorts, Field et al. [51] reported survival rates to hospital discharge of births in the Trent region of England in 2000–2005 of 9% at 23 weeks, 36% at 24 weeks, and 59% at 25 weeks, at the lower end of the rates reported for births in the 1990s. In the state of Victoria, the most recent survival rates to 2 years of age for births in 2005 were 5% at 22 weeks, 22% at 23 weeks, 51% at 24 weeks, 67% at 25 weeks, 82% at 26 weeks, and 89% at 27 weeks [41]. Overall, survival rates to 2 years of age for infants of 22–27 weeks born in Victoria increased significantly from 52.6% in 1991–1992 to 69.6% in 1997, but were not significantly different at 63.7% in 2005. Quality-adjusted survival rates to 2 years, which combine survival and disability data, followed a similar pattern and were 42.1% in 1991–1992, 55.1% in 1997, and 53.4% in 2005 [41]. It seems that survival and quality-adjusted survival rates peaked in the late 1990s, at least in the state of Victoria.

School-Age Outcomes

Early childhood outcomes may not be very predictive of long-term consequences because many cognitive processes are yet to emerge and others are only in the early stages of development; in particular early developmental assessments are only weakly related to intelligence later in childhood [52]. On the one hand, a child who is developing age-appropriately in early childhood (up to 2–3 years of age) may develop problems that only emerge later in childhood, but on the other hand, for many children early developmental delay is only a reflection of maturational lag as they eventually catch up with their peers. In the state of Victoria, the stability of diagnosis of neurodevelopmental disability from 2 to 8 years in a regional cohort of EP or ELBW children born in 1997 was compared with contemporaneous term controls [53]. At 2 years of age the rates of no, mild, moderate and severe disabilities in the EP/ELBW children were 51.9, 20.9, 13.4 and 13.9% respectively, and at 8 years were similar, at 43.9, 36.9, 10.7 and 8.6%, respectively. However, the agreement between disability status at age 2 and 8 years for EP/ELBW children was poor (κ [a measure of agreement beyond chance] = 0.20, $p < 0.001$), but was better for the control children ($\kappa = 0.37$, $p < 0.001$). Most of the change for the EP/ELBW cohort occurred within the classification of cognitive disability, with poor agreement between age 2 and 8 years ($\kappa = 0.11$; $p = 0.02$), whereas the degree of agreement in cognitive abilities for the control group was much higher ($\kappa = 0.37$; $p < 0.001$). The disability classifications for the other impairments (cerebral palsy, blindness, deafness) were relatively stable for the EP/ELBW children. One of 4 children classified as blind at 2 years was found not to have a severe visual defect at 8 years. One child who did not need hearing aids at age 2 years did have hearing aids at 8 years. The agreement in cerebral palsy classification, present in 22 (12%) EP/VLBW children at both ages, was moderate ($\kappa = 0.56$, $p < 0.001$), with 6 children outgrowing the diagnosis replaced by 6 new diagnoses made at 8 years, all of whom had mild cerebral palsy.

Intelligence

In a systematic review of children born before the 1990s, Bhutta et al. [54] reported that preterm children, the majority of whom were neither EP nor ELBW, had IQs approximately two-thirds of a SD lower than term controls. In a cohort of EP/ELBW children born in Victoria in 1991–1992 [55], the IQ difference was also approximately two-thirds of a SD lower than term controls, but in the most recent Victorian EP/ELBW cohort assessed at 8 years of age who were born in 1997, the mean IQ was 12.5 points lower than term controls, a difference of almost 1 SD [53].

In EP children, IQ tends to decrease with decreasing gestational age by approximately 1.7 IQ points per week [54, 56]. This is reflected in results from the EPICure study of children born <26 weeks' gestation in the UK and Ireland, where at 6 years of age IQ scores averaged 1.6 SD lower than controls [57]. Lower IQ scores in the most immature survivors in the EPICure study translated into high rates of intellectual impairment, with 21% of the EP cohort with an IQ <70, or 41% if compared with the mean of the control group. When reassessed at 11 years of age cognitive outcomes had not improved for the EPICure cohort; 40% of the EP group had a serious cognitive impairment compared with only 1% of controls [58]. The degree of intellectual impairment in the EPICure study was greater than that in a sample of 73 children <26 weeks in the Victorian cohort born in 1991–1992, only 9% of whom had an IQ >2 SD below controls at 8 years of age, and who had a mean IQ only 0.8 SD below controls [55]. Similarly, a Finnish study reported that only 12% of 103 children born at <27 weeks' gestation in 1996–1997 and followed-up at age 5 years had severe intellectual impairment compared with the test norm [59].

Attention and Executive Function

Executive function refers to a collection of cognitive processes which are responsible for goal-directed or future-oriented behaviour. The key elements of executive function include: (a) anticipation and deployment of attention; (b) impulse control and self-regulation; (c) initiation of activity; (d) working memory; (e) mental flexibility and utilization of feedback; (f) planning ability and organisation, and (g) selection of efficient problem-solving strategies [60]. Attention and executive deficits can have an important effect on academic achievement as well as social and adaptive functioning. A regional cohort of EP/ELBW children born in Victoria in 1991–1992 compared with term controls had global executive deficits at 8 years of age in the majority of cognitive measures administered [61]. While the magnitude of the significant group differences varied across measures from 0.4 to 1.1 SD, suggesting global impairment rather than deficits in specific executive domains, greater deficits were observed in visual-spatial reasoning and organisational tasks. Important executive deficits in visual organisation and planning deficits were identified at middle school age compared with term peers in a cohort of children <750 g birth weight from Cleveland, Ohio [62], while at follow-up in adolescence significant deficits in planning ability, working memory and mental flexibility were reported [63]. In a recent meta-analysis, Mulder et al. [64] found significant deficits in preterm, but particularly EP children (<26 weeks' gestation), across a range of executive processes. More specifically, the magnitude of the EP compared with the control group difference was 0.58 SD for selective attention, 0.67 SD for sustained attention, 0.50 SD for inhibition, and 0.69 SD for planning.

Academic Progress

In addition to neurosensory impairments, lower IQ, attention difficulties and executive dysfunction, children born EP are also at increased risk for deficits in other cognitive domains including language, visual-perceptual processing, and memory and learning [10]. Given this, it is not surprising that high rates of educational problems are also reported in this population; in the Victorian cohort from 1991 to 1992, 20% of EP/ELBW children had repeated a grade at school compared with only 7% of controls by 8 years of age [55]. At early school age, EP children are scoring well below term peers on academic achievement scales. In the EPICure study the EP cohort scored >1 SD below classmate controls on a scale that assesses general knowledge, language concepts and school-related skills [57]. This is consistent with findings from Taylor et al. [65] who found significantly elevated rates of achievement-based learning disabilities in their <750 g birth weight cohort at early school age, particularly in word identification, applied problems (mathematics reasoning and story problems), and mathematics computation. When reassessed at middle school age, the <750 g birth weight group still performed significantly below term peers, particularly in the area of mathematics [62]. At this follow-up, 36% of the <750 g birth weight cohort had a low achievement score (>2 SD below normative mean), in contrast to only 7% of the 750–1,499 g birth weight group and 2% of the term group. The proportion of children in the <750 g birth weight cohort to receive educational assistance had increased by middle school to 50%, which is in contrast to 27% of the 750–1,499 g and 8% of the term groups. In the 1991–1992 Victorian cohort EP/ELBW children performed worse on formal tests of reading, spelling and particularly arithmetic, and their teachers rated their performance in all academic areas to be substantially below that of term controls [55].

Behaviour

EP children exhibit more behavioural problems than term children. A meta-analysis of 16 studies involving preterm children born prior to the 1990s reported a significant increase of externalising problems in 69% of studies, a significant increase of internalising problems in 75% of studies, and higher rates of attentional problems in 67% of studies [54]. In the Victorian study of 1991–1992 births the EP/ELBW cohort at 8 years of age had more internalising problems, poorer adaptive skills and higher scores on overall behaviour symptoms than the term controls, as assessed by both parents and teachers, independently [55]. Interestingly, significant externalising behavioural problems were not identified in our EP/ELBW cohort. More specifically, as rated by their parents the EP/ELBW children displayed more attentional problems, hyperactivity, somatic complaints, and atypical behaviours, while their social, and leadership skills were less developed. The teachers also rated the behaviour of the EP/ELBW children worse than controls in most of these areas, but also in depression and atypical behaviours.

Conclusion

Compared with term children, EP survivors have more respiratory and neurological morbidity, including higher rates of wheezing and hospital readmission for respiratory illnesses, and significant developmental, sensory and motor problems in early childhood. Later in life, EP children have reduced pulmonary function, particularly airway obstruction, and lower exercise tolerance, as well as higher rates of cognitive impairments, including learning disabilities, and behavioural problems.

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