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Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

Frequency, Risk Factors and 7-year Outcome

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ACADEMIC DISSERTATION

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To my family

CONTENTS

ABBREVIATIONS

AGA	appropriate for gestational age
AoD	diameter of the aorta
AT	acceleration time
BR	bronchial responsiveness
BMI	body mass index
BPD	bronchopulmonary dysplasia
CI	confidence interval
CO_2	carbon dioxide
CP	cerebral palsy
CPAP	continuous positive airway pressure
DHEAS	dehydroepiandrosterone sulfate
DLCO	diffusing capacity of the lung
ECG	electrocardiography
ERV	expiratory reserve volume
ET	ejection time
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
GA	gestational age
HFOV	high frequency oscillatory ventilation
ICAM	intercellular adhesion molecule
IL	interleukin
IVH	intraventricular haemorrhage
IVSd	thickness of interventricular septum at end diastole
LVEDD	left ventricular end diastolic dimension
LVESD	left ventricular end systolic dimension
LVPWd	left ventricular posterior wall thickness at end diastole
LVSF	left ventricular shortening fraction
MUAC	middle upper arm circumference
O_2	oxygen
OR	odds ratio
PAD	diameter of the pulmonary artery
PAP	pulmonary artery pressure
$PaCO_2$	arterial carbon dioxide partial pressure
PD_{20}	provocative dose of metacholine causing a 20% decline in FEV_1
PDA	patent ductus arteriosus
PEF	peak expiratory flow

PEP	pre-ejection period
PaO_2	arterial oxygen partial pressure
PRC	packed red cell
R_{aw}	airway resistance
RDS	respiratory distress syndrome
RV	residual volume
sBPD	severe bronchopulmonary dysplasia
SES	socio-economic status
SD	standard deviation
SDs	standard deviation score
SGA	small for gestational age
sG_{aw}	specific airway conductance
TLC	total lung capacity
VA	alveolar volume
VLBW	very low birth weight
VC	vital capacity
WHR	waist-to-hip ratio

ABSTRACT

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disorder first described in 1967 in prematurely born infants who needed aggressive neonatal intensive care. Since then prenatal corticosteroid and postnatal surfactant therapy have resulted in increased survival of very low birth weight (VLBW, birth weight < 1500 g) infants. These children seem to manifest BPD with a different clinical and pathologic presentation. The frequency of this "new BPD" and its consequences for pulmonary, cardiovascular and growth status are of interest.

The frequency and risk factors in BPD were assessed retrospectively in a cohort of 242 VLBW infants born in Tampere University Hospital during the years 1990-1994, after the introduction of surfactant therapy. The frequency of BPD (oxygen (O_2) dependency and chest X-ray findings typical of BPD) was 30.7% (59/192) among survivors at 28 days' age, and 13.0% (24/184) among survivors at 36 weeks' corrected gestational age. Low birth weight and gestational age, male sex, need of packed red cell infusions and long duration of ventilator therapy were associated with an increased risk of BPD. Surfactant for respiratory distress syndrome (RDS) had been administered in 49% of the BPD infants, and 49% of them recovered from BPD by 36 weeks' corrected gestational age. Preeclampsia, low birth weight, rapid birth weight recovery, haemodynamically significant PDA and hyperoxia increased the probability of severe BPD. No infant born small for gestational age (SGA) recovered from BPD by 36 weeks' corrected gestational age. Other risk factors than RDS, for example low birth weight, early fluid therapy and possibly intrauterine growth retardation, emerge as predictors of BPD during the surfactant era.

At 2-8 years of age, a mailed questionnaire was used to evaluate the surviving VLBW cohort children's (N=180) health and need of rehabilitation and financial support, as well as the impact of the child's health on the family. The parents of 36 (72% of the surviving) BPD cases, 107 (75%) VLBW children without BPD and 131 (73%) term-born sex- and age-matched controls returned the questionnaire. Compared to term controls, VLBW children were reported to have more often current (in the past year) respiratory symptoms provoked by exercise and need for inhaled medications. Also regular hospital-based follow-up, hospitalisations, need for physiotherapy, occupational therapy, technical aids and financial support from society were more frequent in the VLBW groups compared to term children. Low gestational age, small birth weight and small size of family emerged as better predictors of current respiratory morbidity than a BPD diagnosis at 28 days' postnatal age. Greater impact of the child's health on

family life was reported in the families of VLBW children compared to term controls. Consistent evaluation of their social and mental welfare is necessary to facilitate planning and follow-up of supportive interventions.

At 7 years of age, 34 (68% of the surviving) BPD children together with sex- and age-matched groups of 34 VLBW children without BPD (no-BPD group) and 34 term controls were examined at the outpatient clinic.

Current respiratory symptoms were reported in a third of 7-year-old VLBW children, and significantly more often in the no-BPD than in term children. Only half of the symptomatic no-BPD cases were on inhaled medications. Compared to term controls, pulmonary function tests revealed BPD children to have lower expiratory flow rates, more often signs of hyperinflation (high ratio of residual capacity to total lung capacity) and higher airway resistance than term controls. BPD cases also had higher airway resistance in comparison with the no-BPD group. Increased bronchial responsiveness and lower diffusing capacity of the lung were detected in the VLBW compared to term children. Careful respiratory follow-up of all VLBW children would appear to be necessary regardless of the severity of neonatal pulmonary problems.

At 7 years of age, electrocardiography revealed mild left ventricular hypertrophy in 2 children (1 BPD, 1 no-BPD), sinusbradycardia in 3 (2 no-BPD, 1 term) and 1st grade atrio-ventricular block in one (term) child. Echocardiographic findings included PDA in a BPD child and mild aortic valve regurgitation in another born at term. These findings were probably unrelated to the neonatal characteristics of the children. No indirect signs of clinically significant elevated pulmonary pressure or echocardiographic signs of hypertrophy of the cardiac ventricle walls were found.

Regardless of BPD, 7-year-old VLBW children were shorter, and presented with higher adrenal androgen levels at 7 years compared to term children. Especially VLBW children born SGA evinced a tendency to more florid adrenarche than did term children, indicating a possible risk of reduced final height and future metabolic and cardiovascular problems. If these findings are confirmed in further studies, interventions such as early diet counselling may be warranted.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals.

I. Korhonen P, Tammela O, Koivisto AM, Laippala P, Ikonen S. Frequency and risk factors in bronchopulmonary dysplasia in a cohort of very low birth weight infants. Early Hum Dev 1999; 54(3): 245-58. Reprinted with permission from Elsevier.

II. Korhonen P, Tammela O, Koivisto AM, Laippala P, Ikonen S. Very low birth weight, bronchopulmonary dysplasia and health in early childhood. Acta Pædiatr 1999; 88: 1385-91. Reprinted with permission from Taylor & Francis.

III. Korhonen P, Laitinen J, Hyödynmaa E, Tammela O. Respiratory outcome in school-aged very-low-birth-weight children in the surfactant era. Acta Pædiatr (in press). Reprinted with permission from Taylor & Francis.

IV. Korhonen P, Hyödynmaa E, Lautamatti V, Iivainen T, Tammela O. Cardiovascular findings in very low birth weight schoolchildren with and without bronchopulmonary dysplasia. Submitted for publication.

V. Korhonen P, Hyödynmaa E, Lenko HL, Tammela O. Growth and adrenal androgen status at 7 years in very low birth weight survivors with and without bronchopulmonary dysplasia. Arch Dis Child (in press). Reprinted with permission from the BMJ Publishing Group.

In addition, some unpublished data are presented.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disease first described in 1967 in prematurely born infants with hyaline membrane disease (Northway et al. 1967). The condition has since become one of the most significant clinical problems and research topics in neonatology. Nowadays, very immature infants receive treatment, survive, and appear to suffer from BPD with a different clinical picture and pathology (reviewed by Eber and Zach 2001). There has been concern that the increased survival of the most premature infants would lead to an increase in BPD frequencies (Parker et al. 1992).

Reports from the pre-surfactant era suggest that infants with BPD may also later in life manifest frequent respiratory symptoms and infections (Kitchen et al. 1990) and abnormalities of lung function (Pelkonen et al. 1997, Gross et al. 1998), cardiovascular status (Smyth et al. 1981) and growth (Northway et al. 1990). The birth of a very low birth weight (VLBW, birth weight < 1500 g) child also has an impact on the life of other family members (Cronin et al. 1995), as well as on the requirement of supportive measures from society (McCormick et al. 1986). The availability of new therapies might be thought to alleviate the initial pulmonary problems of these infants and thus reduce the risk of future health problems. On the other hand, surfactant therapy may have contributed to the survival of particularly sick and vulnerable infants. At the initiation of our study, scant data were available on the outcome of VLBW children born after the introduction of surfactant therapy.

According to clinical observations of a local experienced paediatric endocrinologist, VLBW children seem to be over-represented among children with premature pubarche, puberty of the adrenal gland. Term-born small for gestational age (SGA) infants have been shown to carry an increased risk of premature pubarche (Dahlgren et al. 1998, Ibáñez et al. 1998a), but less is known on the subject among VLBW children born SGA. These observations led us to combine data on growth and adrenal androgen status in our VLBW population.

Our study aimed to assess the frequency of BPD and risk factors associated with it among VLBW infants born during the surfactant era. We also wanted to evaluate their health, need for rehabilitation, support from society and impact on family in the first years of life. Furthermore, information was sought on their pulmonary function, cardiovascular findings and growth and adrenal androgen status at early school age.

REVIEW OF THE LITERATURE

1. Definition of bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) was first described more than 35 years ago among prematurely born children whose hyaline membrane disease had been treated with ventilator therapy with high inspiratory pressures and oxygen (O_2) concentrations (Northway et al. 1967). Four successive radiological and pathological stages of this condition were presented.

Not all the radiological phases of BPD described by Northway and associates (1967) are seen in every infant with BPD-like condition, and several other definitions, also including clinical aspects, have been introduced (Bancalari et al. 1979, Tooley 1979, O'Brodovich and Mellins 1985). In most of them, the cornerstones of diagnosis have been the need for O_2 supplementation with or without ventilator therapy and the presence of radiographic findings in chest X-rays. Bancalari and associates (1979) presented the following criteria for BPD: (1) Need of intermittent positive ventilation during the first week of life and for a minimum of 3 days. (2) Clinical signs of chronic respiratory disease (tachypnoea, intercostal and subcostal retraction, rales at auscultation) persisting for longer than 28 days. (3) Need of O_2 supplementation for more than 28 days to maintain an arterial O_2 partial pressure (paO_2) of 50 mmHg. (4) Chest radiograph showing persistent strands of densities in both lungs, alternating with areas of normal or increased lucency.

The chronological age of 28-30 days long remained the most widely used diagnostic time point. However, very prematurely born children may require supplemental O_2 at one month's postnatal age due to their immaturity and not necessarily due to a chronic pulmonary problem. Need of O_2 supplementation at 36 weeks' corrected gestational age (GA) has been suggested to be predictive of abnormal pulmonary outcome (Shennan et al. 1988). This definition has come to widely applied in the literature. However, the predictive value of BPD definitions based solely on the duration of O_2 therapy has been challenged (Davis et al. 2002, Ellsbury et al. 2002), and attention has been drawn to the contribution of radiological findings of BPD in predicting future respiratory outcome (Palta et al. 1998, Thomas et al. 2003). Furthermore, dichotomous definitions of BPD, although useful especially for epidemiologic purposes, have

been criticised, and the dynamic and continuous process in its development emphasised (reviewed by Abman and Groothius 1994, Eber and Zach 2001).

A new definition for BPD was proposed in a recent American workshop, presenting different BPD criteria for infants below and above 32 weeks' GA and three categories according to the severity of the disease (reviewed by Jobe and Bancalari 2001). Radiographic findings did not feature in this definition.

The terminology and naming in BPD has been extensively discussed. Northway (1967) primarily used the term BPD. Some authors have preferred the term "chronic lung disease of the newborn" as a broad definition and would reserve the name "BPD" for severe forms of the condition. Recently, an American workshop recommended the designation "BPD" for all forms of the disease to differentiate BPD from multiple chronic lung diseases in later life (reviewed by Jobe and Bancalari 2001). In the present work, the term "BPD" is adopted.

2. Epidemiology

The reported frequencies of BPD vary widely, due partly to differences in patient populations, referral patterns or treatment practices, but also to discrepancies in BPD definitions. In the following, focus is set on studies presenting BPD incidences in VLBW populations.

In the pre-surfactant era, BPD frequencies of 10.6 to 54% have been reported in VLBW survivors at 28 days' postnatal age (Kraybill et al. 1987, Avery et al. 1987, Palta et al. 1991, Darlow and Horwood 1992, Parker et al. 1992). The BPD rates appeared to range from 96% in the birth weight group 501-750 g to 12.9-25% in the group 1250-1500 g (Kraybill et al. 1987, Avery et al. 1987). Between the periods 1976-1980 and 1986-1990, the BPD incidence among VLBW survivors (at 28 days) increased from 10.6 to 32.9% (Parker et al. 1992). This increase could only partly be explained by increased survival. At 36 weeks' corrected GA, BPD seemed to manifest in 8.1 to 23.1% of VLBW survivors (Hack et al. 1991, Darlow and Horwood 1992); the rates ranged from 26.3 % in the smallest (501-750 g) to 3.6 % in the largest (1251-1500 g) VLBW infants (Hack et al. 1991).

Since the initiation of our study, several authors have evaluated BPD incidences in VLBW infants born in the surfactant era. Palta and associates (1994) detected an increase from 21% to 36% in BPD frequency (at 28 days) in VLBW survivors during the introduction of an investigational synthetic surfactant and a decrease to 27% after the release of surfactant therapy. Darlow and associates (2003) investigated two VLBW populations at ten years' intervals (1986 and 1998-1999), and indicated a decrease in the incidence of O_2 dependency at 28 days' postnatal (39 vs 29%) and 36 weeks' corrected GA (23% vs 16%). Despite the progressive increase in survival between the years 1992 and 1997, Lemons and associates (2001) discovered no further change in BPD

frequency. Of VLBW survivors from the years 1993-1999, 16.8-26% required O_2 therapy at 36 weeks' corrected GA (Marshall et al. 1999, Young et al. 1999, Lee et al. 2000, Lemons et al. 2001, Darlow et al. 2003), the proportions ranging from 35.0 % in the birth weight group 501-750 g to 5.6 % in the group 1251-1500 g (Lemons et al. 2001).

3. Clinical presentation

With the advent of new perinatal and neonatal therapies such as prenatal corticosteroid and surfactant treatment, as well as gentler ventilation techniques, the clinical presentation of BPD appears to be altering. The concepts "classic" and "new" BPD have been introduced.

3.1. Classic BPD

"Classic" BPD, as described by Northway and associates (1967), develops sequentially after respiratory distress syndrome (RDS) and may in its severe form lead to prolonged need for O_2 supplementation, elevation of pulmonary artery pressure (PAP) and hypertrophy of the right cardiac ventricle, i.e. "cor pulmonale". Feeding problems (Mercado-Deane et al. 2001), gastro-oesophageal reflux (Radford et al. 1995), acute pulmonary infections and tracheobronchomalasia may complicate the clinical course of the infants (reviewed by Eber and Zach 2001).

3.2. "New" BPD

In the last 10-15 years the probability of BPD would appear to be greatest among infants with birth weights below 1000 g, and an increased incidence of BPD has been reported among preterm infants with mild or no RDS (Rojas et al. 1995, Charafeddine et al. 1999). Their RDS usually responds favourably to surfactant administration, and the need of ventilator and O_2 therapy diminishes rapidly in the first days of life. Thereafter, however, most of the infants present progressive signs of respiratory failure (retractions, need for O_2 supplementation) and lung function impairment, frequently in association with patent ductus arteriosus (PDA) and/or infection (Rojas et al. 1995, Gonzalez et al. 1996). Prolonged ventilatory support may be necessary for apnoea and poor respiratory effort (Rojas et al. 1995).

4. Radiographic findings

As noted, Northway and associates (1967) initially described four successive radiological stages of BPD (Table 1). Not all of these stages are present in all infants with BPD, cystic BPD being a rare condition. Thus, other radiographic classifications of BPD have been introduced. Among the most recent, two categories of radiologic BPD findings were proposed among premature infants who had received surfactant (Swischuk et al. 1996). Hazy-opaque chest X-ray findings (leaky lung) resembling the initial Northway stages I-II were held to reflect the presence of capillary damage and pulmonary oedema. Bubbly lung changes (resembling Northway stages III-IV) were thought to manifest the bronchial and parenchymal dysplastic changes in BPD. Either type can develop irrespective of the other. The term leaky lung syndrome has been suggested to represent the problem with pulmonary oedema alone, and BPD the situation with bubbly lung changes (Swischuk et al. 1996).

Table 1. Radiological and pathological classification of BPD according to Northway et al. (1967).

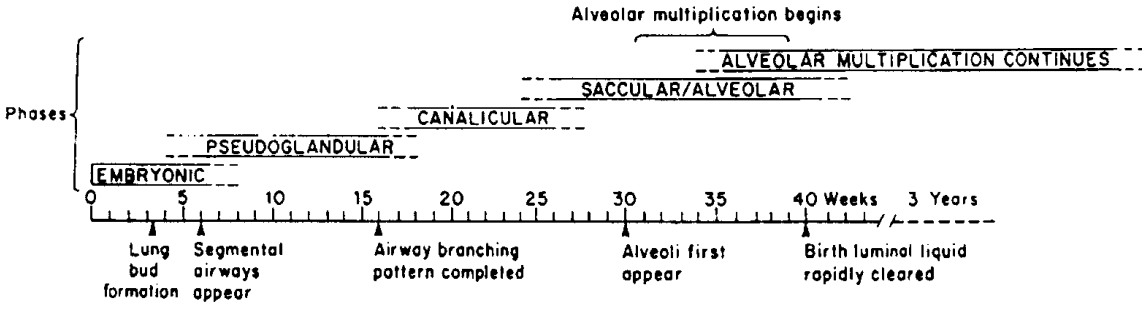
Stage	Age	Radiological findings	Histological findings
I	2-3 days	Generalised granular pattern of the lung, increased pulmonary density, air bronchogram	Hyaline membranes, hyperemia, atelectasis, lymphatic dilatation, patchy loss of the ciliated cells
II	4-10 days	Opacification of the lung fields	Necrosis and repair of alveolar epithelium, hyaline membranes, emphysematous coalescence of alveoli
III	10-12 days	Areas of irregular density, small radiolucent areas	Circumscribed groups of emphysematous alveoli surrounded by atelectatic areas
IV	> 1 month	Enlargement of the radiolucent areas	Groups of emphysematous alveoli and bronchioles, hypertrophy of peribronchial smooth muscle, perimucosal fibrosis, vascular medial hypertrophy, degeneration and regeneration of elastin

5. Normal lung development

Human pulmonary development can be divided into five overlapping phases (reviewed by Jeffery 1998, Bolt et al. 2001). During the *embryonic* period (up to the 6th week of gestation), the lobar buds and bronchopulmonary segments are formed. During the *pseudoglandular* phase (7th-16th week of gestation), the conducting airways are formed and surrounded by mesenchyme. The respiratory epithelium starts to differentiate into alveolar pneumocytes, and cilia and cartilage begin to form. At the beginning of the *canalicular* phase (16-26 weeks' gestation), the airway branching is completed, vascularisation of the peripheral mesenchyme increases rapidly, and type I pneumocytes (the cells ultimately responsible for gas exchange) differentiate from type II pneumocytes (the cells ultimately responsible for surfactant production). At the end of this phase, surfactant production commences and the gas-exchange units of the lungs are formed and vascularised. The *saccular* (terminal sac) phase (24-26 weeks' gestation until term) includes a substantial decrease in interstitial tissue and a marked thinning of the airspace walls, necessary for effective gas exchange. A two- to fourfold increase in gas-exchanging surface occurs between 30 and 40 weeks' gestation (reviewed by McColley 1998). The fifth, *alveolar* phase continues from 36 weeks' gestation until the final number of alveoli is reached approximately by the age of 2-3 (reviewed by Jeffery 1998), possibly even 8 years (reviewed by Laudy and Wladimiroff 2000).

By 7 weeks of gestation, the vessels connecting heart and lungs reach adult form. All pre-acinar arteries are present by the completion of the branching of the conducting airways. In contrast, the intra-acinar arteries develop relatively late and continue to form after birth. The development of the pulmonary venous system parallels that of the arteries and airways, except for the greater number of veins (reviewed by Laudy and Wladimiroff 2000).

Figure 1. Scheme of major events during lung development (from Jeffery 1998, with permission).



6. Pathological findings in BPD

6.1. Airways and alveoli

The relevant histological findings in classic BPD reported by Northway and associates (1967) are presented in Table 1.

Perinatal injury to the lungs of infants born as early as 24-27 weeks' gestation seems to have different pathologic consequences for lung development than in more mature infants. The typical features of the "new BPD" include minimal alveolarisation, less airway epithelial disease and less interstitial fibrosis (Husain et al. 1998, reviewed by Eber and Zach 2001). Partial to complete arrest in acinar development (saccular and alveolar) seems to take place regardless of surfactant therapy (Husain et al. 1998).

6.2. Pulmonary vasculature

Medial hypertrophy, elastin deposition in normally non-vascularised arterioles and right ventricular hypertrophy consistent with pulmonary hypertension, have been described in "classic BPD" (Northway et al. 1967). Infants with "new BPD" appear to have decreased numbers of capillaries with dysmorphic features and less severe arterial/arteriolar vascular lesions (Husain et al. 1998, reviewed by Coalson 2003). Reduced vascular growth seems to concur with the simplified alveolar structure (reviewed by Jobe 1999).

7. Factors involved in the pathogenesis of BPD

7.1. Prematurity and low birth weight

The smaller, thicker and less well vascularised epithelial gas-exchanging surface and chest wall softness in prematurely born infants all contribute to their liability to respiratory disorders (reviewed by McColley 1998). Some biochemical abnormalities such as surfactant deficiency can be alleviated, whereas the structural hypoplasia and decreased number of alveoli persist.

A prematurely born infant is exposed to many environmental factors capable of causing injury to immature tissues. A summary of current conceptions of the pathogenesis in BPD is presented in Figure 2. In view of the extremely close

relation between pathogenesis, treatment and preventive measures in BPD, all these aspects will be addressed concurrently in the following sections.

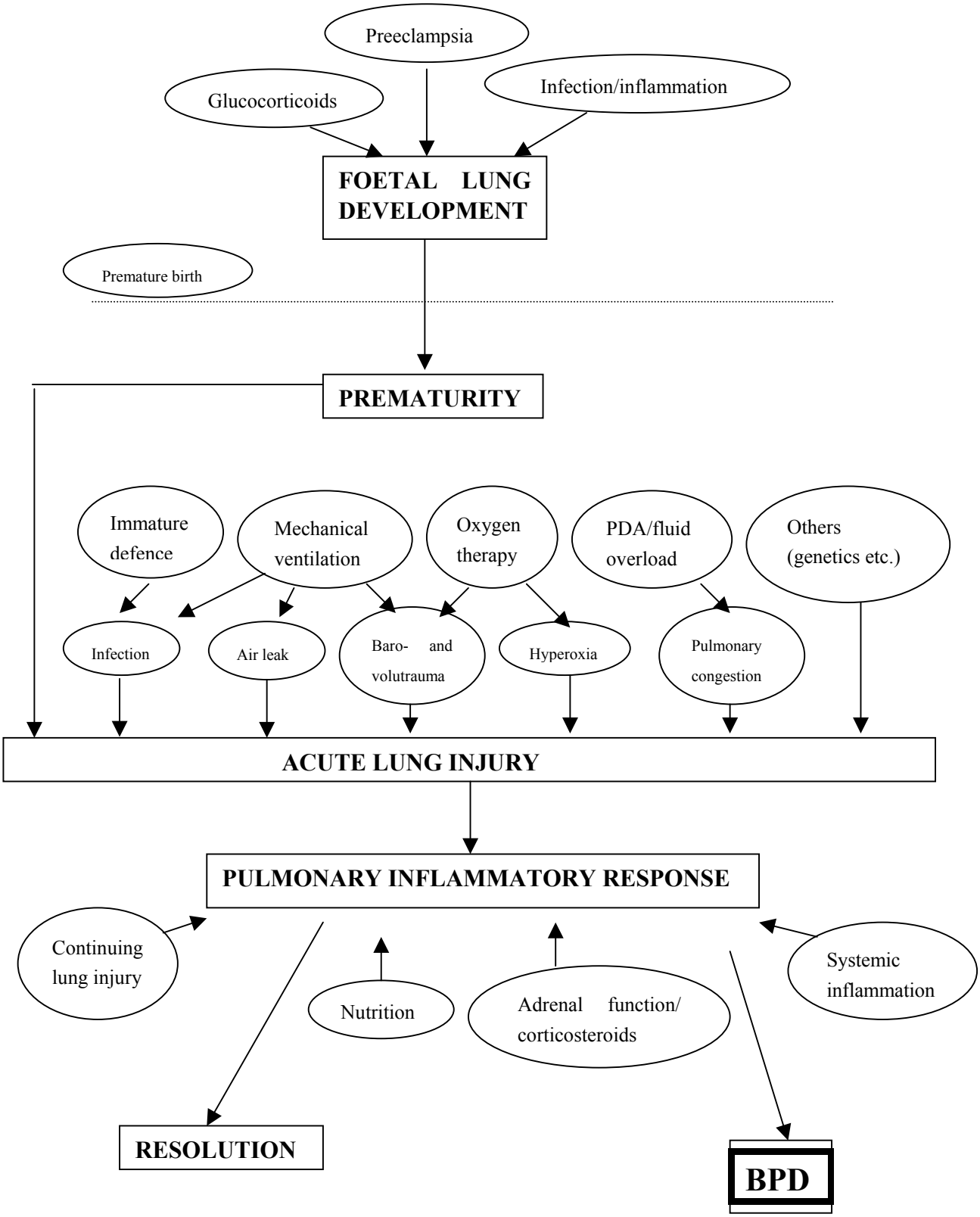
7.2. Prenatal factors

The impact of intrauterine growth retardation on the risk of BPD is a matter of controversy (Palta et al. 1991, Egreteau et al. 2001, Regev et al. 2003). *Preeclampsia* of the mother is a common cause of intrauterine growth retardation. In some studies, preeclampsia has been suggested to enhance foetal lung maturity and to diminish the risk of RDS and BPD (Kim et al. 1996). Others have found no such effect (Schiff et al. 1993).

Intrauterine infection may accelerate lung maturation but also increase the probability of BPD development by exposing the foetus to inflammatory cytokines (Watterberg et al. 1996). It may also contribute to the initiation of premature delivery (reviewed by Goldenberg et al. 2000).

Prenatal corticosteroid therapy has been shown to have effects beneficial for the survival and lung maturation of premature infants (reviewed by Crowley 1995). It may accelerate the maturation of type II pneumocytes and surfactant production, enhance foetal lung antioxidant systems, reduce the number of pro-inflammatory cytokines, but also adversely affect lung growth and alveolarisation (reviewed by Bolt et al. 2001). Prenatal corticosteroid treatment has not been shown to have an effect on BPD incidence (reviewed by Crowley 1995).

Figure 2. Summary of pathogenetic factors involved in BPD.



7.3. Oxygen toxicity

A preterm infant may receive high inhaled concentrations of O_2 due to lung immaturity. Periods of O_2 depletion and reperfusion are common. A lowered antioxidant capacity, insufficient ability to induce the antioxidant system (reviewed by Davis 2002), as well as susceptibility to infection and inflammation (reviewed by Speer 2003) further increase the risk of oxidative injury. In addition, premature infants frequently receive packed red cell (PRC) infusions, this resulting in increased levels of non-transferrin bound ”free” iron, a possible participant in the generation of reactive O_2 species (Hirano et al. 2001).

Elevated levels of lipid peroxidation products in the serum (Ogihara et al. 1999) and exhaled air (Pitkänen et al. 1990) of preterm infants have been attributed to the development of BPD. Also raised levels of protein carbonyls, markers of protein oxidation, have been detected in tracheal aspirates from newborn infants subsequently developing BPD (Varsila et al. 1995). O_2 radicals may also participate in the development of fibrosis and oxidative damage to surfactant (reviewed by Saugstad 2003).

7.4. Inflammation

An acute inflammatory response to a pulmonary insult such as ventilator and O_2 therapy, nosocomial infection or increased blood flow secondary to PDA, appears to be important in the pathogenesis of BPD (reviewed by Speer 2003, Watterberg et al. 2000).

Prolonged influx of neutrophils to the lung has been shown to be associated with the development of BPD. The epithelial lining fluid of BPD infants manifests elevated elastase activity (a proteolytic enzyme elaborated by neutrophils) and protease/antiprotease imbalance (reviewed by Speer 2003).

Markers of neutrophil and monocyte recruitment are more abundant in the airway secretions (leukotriene B_4, complement component C5-derived anaphylotoxin (C5a), interleukin (IL)-8) and plasma (soluble E-selectin, intercellular adhesion molecule-1 (ICAM-1)) of premature infants with BPD than in those without (Groneck et al. 1994, Ballabh et al. 2003). Also increased lung lavage levels of proinflammatory cytokines (IL-1, IL-1β_2, IL-6, IL-8, tumour necrosis factor-α) (Watterberg et al. 1996, Jónsson et al. 1997) and an imbalance between pro- and anti-inflammatory cytokines may play a role in the pathogenesis of BPD (Blahnik et al. 2001).

7.5. Infection

Postnatal infection aggravates the inflammatory reaction in the lung and may thus increase the risk of BPD, especially in combination with prolonged mechanical ventilation (Van Marter et al. 2002) and PDA (Gonzalez et al. 1996).

7.6. Mechanical ventilation

7.6.1. Baro- and volutrauma

Although nowadays BPD often develops in infants without severe initial respiratory problems, mechanical ventilation is held to constitute an important risk factor in BPD also in the surfactant era (Marshall et al. 1999, Young et al. 1999, Van Marter et al. 2002).

The term *barotrauma* refers to the effect of mechanical ventilation on the lungs. Air leaks resulting in extra-alveolar accumulation of air, interstitial emphysema, and at worst, tension pneumothorax, are dreaded complications of ventilator therapy. The term *volutrauma*, again, has been proposed to describe the pulmonary consequences of ventilator therapy better than barotrauma because especially high end-inspiratory volumes have proved to be important determinants of ventilator-induced lung oedema (reviewed by Dreyfuss and Saumon 1998). According to one animal study, manual ventilation with few large breaths at birth may cause significant lung injury and compromise the effect of subsequent surfactant therapy, as well as predispose the lung to further volutrauma during mechanical ventilation (Björklund et al. 1997). Prolonged aggressive mechanical ventilation after premature birth may also inhibit the normal postnatal decrease in pulmonary vascular resistance (Bland et al. 2000), trigger white cell migration and induce the inflammatory cascade (Ranieri et al. 1999). Surfactant deficiency or inactivation further aggravates ventilator-induced lung injury (Coker et al. 1992).

7.6.2. Hypo- and hypercarbia

Hypocarbia, low arterial carbon dioxide partial pressure ($paCO_2$), has been suggested to be associated with the risk of BPD (Garland et al. 1995). Avery and associates (1987) compared BPD incidences in 8 centres and found the BPD incidence to be lowest in the one relying on spontaneous ventilation and nasal continuous positive airway pressure (CPAP) systems and accepting higher $paCO_2$ levels.

Mechanical ventilation with lower tidal volumes and positive end-expiratory pressures resulting in higher $paCO_2$ values (*permissive hypercapnia*) has been evaluated by Carlo and associates (2002), who reported reduced ventilator support at 36 weeks' corrected GA among mechanically ventilated and surfactant-treated infants of birth weight 501-1000 g with hypercapnia ($paCO_2$ target >52 mmHg) compared to those with normocapnia. Further research is necessary, however, before the permissive hypercapnia strategy can be applied as a routine in the treatment of VLBW infants (reviewed by Woodgate and Davies 2003).

7.6.3. Mode of ventilatory support

Intermittent positive pressure ventilation (IPPV) has been the most widely used mode of ventilation in preterm infants since the 1960s. Synchronised mechanical ventilation, during which the infant's spontaneous inspiration and the ventilator's inflation coincide, introduced in the 1980s, has been considered promising in reducing ventilator-induced lung injury and thus the incidence of BPD. However, in a recent Cochrane analysis, *patient-triggered ventilation* and *synchronised intermittent mandatory ventilation* were found to be associated with shorter duration of ventilation compared to conventional mechanical ventilation, but no effect was found on BPD incidence (reviewed by Greenough et al. 2003).

High-frequency oscillatory ventilation (HFOV) is a ventilatory technique involving rapid ventilation with the use of very small tidal volumes. According to a recent meta-analysis of ten studies comparing HFOV with conventional ventilation, the impact of HFOV on BPD frequency remained controversial (reviewed by Henderson-Smart et al. 2003).

The use of CPAP is believed to improve gas exchange by enhancing alveolar recruitment and inflation, to reduce the intrapulmonary shunt, as well as to lower the risk of apnoea. The impact of early nasal CPAP on BPD incidence is contended (Avery et al. 1987, Horbar et al. 1988, Gittermann et al. 1997). *Nasal synchronised intermittent positive pressure ventilation* may be more effective than nasal CPAP in weaning premature infants with RDS from the ventilator and preventing extubation failure (Barrington et al. 2001), but no significant impact on BPD incidence has so far been detected (reviewed by Davis et al. 2003).

7.7. Surfactant deficiency

Pulmonary surfactant is a mixture of phospholipids (mainly dipalmitoylphosphatidylcholine) and four surfactant-associated proteins (SP-A, SP-B, SP-C and SP-D) secreted by the alveolar type II cell. It reduces surface tension at the air-liquid interface and contributes to the maintenance of alveolar stability at low lung volumes. Surfactant deficiency is a major factor in the development and progression of RDS. Surfactant administration rapidly improves oxygenation and reduces the need for ventilatory support (Fujiwara et al. 1980). The beneficial effect of surfactant therapy for survival is clear, but no statistically significant effect on the incidence of BPD is so far evident (reviewed by Shah 2003). However, compared to "rescue" or selective use in premature infants with established RDS, prophylactic administration of surfactant during initial resuscitation has been suggested to reduce mortality and the risk of mortality and BPD (reviewed by Soll and Morley 2003). The criteria for "at risk" infants requiring prophylactic surfactant are so far unclear.

7.8. Fluid accumulation

Increased alveolar capillary permeability is an important pathophysiological feature in RDS and subsequent chronic lung disease (Jefferies et al. 1984). Inflammatory cells and mediators may have direct effects on the alveolar and capillary membranes, inactivate the surfactant system (Beers et al. 1998), modulate vascular perfusion in the inflamed area or increase shunting via the ductus arteriosus, as well as affect microbial colonisation and infection of the airways (reviewed by Ozdemir et al. 1997). In severe BPD, water retention may develop in response to the hypersecretion of arginine vasopressin (Kojima et al. 1990).

An association has been suggested between high fluid intake in the first days of life and the development of BPD (Marshall et al. 1999). A recent meta-analysis on the effect of early fluid restriction policy showed a trend, albeit statistically non-significant, towards a decreased BPD incidence (Bell and Acarregui 2001).

7.9. Patent ductus arteriosus (PDA)

The ductus arteriosus is a vessel which allows blood to bypass the lungs during foetal life. Its spontaneous closure after birth is sometimes delayed in a prematurely born infant. Substantial systemic-to-pulmonary shunting through a PDA predisposes the child to heart failure and pulmonary oedema. An increased incidence of BPD has been reported in infants with PDA with a persistent significant shunt (Brown 1979, Marshall et al. 1999), especially in connection with nosocomial infection (Rojas et al. 1995).

7.10. Adrenal insufficiency

VLBW infants who later develop BPD have been reported to have decreased basal cortisol concentrations and a lower cortisol response to adrenocorticotropin in the first week of life (Watterberg and Scott 1995) compared to those who recover without BPD. Early adrenal insufficiency may in part explain the association of increased lung inflammation and PDA with an adverse respiratory outcome in VLBW infants (Watterberg et al. 2000).

7.11. Intravenous fatty acids

By administration of intravenous lipids caloric intake can be effectively increased and essential fatty acid deficiency prevented. Early administration of intravenous lipids in the premature infant has been suggested to increase the incidence of BPD (Cooke 1991), while in other surveys it has proved safe

(Gilbertson et al. 1991). At present, intravenous lipids are commonly introduced in VLBW infants in the first days of life to maintain a positive energy balance.

7.12. Genetic predisposition

In several studies, male infants have been suggested to run an increased risk of BPD (Palta et al. 1991, Darlow and Horwood 1992). The reason for this preponderance is not clear. Mutations in the surfactant proteins (especially SP-A) would appear to have a role in the pathogenesis of RDS, but no allelic association with susceptibility to severe BPD has been so far detected (reviewed by Hallman and Haataja 2003).

8. Treatment of infants with bronchopulmonary dysplasia

8.1. Oxygen

Although O_2 is a well-known risk factor associated with BPD, it is, at the same time, part of its treatment. Avoidance of hypoxia may reduce the progressive muscularisation of small pulmonary arteries and enhanced vasoreactivity in BPD infants (reviewed by Parker and Abman 2003). Hypoxic episodes in BPD infants have been suspected to be associated with the risk of sudden unexpected death (Abman et al. 1989) and growth impairment (Moyer-Mileur et al. 1996).

The ideal O_2 saturation threshold below which supplemental O_2 should be administered to preterm infants is not known. According to present recommendations, O_2 saturations of 94-96% should be targeted and those below 92% avoided in BPD infants who are not at risk of further progression of retinopathy of prematurity (reviewed by Kotecha and Allen 2002).

8.2. Corticosteroids

8.2.1. Systemic corticosteroids

Corticosteroids have many beneficial effects on the lung. They exert anti-inflammatory effects (Ballabh et al. 2003), may stimulate the synthesis of surfactant and antioxidant enzymes, reduce alveolar-capillary permeability, induce PDA closure, enhance diuresis, induce bronchodilatation by increasing β-

adrenergic activity, and stabilise cellular and lysosomal membranes (reviewed by Bancalari 1998). Furthermore, VLBW infants at risk of developing BPD have been shown to be prone to early adrenal insufficiency and may therefore benefit from corticosteroid treatment (Watterberg et al. 1999).

In the 1980s, postnatal corticosteroid therapy was administered mostly to wean BPD infants from ventilators (Mammel et al. 1983). In a recent Cochrane review of 21 randomised controlled trials, early dexamethasone treatment appeared to facilitate extubation and to reduce the incidence of BPD (Halliday et al. 2003). However, its short-term adverse effects (gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy, infection and growth failure) and long-term sequelae (neurodevelopmental deficits, impaired growth) have been a source of concern (Yeh et al. 1998). Promising results have been reported on other steroid types in BPD prevention, e.g. low-dose hydrocortisone (Watterberg et al. 1999) and methylprednisolone (André et al. 2000). At present, cautious low-dose administration of systemic postnatal corticosteroids with parental consent is recommended in ventilator-dependent BPD cases considered unlikely to survive without steroids (American Academy of Pediatrics/ Canadian Paediatric Society 2002).

8.2.2. Inhaled corticosteroids

Inhaled corticosteroids have been shown to shorten the duration of mechanical ventilation in VLBW infants, without significant side-effects (Cole et al. 1999, reviewed by Lister et al. 2003), but no protective effect on BPD has been demonstrable (Cole et al. 1999, reviewed by Shah et al. 2003).

8.3. Bronchodilators

Bronchodilators possess the potential to dilate small airways with smooth muscle hypertrophy. High airway resistance in connection with chronic lung disease may be at least partly alleviated by inhaled bronchodilators such as salbutamol, ipratropium bromide (Wilkie and Bryan 1987), isoprotenonol (Kao et al. 1984) and metaprotenonol (Cabal et al. 1987). Methylxanthines such as theophylline and caffeine may, additive to bronchodilatation, also beneficially stimulate diuresis and the respiratory centre (Kao et al. 1987).

8.4. Diuretics

Diuretic therapy has been used in the treatment of fluid accumulation in BPD patients. The parenterally administered loop diuretic *furosemide* has proved efficient in improving lung mechanics, but may carry a risk of significant side-

effects, such as electrolyte imbalance, volume contraction, nephrolithiasis, bone demineralisation, metabolic alkalosis, hypoventilation and cholelithiasis (reviewed by Blanchard et al. 1987).

Oral non-loop diuretics such as *chlorothiazide* and *spironolactone* have been shown to improve dynamic pulmonary compliance and reduce airway resistance and O_2 requirement in infants with O_2-dependent BPD. However, the duration of O_2 supplementation was not decreased, and the improvement in pulmonary function was not maintained after discontinuation of treatment (Kao et al. 1994). A recent meta-analysis showed no benefit of thiatzide and spironolactone treatment regarding the need of ventilatory support, length of hospital stay or long-term outcome in preterm infants (Brion et al. 2003).

8.5. Concurrent drug therapy

Use of pulmonary vasodilators is sometimes necessary to treat chronic pulmonary hypertension, a possible sequel to severe BPD. *Nifedipine*, a calcium channel blocker, has the ability to alleviate hypoxic pulmonary vasoconstriction, and has been suggested to lower pulmonary artery pressure in 5-68-month-old BPD infants (Johnson et al. 1991). So far, its effect in BPD patients has been studied only in small series.

Low-dose *inhaled nitric oxide*, an endothelium-derived smooth muscle relaxant, might improve oxygenation in some infants with severe BPD (Banks et al. 1999). This observation needs to be confirmed in randomised controlled studies.

8.6. Nutrition

VLBW infants are born with limited endogenous energy reserves, which need to be supplemented starting as soon after birth as possible. Gut immaturity and the severity of initial illness often restrict the onset and quantity of enteral nutrition. Therefore, a VLBW infant is dependent on parenterally administered energy and nutrients.

Infants with BPD often suffer growth failure, possibly due to increased energy expenditure and a high metabolic rate (Yeh et al. 1989). Inadequate nutritional intake is common due to feeding problems, swallowing dysfunction (Mercado-Deane et al. 2001) and gastro-oesophageal reflux. Short-term use of high-fat formulae may lower CO_2 production in premature infants with BPD compared to a high-carbohydrate formula (Pereira et al. 1994).

8.6.1. Inositol

Inositol, a sugar alcohol, is found in several mammalian tissues and cell membranes, and promotes maturation of surfactant phospholipids (reviewed by Howlett and Ohlsson 2003). In a study by Hallman and associates (1992), intravenous administration of inositol to premature infants with RDS in the first weeks of life was associated with increased survival without BPD. A similar trend was reported in a recent meta-analysis (reviewed by Howlett and Ohlsson 2003). Further studies are required, however, before routine inositol supplementation can be recommended to surfactant-treated VLBW infants.

8.7. Therapeutic approaches to counter O_2 toxicity

8.7.1. Antioxidants and antioxidant enzymes

Several antioxidants, for example allopurinol, N-acetylcysteine, erythropoietin, aminosteroid steroids, as well as antioxidant enzymes (superoxide dismutase and catalase) have been tested in the prevention of BPD, with no clinically significant benefit (reviewed by Saugstad 2003).

8.7.2. Vitamins A and E

Vitamin A participates in the regulation and promotion of growth in many cells, including those of the respiratory tract. It may also have immunologic functions and serve as a scavenger of free radicals. In a recent meta-analysis, supplementing VLBW infants with vitamin A seemed to reduce the risk of death or O_2 requirement at one month's age (reviewed by Darlow and Graham 2003).

Vitamin E is also an antioxidant, which has been suggested to protect from BPD (Ehrenkranz et al. 1978), but further studies have failed to prove this benefit (Watts et al. 1991).

8.7.3. Selenium

Selenium, a trace mineral, is an essential component of the antioxidant enzyme glutathione peroxidase, which protects against oxidative injury. In a randomised controlled trial, lower maternal and infant selenium levels before randomisation appeared to be related to an increased risk of O_2 dependency at 28 days of age, but selenium supplementation did not improve the neonatal respiratory outcome of VLBW infants (Darlow et al. 2000).

8.8. General management

According to some authors, an individualised, developmentally based neonatal intensive care protocol is associated with a trend towards a decreased frequency of radiologically diagnosed severe BPD (Als et al. 1994, Westrup et al. 2000). However, a recent meta-analysis reported no evidence of benefit from a newborn individualised developmental care and assessment program on the incidence of severe BPD, but a significant reduction in the need for O_2 supplementation was found (Jacobs et al. 2002). Further research is necessary to establish the effects of this protocol on clinical outcomes.

9. Outcome of patients with bronchopulmonary dysplasia

9.1. Mortality

BPD has been reported to be the leading cause of death among VLBW infants between one month and 2 years of age (Corchia et al. 1997). In the initial study by Northway and associates (1967), 9 patients survived with pulmonary disease beyond 2 weeks of age, and 5 of them died of cardiac enlargement and right-sided congestive heart failure. Markestad and Fitzhardinge (1981) reported a 23 % mortality among BPD infants diagnosed at 30 days postnatal age; all but one died of cardiopulmonary complications of BPD. Between 1975 and 1982, 20/179 BPD infants died after discharge from a regional neonatal intensive care unit. BPD was the cause of death in 7 out of 12 who underwent autopsy (Sauve and Singhal 1985). In a retrospective 5-year review of 265 VLBW infants admitted to one neonatal intensive care unit, 5 out of 27 infants who had needed O_2 therapy at 36 weeks' corrected GA died, all with cor pulmonale (Yeo et al. 1997). BPD infants may carry an increased risk of sudden unexpected death (Abman et al. 1989).

After the introduction of surfactants, a 30% reduction was reported in the likelihood of death among VLBW infants. Among BPD infants, mortality declined by 40% (Schwartz et al. 1994). Fillmore and Cartlidge (1998) examined postneonatal deaths among 2013 VLBW infants born in Wales during the years 1993-1996, and reported BPD to be the cause in 19 out of 59 deaths, and to coexist in 12/20 deaths from infection and in 9/20 deaths from other causes.

9.2. Respiratory symptoms

Before the surfactant era, several authors suggested an increased risk of respiratory symptoms such as wheezing and chronic cough among VLBW

children compared to term controls (Kitchen et al. 1992b, Elder et al. 1996, McLeod et al. 1996, Gross et al. 1998, Anand et al. 2003). According to some, the symptom rate was even greater in BPD children (Gross et al. 1998). In a population-based study (Schaubel et al. 1996), RDS in the presence or absence of BPD was a significant predictor of physician-diagnosed preschool asthma as well as hospitalisation due to asthma. Another study showed little or no impact of BPD on the respiratory morbidity of prematurely born 5-year-old children (Greenough et al. 1996).

With the introduction of pulmonary surfactants, the frequency of wheezing in 8-year-old BPD children decreased from 50% to 16%, but increased from 14% to 38% among those with milder neonatal respiratory problems (Palta et al. 2001).

9.3. Respiratory infections

Children with former BPD seem to suffer more respiratory tract infections than preterm children without BPD (Parat et al. 1995), particularly in the first 2 years of life (Hakulinen et al. 1990). Lower respiratory tract infections have been shown to occur in 85% of BPD children during the first year of life; 50% of these required hospitalisation (Markestad and Fitzhardinge 1981). A retrospective Danish study detected a 30% rate of hospital admission for respiratory syncytial virus infection among children with former BPD (Pedersen et al. 2003).

9.4. Neurodevelopmental outcome

Approximately 50-60% of VLBW infants seem to have normal neurodevelopmental outcomes, and 40-50% some kind of impairment (20-30% mild to moderate, and 20% severe) (reviewed by Bregman 1998). Also VLBW children without major impairment may have learning difficulties which become more evident with advancing age (Bregman 1998).

BPD infants have been held to carry an increased risk of later neurologic and developmental problems compared to VLBW controls without BPD (Vaucher et al. 1988, Singer et al. 1997, Gregoire et al. 1998, Majnemer et al. 2000). However, some of these might be linked to neonatal morbidities other than BPD per se (Gray et al. 1995).

In a report by Singer and associates (1997), BPD seemed to independently predict poorer motor outcome in VLBW children at 3 years of age, even after controlling for social and medical risk factors. A 21% incidence of mental and/or motor retardation was found in BPD cases (Singer et al. 1997). In another survey, VLBW children with severe BPD (O_2 requirement at 36 weeks' corrected GA) evinced more developmental abnormalities (lower developmental quotient, cerebral palsy (CP), and/or deafness/blindness) than those without BPD or with BPD diagnosed at 28 days' postnatal age (Gregoire et al. 1998). Palta

and associates (2000) reported a CP frequency of 12.6% in a multicentre cohort of VLBW children at 5 years of age. BPD and intraventricular haemorrhage (IVH) seemed to independently predict CP and functional outcome. No change was found in CP frequency subsequent to surfactant availability (Palta et al. 2000).

Preterm infants with BPD have been reported to be at a higher risk of persistent conductive hearing loss late in the first year of life compared to controls with similar GAs and without BPD (Gray 2001).

9.5. Use of medical care

9.5.1. Hospital admissions

VLBW children appear to be more prone to hospitalisation at 2-5 years of age compared to controls with normal birth weights, the risk of rehospitalisation increasing with decreasing birth weight (Yüksel et al. 1994). The most frequent reasons for hospitalisation are infections (especially respiratory), asthma and surgery (Kitchen et al. 1990, Yüksel et al. 1994, McLeod et al. 1996). One study showed no difference in total hospitalisation rate between 18-month-old VLBW children with and without BPD (Gregoire et al. 1998). However, BPD children diagnosed at 36 weeks had more hernia repairs and higher numbers of hospital days due to respiratory reasons than those without BPD diagnosis or diagnosed at 28 days (Gregoire et al. 1998). Also in another study, BPD children had more postneonatal hospital days up to 2 years of age compared to VLBW controls (Hakulinen et al. 1988).

9.5.2. Need of rehabilitation

By reason of their tendency to developmental problems, VLBW preschool children, independent of BPD, need more supportive measures such as physiotherapy, occupational therapy and speech therapy compared to term controls (Hanke et al. 2003). In a series reported by Cronin and associates (1995), 45% of VLBW children received speech therapy, physiotherapy or occupational therapy.

9.6. Impact on family

Scant data are available on the impact of BPD on the VLBW family. In a longitudinal study by Singer and associates (1999), mothers of 2-year-old BPD children reported more psychological stress than did mothers of VLBW children

without BPD or term controls. By 3 years, no difference was found between mothers of BPD children and term controls in distress symptoms, whereas the BPD mothers reported greater parenting stress (Singer et al. 1999).

Cronin and associates (1995) found significantly more financial, familial and personal stress in the parents of 1-6-year-old VLBW children compared to those of full-term controls matched for age, sex, race, domicile, singleton or multiple pregnancy and birth order. The families experienced greater financial and familial/social impact when the child had a mild developmental impairment than in cases of severely delayed children (Cronin et al. 1995). In another study, families of 1-6-year-old VLBW children, regardless of developmental delays of the children, did not report more negative family impact compared to the families of term-born healthy infants (Lee et al. 1991).

However, the actual physician-diagnosed problems of a VLBW infant seem to have less impact on the family than the consequent medical care use and limitations in ordinary daily activities (McCormick et al. 1986). Over one-third of VLBW children reported health-related limitations in at least one activity, and nearly 10% were judged by their parents to be in only fair or poor health (McCormick et al. 1986).

9.7. Pulmonary function at school age

9.7.1. Spirometric abnormalities

A number of studies have revealed spirometric evidence of bronchial obstruction in schoolchildren with former BPD (Smyth et al. 1981, Hakulinen et al. 1990, Blayney et al. 1991, Parat et al. 1995, Doyle et al. 1996, Koumbourlis et al. 1996, Giacoia et al. 1997, Pelkonen et al. 1997, Jacob et al. 1998, Gross et al. 1998, Pelkonen et al. 1998, Kennedy et al. 2000). At 18 years of age, 68% of the BPD cases originally described by Northway and associates (1967) had decreased forced expiratory volume in one second (FEV_1) and forced expiratory flow between 25 and 75 % of vital capacity (FEF_{25-75}) (Northway et al. 1990). Pulmonary function may remain abnormal for many years, also without marked respiratory symptoms (Blayney 1991, Parat et al. 1995). Lung function indices gradually improve during school years (Blayney 1991, Doyle et al. 1999), and only a few BPD cases seem to have clinically significant lung function abnormalities at 11 years of age (Doyle et al. 1996). However, VLBW children, especially those with BPD, may have some reductions in airflow possibly preceding obstructive airway disease in adult life.

Spirometric abnormalities lasting up to school age may arise from prematurity and small birth weight, not necessarily from neonatal pulmonary problems (Galdès-Sebaldt et al. 1989, Parat et al. 1995, Hakulinen et al. 1996, Anand et al. 2003). Kitchen and associates (1992b) reported BPD children to

have lower forced vital capacity (FVC) and FEV_1 at 8 years of age compared to VLBW controls without BPD, but after adjustment for confounding perinatal variables such as birth weight, FVC and FEV_1 no longer related to BPD. Also intrauterine growth retardation may have a role in the development of later pulmonary function abnormalities (Rona et al. 1993, Nikolajev et al. 1998).

Surfactant therapy has been thought to improve spirometric lung function at follow-up (Pelkonen et al. 1998). On the other hand, Gappa and associates (1999) found no differences in lung function at 6 years of age between VLBW cases treated with surfactant and those without this treatment.

9.7.2. Bronchial responsiveness

Increased bronchial responsiveness (BR) has been discovered in BPD survivors (Smyth et al. 1981, Northway et al. 1990, Pelkonen et al. 1997). It is not known whether this is due to genetic predisposition, neonatal lung injury or anatomically smaller airways. Also inflammatory factors may contribute to BR in school-aged VLBW children (Pelkonen et al. 1999). In the initial cohort, 52% of the BPD cases had reactive airway disease (positive metacholine or bronchodilatation test) at 18 years of age (Northway et al. 1990). According to Pelkonen and associates (1997), 8-12-year-old VLBW children with former BPD were more responsive to histamine compared to those without. In another study, 69% of 7-year-old BPD children proved positive to metacholine challenge (Blayney et al. 1991). BR may contribute to the development and persistence of airflow obstruction in BPD (Koumbourlis et al. 1996).

9.7.3. Plethysmographic findings

Hyperinflation (high RV/TLC ratio) is a common finding among school-aged subjects with former BPD (Hakulinen et al. 1990, Northway et al. 1990, Blayney et al. 1991, Kitchen et al. 1992b, Doyle et al. 1996, Jacob 1998), and it appears gradually to normalise well into adolescence (Koumbourlis et al. 1996). Also prematurely born children without BPD may present with elevated RV/TLC (Galdès-Sebaldt et al. 1989, Kennedy et al. 2000) or high functional residual capacity (FRC) suggestive of hyperinflation (Thompson and Greenough 1992). In infants exposed to lung injury at an early stage of gestation, hyperinflation may result from obstructive airway disease, impaired alveolarisation and abnormal lung growth (reviewed by Eber and Zach 2001).

Higher airway resistance (R_{aw}) and lower specific conductance (sG_{aw}) have been reported in BPD children compared to VLBW and term controls (Northway et al. 1990, Hakulinen et al. 1990). Yüksel and associates (1993) showed that surfactant therapy had beneficial effects on R_{aw} and sG_{aw} at 7 months in infants of 26-29 weeks' gestation.

9.7.4. Diffusing capacity of the lung

Northway and associates (1990) found slightly lower diffusing capacity of the lung (DLCO) among adolescents with former BPD compared to term-born controls. In a series studied by Blayney and associates (1991), 10-year-old BPD children had normal DLCO. In another study, VLBW children, regardless of BPD, had lower DLCO than term controls, whereas specific DLCO values (corrected for alveolar volume) were comparable (Hakulinen et al. 1996). Galdès-Sebaldt and associates (1989) detected lower DLCO in VLBW children without a history of RDS or BPD compared to children with birth weights >2500 g. Structural changes in the lung tissue may persist for years in VLBW children with and without BPD.

9.8. Cardiovascular complications

Systemic hypertension may manifest in up to 43% of infants with severe BPD (Abman et al. 1984, Alagappan and Malloy 1998). This is in most cases reactive to antihypertensive medication and resolves by the age of one year (Abman et al. 1984, Alagappan and Malloy 1998). The reasons for this are unknown, but the roles of chronic hypoxaemia, hypercarbia, stress and decreased pulmonary vascular clearance of norepinephrine seen in BPD infants remain to be determined (Singh et al. 1992).

Infants with former BPD have manifested e*levated pulmonary artery pressure (PAP)* in the first years of life (Berman et al. 1982, reviewed by Abman 1999, Subhedar and Shaw 2000). Structural changes in the lung vasculature, decreased vascular growth, abnormal vasoreactivity (reviewed by Abman 1999) and disturbed metabolic function of the lung (Abman et al. 1987) probably contribute to this. Elevated PAP may be associated with prolonged O_2 dependency (Gill and Weindling 1995) or severe peripheral pulmonary obstruction (Farstad et al. 1995), but may also be asymptomatic (Fitzgerald et al. 1994). Indirect echocardiographic parameters such as the direction of blood flow in the PDA (when possible), the intensity of tricuspid regurgitant flow and systolic time intervals, are used in the diagnosis. The reliability of the latter in assessing PAP is controversial (Benatar et al. 1995, Newth et al. 1985).

Systemic to pulmonary collateral vessels may increase collateral pulmonary blood flow and reduce lung compliance and thus destabilise the condition of a BPD infant (Acherman et al. 2000). Adequate oxygenation and diuretic therapy usually alleviate the symptoms, and the collaterals close spontaneously. Coiling is sometimes necessary.

Hypertrophy of the left or right cardiac ventricle (or both) is a possible cardiovascular consequence of severe BPD (Smyth et al. 1981, McConnell et al. 1990). Small left ventricular internal dimensions in infants with severe BPD may be associated with an increased risk of death (McConnell et al. 1990).

9.9. Growth

Impaired long-term growth has been reported in school-aged VLBW infants compared to children with normal birth weights (Kitchen et al. 1992a, Robertson et al. 1992, McLeod et al. 1996, Powls et al. 1996, Giacoia et al. 1997). Some authors have attributed this especially to children with BPD (Northway et al. 1990). Vrlenich and associates (1997) detected lower weight and head circumference but similar height among 8-10-year-old VLBW children with BPD than in those without. However, the differences disappeared after accounting for confounding variables such as race, GA, birth weight, SGA status and Apgar scores (Vrlenich et al. 1997). Apart from BPD itself, repeated infections and respiratory symptoms, feeding problems as well as the need for corticosteroid treatment may further influence the growth of BPD children in childhood. Intrauterine growth retardation may also have an impact on the growth of VLBW infants, at least up to 5 years of age (Gutbrod et al. 2000).

10. Adrenarche

10.1. Physiology of the adrenal gland

At birth, the human foetal adrenal weighs approximately the same as the adult adrenal by reason of a large foetal zone. The involution of the gland after birth results in a sharp decrease in dehydroepiandrosterone sulfate (DHEAS) concentrations. At age 1-6 years, the levels of the adrenal androgens, i.e. dehydroepiandrosterone, DHEAS and androstenedione are usually low (reviewed by Saenger and DiMartino-Nardi 2001). *Adrenarche*, the puberty of the adrenal gland, refers to a prepubertal increase in the secretion of the adrenal steroids. This may result in the appearance of pubic hair (*pubarche*), possibly axillary hair and pubertal odour.

Pubarche is considered premature if occurring before the age of 8 years in girls and 9 years in boys (reviewed by Saenger and DiMartino-Nardi 2001). The exact mechanism by which adrenal androgen production is regulated is unknown. The process is held to be independent of gonadotropins (reviewed by Saenger and DiMartino-Nardi 2001). Several regulators have been suggested, including growth-hormone/insulin-like growth factor-I axis and insulin resistance in girls (Guercio et al. 2003), and prolactin, dopamin (Francois and de Zegher 1997), corticotropin releasing hormone (Ibàñez et al. 1999) and changing nutritional status (Remer and Manz 1999) in both sexes.

10.2. Intrauterine growth, birth weight and adrenarche

Term SGA children seem to carry an increased risk of premature adrenarche (Dahlgren et al. 1998, Ibàñez et al. 1998a). However, only limited data are available on VLBW infants and adrenarche, and to our knowledge, none on adrenarche in BPD infants. Turnipseed and associates (1976) found high DHEAS levels in newborn infants of less than 33 weeks' gestation. These correlated to severe clinical stress, and tended to normalise by 5-10 weeks of age (Turnipseed et al. 1976). The interaction between pre- and postnatal growth and adrenal androgen secretion has been studied in 13 premature sibling pairs from multiple pregnancies (Francois and de Zegher 1997). At birth, one of each pair had been SGA and the other had a birth weight appropriate for GA (AGA). In 10 pairs with weight difference less than 1 stardard deviation (SD) at 8.2 years' median age, the SGA infants had higher serum DHEAS levels than the AGA siblings. In contrast, in the 3 pairs with persisting weight discordance (> 2 SD), the DHEAS concentrations were lower in the SGA cases (Francois and de Zegher 1997).

10.3. Long-term consequences of premature adrenarche

Reports on the impact of premature adrenarche on *final height* are controversial. According to Pere and associates (1995), mild childhood hyperandrogenism may be associated with an earlier mid-childhood growth spurt but not necessarily with reduced final height. Conversely, among term-born SGA girls, increased DHEAS levels before puberty have been reported to have effects on bone maturation, with a reduced final height (Ghirri et al. 2001).

Premature adrenarche was long regarded as a benign normal variant of puberty. However, data have accumulated on premature adrenarche and the risk of further *metabolic* (insulin resistance, diabetes mellitus) and *cardiovascular* problems (Ibàñez et al. 1998b, Denburg et al. 2002) among term children. In addition, premature pubarche may precede *ovarian hyperandrogenism* (Ibàñez et al. 1998a) and *dyslipidaemia* (Ibàñez et al. 1998b) in term girls. Intrauterine programming of the hypothalamus-pituitary-adrenal axis with increased cortisol production might be a link between reduced foetal growth and these future problems (Phillips et al. 1998).

To our knowledge, the metabolic consequences of premature adrenarche among preterm infants have been less fully investigated.

AIMS OF THE STUDY

The purpose of this study was to establish the frequency and possible predictors of BPD in VLBW infants born after the introduction of surfactant treatment. We also sought to assess the impact of BPD and other neonatal and perinatal factors on the future health of these children, on the need for financial support and on the rest of the family.

The specific goals of the study were:

1. To establish the frequency and most important risk factors in BPD in a cohort of VLBW infants born during a five-year-period in one hospital with available surfactant therapy (I).

2. To assess whether VLBW children with BPD have more problems with health and need more rehabilitation and financial support during the early years of life compared to VLBW children without BPD and term-born controls (II).

3. To establish whether VLBW children with BPD born after the introduction of surfactant therapy have poorer lung function at early school age than those without BPD or children born at term, and to evaluate other possible predictors of pulmonary function among these children (III).

4. To ascertain whether BPD is associated with abnormal cardiac findings at early school age (IV).

5. To assess whether BPD children born during the surfactant era grow less well at early school age than VLBW children without BPD and term controls (V).

6. To establish whether VLBW children have higher adrenal androgen levels at 7 years of age compared to children born at term, and whether these levels are associated with the presence of BPD or with other peri- or neonatal factors (V).

SUBJECTS AND METHODS

1. Subjects and study design

In all studies (I-V), VLBW children were derived from a cohort comprising all 242 VLBW (birth weight ≤ 1500 g) infants born alive in Tampere University Hospital during the years 1990 to 1994. Figure 3 presents the selection of VLBW infants for the studies. In addition, next-born sex-matched non-SGA term children from the same hospital were recruited as term controls for all VLBW cases in Study II, and for the BPD cases in studies III-V.

In Study I, peri- and neonatal data were retrospectively obtained from the hospital records of all 242 VLBW children of the original cohort. BPD diagnosis was based on the need for supplemental O_2 combined with chest X-ray findings typical of BPD (Northway 1967) assessed by a paediatric radiologist, non-blinded for the clinical situation of the children. These criteria were evaluated at both 28 days' postnatal (BPD) age and 36 weeks' corrected GA (severe BPD, sBPD). In all, 180 VLBW children survived, including 50 with BPD and 24 with sBPD. Predictors were sought for BPD at 28 days' postnatal age and for late recovery from BPD (later than 36 weeks' corrected GA).

In Study II, all 178 traceable children of the 180 surviving VLBW cases in the basic cohort (I) and 179 term age- and sex-matched children and their families received a mailed questionnaire (Study II/Appendix). In all, 36(72%) BPD children, 107(75%) VLBW cases without BPD, and 131 (73%) term children and their families participated. The BPD group included 15 sBPD cases. The birth weights and GAs of the responding and non-responding VLBW or BPD cases did not differ. At evaluation, the mean (SD) ages of the children were 4.9(1.3) y in the BPD group, 5.0(1.4) y in VLBW controls and 5.0(1.4) y among term children.

In Studies III-V, all 50 surviving BPD children in the basic cohort were invited to participate and 34 (68%), including fourteen with sBPD, gave consent. The age- and sex-matched control groups included 34 VLBW cases without BPD and 34 next-born term children. The birth weights and GAs of the participating BPD, no-BPD and term children did not differ from those who declined. The median (range) ages of the children were 7.1(6.7-7.8) in the BPD, 7.1(6.9-8.1) in the no-BPD and 7.2(6.9-8.3) in the term group. The children underwent a thorough growth, respiratory and cardiovascular evaluation at a day as close to

their 7th birthday as possible. For the purposes of the study, children with severe CP, in whom height measurement was considered unreliable, were excluded from Study V. Peri- and neonatal data collected in Study I were exploited in all of these studies.

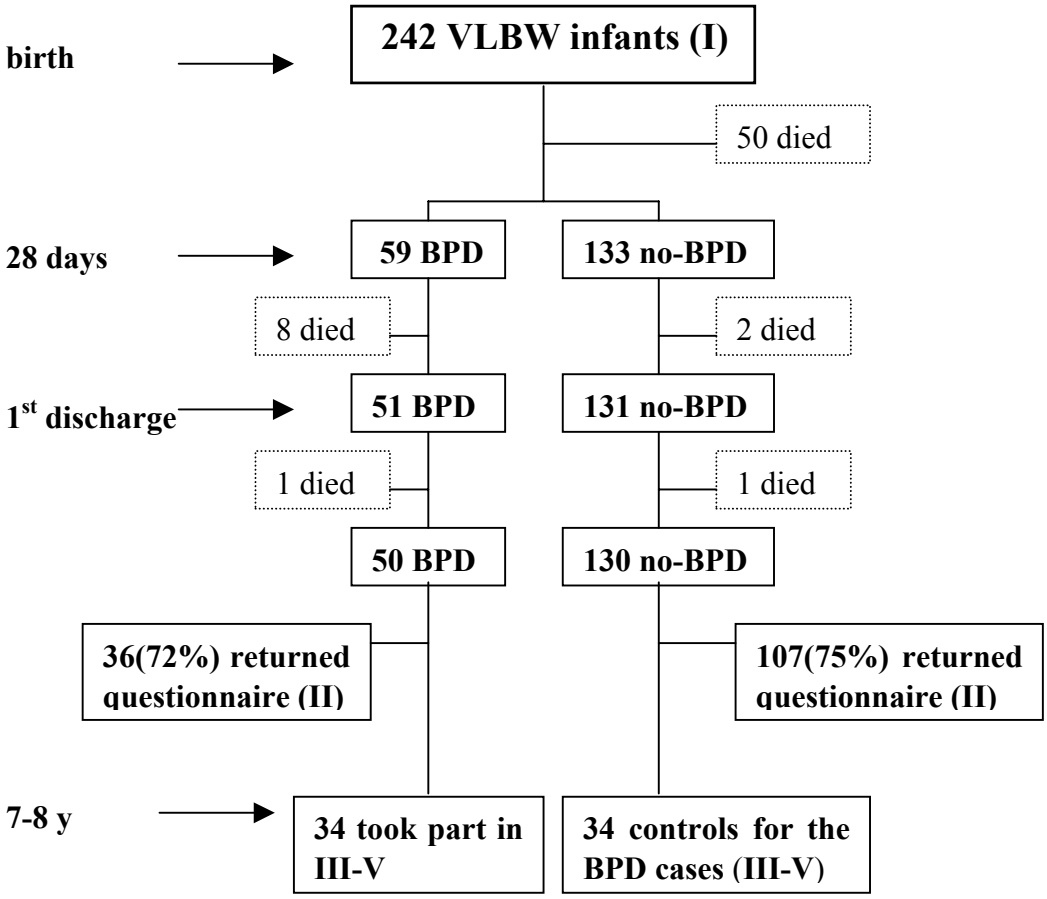


Figure 3. *The participating VLBW infants (Studies I-V).*

2. Neonatal management of the VLBW cohort

Gestational ages were estimated in completed weeks from both obstetric dates and foetal ultrasound measurements (mainly crown-rump length and biparietal diameter) (Robinson and Fleming 1975, Hadlock et al. 1982) before 17th weeks' gestation. If these two estimations differed by more than a week, the age estimated by ultrasound was preferred.

All infants were treated in incubators except for the first few hours of life. Time-cycled pressure-controlled ventilators (Baby Bird) were used. None of the

infants was treated with nasal CPAP. O_2 saturations between 90% and 95%, paO_2 between 6.5 and 8.0 kPa, $paCO_2$ between 5.0 and 7.0 kPa and arterial pH between 7.30 and 7.42 were targeted.

Surfactant (Exosurf® or Curosurf®) was used as rescue therapy for infants who yielded radiological findings typical of RDS and in whom the fraction of inspired O_2 exceeded 50%. Infants with mean arterial pressures below 30 mmHg received a plasma expander infusion and, if necessary, dopamine and dobutamine. If the baby was ventilator-dependent at two weeks of age, parenteral corticosteroids were administered in 9-day courses. Corticosteroid and ipratropium bromide inhalations and peroral diuretics (hydrochlorothiatzide and spironolactone) were used if the infants had a prolonged need of O_2 supplementation and radiographic BPD findings. The hematocrit threshold for PRC infusions ranged from 0.40 (1st week of life and ventilator-dependent infants) to 0.30 (after one month).

Fluid therapy was usually planned according to a scheme of 60-70-80-90-100-110-120 ml/kg/day during the 1st week of life and 180 ml/kg/day thereafter. Breast milk administration was initiated on the 1st day of life if the infant was not receiving inotropics. If milk was contraindicated or not tolerated, parenteral amino acids and lipids were started on the 2nd to 3rd day of life.

All infants with a clinical suspicion of PDA, congenital heart disease or elevated pulmonary pressure underwent transthoracic echocardiograpy. Symptomatic PDAs were managed pharmacologically or by surgical ligation at the discretion of the attending neonatologist. Cranial ultrasound scan was followed up in all VLBW infants, first at 3-4 days' age and at 1-2 weeks' intervals thereafter.

3. Methods

3.1. Definitions

BPD was defined as the need for O_2 supplementation combined with radiologic findings typical of BPD (Northway et al. 1967) at 28 days' postnatal age. Infants who still fulfilled the same criteria at 36 weeks' corrected GA were classified as having severe BPD (sBPD).

Infants with birth weights more than 2 SD below the Finnish average for GA and sex were considered SGA (Pihkala et al. 1989). IVH grading was performed according to Papile and associates (1978).

In Studies II-V, parents were divided into 5 groups according to socio-economic status (SES): employers and own-account workers, upper-level white-collar workers, lower level white-collar workers, blue-collar workers and persons

not involved in work life (students, pensioners and unemployed) (Central Statistical Office of Finland 1989).

The term child-care allowance (Study II) refers to monthly financial support granted by the State to families whose children need special medical care. This support is independent of the family's financial situation and its purpose is to cover some of the additional burden constituted by the child's problems.

3.2. Assessment of medical history and health status (II-V)

A non-validated mailed questionnaire (Study II/Appendix) was used in studies II-V. Questions were included on the child's family background, past and present health (II-V), need for rehabilitation and financial support, as well as on the impact of the child's health on family life (II). In Studies III-V, questions were included on the mother's menarche, father's growth pattern and the child's exercise habits, and the responses were corroborated at the hospital visit.

In Study III, atopic tendency was evaluated by determining serum levels of specific IgE antibodies against common food (egg ovalbumin, milk, codfish, peanut, soybean) (MultiRAST®, Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) and inhalation allergens (birch, timothy grass, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus and Cladosporium herbarum) (Phadiatop®, Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

3.3. Evaluation of lung function (III)

A respiratory infection within 2 weeks was considered an indication for postponement of testing. The detailed methodology of the lung function tests is described in the original publication III.

3.3.1. Flow-volume spirometry

Flow-volume spirograms were recorded by mass flow sensor (2200/Vmax 22, SensorMedics BV, Bilthoven, Netherlands). The spirometer was calibrated volumetrically at the start of each study. Indoor temperature was recorded at the time of calibration and the parameters automatically corrected to body temperature. At least two repeatable maximal flow-volume curves, with a variation of less than 5%, were measured. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), ratio of FEV_1 to FVC (FEV%) and peak expiratory flow rate (PEF) were calculated for each study. The best curve with the greatest sum of FEV_1 and FVC was recorded (Standardization of spirometry/American Thoracic Society 1987). The results were interpreted against Finnish reference values for children (Koillinen et al. 1998).

3.3.2. Assessment of bronchial responsiveness

Metacholine challenge was performed using a dosimeter technique with controlled tidal breathing (Nieminen et al. 1988) by an automatic, inhalation-synchronised dosimetric jet nebulizer (Spira Electro 2, Respiratory Care Center, Hämeenlinna, Finland). Metacholine was delivered in five cumulative doses of 18, 72, 270, 810 and 2610 µg at intervals of about 5 minutes. The test was terminated when FEV_1 fell by at least 20% of the post-saline value. The fall in FEV_1 was plotted against the dose of metacholine on a log scale and the dose provoking a 20% fall in FEV_1 (PD_{20}) calculated (Nieminen 1992). Children who did not reach a 20% fall in FEV_1 after the highest cumulative dose of metacholine received a PD_{20} value of 7500 µg. Bronchial responsiveness was analysed using two cut-off points: 2610 µg (BR_{2610}) and 810 µg (BR_{810}) (modified according to Vasar et al. 1996 and Lonnkvist et al. 1999).

In the bronchodilatation test, 0.2 mg of salbutamol was given with a metered dose inhaler with a spacer, and FVS repeated after ten minutes. The bronchodilator response was considered significant if a rise of 15% or more was detected in FEV_1.

3.3.3. Whole-body plethysmography

Whole-body plethysmography was recorded by a volume-displacement plethysmograph (6200 Autobox, SensorMedics, Bilthoven, Netherlands). The panting method was used. Vital capacity (VC), total lung capacity (TLC), functional residual capacity (FRC), expiratory reserve volume (ERV), residual volume (RV) and the ratio of RV to TLC (RV/TLC), airway resistance (R_{aw}), and specific airway conductance (sG_{aw}) were recorded. The reference values of Polgar and Promadhat (1971) were used for R_{aw} and sG_{aw}, and those of Cotes and associates (Quanjer et al. 1989) for other plethysmographic parameters.

3.3.4. Diffusing capacity measurement

The single-breath carbon monoxide diffusing capacity test was performed on the same equipment as flow-volume spirometry. The breath-hold interval was to be as close to 10 seconds as possible and variation between two successful tests less than 10%. The diffusing capacity of the lungs (DLCO), alveolar volume (VA) and specific diffusing capacity (DLCO/VA), corrected for haemoglobin concentration, were recorded in each study. The results were interpreted using the reference values of Cotes and associates (Quanjer et al. 1989).

3.4. Cardiac examinations (IV)

3.4.1. Blood pressure measurement

Blood pressure was measured oscillometrically (Dinamap Adult/Paediatric and Neonatal Vital Signs Monitor Model 1846 SX, Criticon, Inc. USA) in sitting position from the right arm with a cuff covering two thirds of the upper arm. The lowest result of 2-3 measurements was recorded. Hypertensive values were defined using previous standards (Task Force on Blood Pressure Control in Children 1987).

3.4.2. Electrocardiography (ECG)

Thirteen-lead-ECG (I, II, III, aVR, aVL, aVF, V_4R, V_{1-6}) was recorded (Hewlett Packard, M1700A, 1993, USA) after five minutes' rest, the child lying on the back.

3.4.3. Transthoracic echocardiography

Echocardiograms were recorded on videotape by three experienced clinical physiologists, blinded for the perinatal characteristics of the children. The recordings were subsequently analysed by one of the investigators (VL).

Transthoracic echocardiography was performed after 5 minutes' rest using an Acuson computed sonography 128/XP10 system (Mountain View, USA) with a 5 MHz probe. The child was lying in the left lateral recumbent position. The parasternal, apical, sub- and supracostal windows (Henry et al. 1980) were used.

Spectral Doppler measurements of blood flow were performed by pulse wave Doppler by aligning the interrogating beam with the direction of flow using anatomical and colour Doppler information. No angle correction was used. Systolic pulmonary artery pressure (PAP) was evaluated from the right ventricular - right atrial tricuspid blood flow (Hamer et al. 1988, Lavie et al. 1993). The right atrial pressure was assumed to be 10 mmHg. The upper limit of the systolic gradient was set at 20 mmHg, corresponding to a PAP of 30 mmHg (Hamer et al. 1988, Lavie et al. 1993).

The Doppler-derived pulmonary vascular contour was analysed to evaluate pulmonary flow indices. Three consecutive cardiac cycles were measured and averaged. The right ventricular acceleration time (AT) was determined as the time interval from the onset to the peak of the systolic Doppler velocity waveform, and the right ventricular ejection time (ET) as the time interval between the onset and determination of the velocity curve. The right ventricular pre-ejection period (PEP) was defined as the interval between the Q wave

recorded on a simultaneous ECG, and the opening of the pulmonary valve. AT/ET and PEP/ET ratios were computed. AT, PEP, AT/ET and PEP/ET were corrected for heart rate by division by the square root of the previous R-R interval (Akiba et al. 1988). AT/ET ratios below 0.36 were considered low and PEP/ET ratios above 0.34 elevated (Snider et al. 1997).

Transthoracic M-mode recordings (Sahn et al. 1978, Roelandt and Gibson 1980) were used to measure cardiac dimensions, including thickness of interventricular septum at end diastole (IVSd), left ventricular end diastolic dimension (LVEDD), left ventricular posterior wall thickness at end diastole (LVPWd) and left ventricular end systolic dimension (LVESD). The diameter of the pulmonary artery (PAD) was measured from the parasternal short-axis and the diameter of the aorta (AoD) from the parasternal long-axis window. Left ventricular shortening fraction (LVSF) was calculated using the formula (LVEDD-LVESD):LVEDD. The reference values given by Kampmann and associates (2000) were used for IVSd, LVEDD, LVESD, LVPWd, PAD and AoD and those of Colan and associates (1992) for LVSF.

3.5. Assessment of growth (V)

3.5.1. Anthropometrics

Height was measured with a Harpenden stadiometer (Holtain Limited, England), plotted against standardised Finnish growth curves, and expressed as height standard deviation score (height SDs, deviation of height in SD units from the mean height for age and sex) (Sorva et al. 1984). Low height SDs was defined according to the lowest quartile in our material (< 1.2 SD). Catch-up growth was considered incomplete if the child's height SDs at 7 years of age was more than 1.5 SD below the midparental height (mother's height (SD) + father's height (SD)/2).

The children were weighed with a digital scale (Seca 707, Germany). Body mass index (BMI), the ratio of weight (kg) and squared height (m^2) was calculated. Finnish reference values were used to define low (< 10^{th} percentile) and high BMI (> 90^{th} percentile) (Dahlström et al. 1985). Waist, hip and middle upper arm circumferences (MUAC) were measured with a plastic tape measure, and waist-to-hip ratios (WHR) computed. The biceps, triceps, subscapular and suprailiacal skinfold thicknesses were measured with a Harpenden skinfold caliper, as previously described (Cameron 1978). The skinfold thicknesses were expressed as means of 3 successive measurements, allowing for a 20% variation between the lowest and highest value.

3.5.2. Bone age assessment

Blinded for the perinatal characteristics of the children, an experienced paediatric endocrinologist determined the child's skeletal age (Greulich and Pyle 1959) from a radiograph of the left wrist and hand. Appropriate shields for stray radiation were used.

3.6. Evaluation of adrenarche (V)

Pubertal development was assessed clinically, and the breast and pubic hair status staged according to Tanner (1962). Adrenal androgen (androstenedione, dehydroepiandrostenedione sulfate (DHEAS)) levels were determined from serum samples. Radioimmunologic assays from Diagnostic Systems Laboratories Inc. (Webster, Texas, USA) were used for androstenedione and those of DiaSorin Biomedica S.P.A. (Saluggia, Italy) for DHEAS. Frequencies were calculated for hormone levels in the highest quartile in our patient population and for those exceeding the reference limits of the hospital laboratory.

3.7. Statistical methods

Continuous variables with normal distribution were tested by analysis of variance with Bonferroni correction (three-group comparisons), Student's t-test (two-group comparisons) or analysis of variance for repeated measures (serial measurements in Study I), and those with non-normal distribution by Kruskal-Wallis test (three-group comparisons) or Mann-Whitney U-test (two-group comparisons). Differences in proportions were analysed by Chi-square test or Fisher's exact test. When appropriate, a p-value adjustment for multiple comparisons was applied. Cronbach's α was used in testing the consistency of impact on family questions in the questionnaire (II).

Risk factor analyses (I-V) were performed using forward stepwise logistic regression analysis, the limit for significance set at 0.05 to enter and 0.10 to remove the factors. The risk factor categories were first tested separately. Eventually, if several predictors emerged, a combined model was formed from the significant factors in each category. The results were expressed as odd ratios (OR) and 95% confidence intervals (95% CI).

Statistical significance was defined as $p<0.05$ (two-sided). BMDP Statistical Software (Version 1990) (I, II) and SPSS Versions 6.1 (II) and 10.1 (III-V) were used in the analyses.

4. Ethics

All studies were approved by the Ethical Committee of Tampere University Hospital. The parents of the study patients gave written informed consent.

RESULTS

1. Frequency and risk factors in BPD (I)

At 28 days' postnatal age, the frequency of BPD was 30.7 % (59/192) among the infants alive. Severe BPD (sBPD) had been diagnosed in 13.0 % (24/184) of the survivors at 36 weeks' corrected GA. In postmortem examination, histological features of BPD (fibroblast proliferation) had been detected in three infants who died before 28 days' postnatal age.

Compared to VLBW children without BPD, the BPD cases were of lower GA and birth weight, more often male and less frequently SGA (Table 2). Surfactant therapy for RDS and indomethacin and/or surgery for PDA were more common in the BPD than the no-BPD group. In addition, the BPD children needed more PRC infusions after the 1st week of life and longer ventilator therapy than the no-BPD cases. The detailed perinatal and neonatal features of the subjects are given in Study I. Infants who recovered from BPD by 36 weeks' corrected GA had lost weight up to the 6th day of life, while those with sBPD had started to gain weight after the 3rd day of life (Figure 4).

According to logistic regression analysis (combined model), the most important predictors of BPD were low (≤ 27 wk) GA (OR 3.18, 95% CI 1.38-7.35), male sex (OR 2.81, 95% CI 1.21-6.54) and frequent (> 3) PRC infusions after the 1st week of life (OR 18.3, 95 % CI 6.68-49.9). The risk of delayed recovery from BPD (after 36 weeks' corrected GA) seemed to be increased in connection with preeclampsia (OR 31.5, 95% CI 1.86-534) and long duration (> 26 d) of mechanical ventilation (OR 19.7, 95% CI 2.74-141), whereas surfactant therapy appeared to be associated with enhanced early recovery (OR 0.07, 95% CI 0.01-0.54).

Table 2. Clinical characteristics of the VLBW cohort.

	BPD N= 59	No-BPD N=133	P
Gestational age (wk)	27(2) [23-30]	29(2) [23-36]	<0.0001
Birth weight (g)	937(230)[485-1470]	1209(207)[605-1500]	<0.0001
Male	37(63%)	59(44%)	0.0190
SGA	10(17%)	33(25%)	NS
Prenatal corticosteroid	19(32%)	52(39%)	NS
PDA	26(45%)	33(25%)	0.0059
Surfactant	29(49%)	28(21%)	<0.0001
PRC infusions after 1st week, median(range)	8(0-28)	2(0-21)	<0.0001
Ventilator therapy	57(97%)	85(64%)	<0.0001
- duration (d), median(range)	28(0-89)	1(0-49)	<0.0001
O_2 supplementation	59(100%)	120(92%)	0.0130
- duration (d), median(range)	61(29-163)	13(0-103)	<0.0001

Values are mean(SD)[range] and N(%) unless indicated otherwise. SGA, small for gestational age; PDA, patent ductus arteriosus treated with indomethacin and/or surgery; PRC, packed red cell; O_2, oxygen.

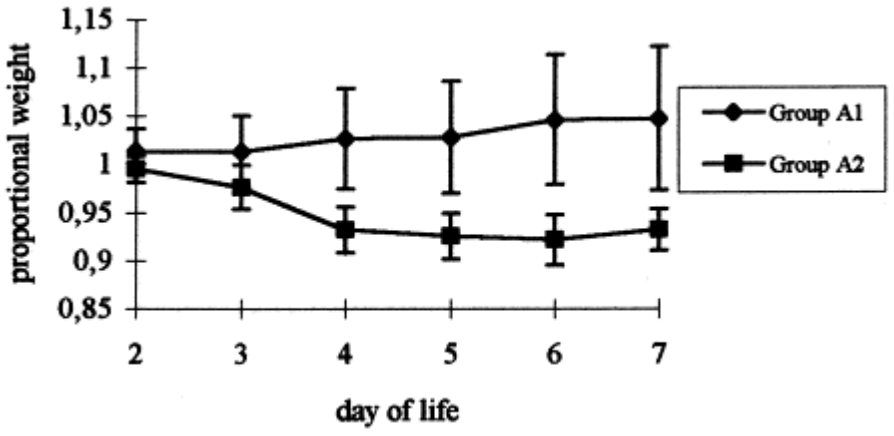


Figure 4. Means and confidence intervals of proportional daily weights (weight/birth weight) in infants with BPD both at 28 days' postnatal age and 36 weeks' corrected gestational age (A1) and infants who recovered from BPD by 36 weeks' corrected gestation (A2). (from Study I, with permission)

2. Health of the children up to early school age

2.1. Respiratory health (II, III)

2.1.1. Respiratory symptoms and medications (II, III)

More of the 2-8-year-old VLBW children than term controls had undergone adenotomy and/or tympanostomy (II). In the preceding year, cough and/or wheezing upon exercise, need for inhaled medications and hospitalisation for respiratory infection were more often reported in both VLBW groups compared to term controls. Respiratory infection in excess of five times per year was a more frequent finding in the BPD than term children (5(14%) vs 6(5%), $p<0.05$). Need for more than 2 antibiotic courses per year was more common in the BPD group (17(47%)) than in the no-BPD (21(21%), $p<0.05$) and term group (21(16%), $p<0.05$).

In the whole study population, children with higher GA at birth and with many siblings seemed to have less risk of respiratory symptoms provoked by cold and/or exercise in the past year (Table 3). A negative association was found between birth weight and the use of inhaled medications. Higher GA and age at evaluation seemed to diminish the risk of frequent respiratory infections.

Table 3. Logistic regression analysis (combined model) of the respiratory health of the children in the preceding year.

Dependent	Independent	OR	95% CI
All children			
Cough/wheezing	Gestational age (wk)	0.92	0.87-0.99
Upon cold air/exercise	Number of siblings	0.63	0.41-0.98
Inhaled medications	Birth weight (g)	0.92	0.89-0.97
>5 respiratory	Age at response (y)	0.64	0.44-0.94
infections/y	Gestational age (wk)	0.79	0.60-1.05
VLBW children			
>5 respiratory infections/y	Gestational age (wk)	0.92	0.84-1.01

OR, odds ratio; CI, confidence interval

At 7 years of age (III), respiratory symptoms (cough and/or wheezing) provoked by cold air and/or exercise were reported in approximately a third of VLBW children with and without BPD and in 9 per cent of term cases. A significant difference was found between the no-BPD and term groups in the frequency of current respiratory symptoms upon exercise (11(32%) vs 2(6%), $p<0.05$). Half of the symptomatic no-BPD children had inhalator therapy. Among VLBW children, the most significant predictors of current respiratory symptoms were low SES (OR 3.27, 95% CI 1.04-10.3) and absence of exposure to animal dander (OR 0.28, 95% CI 0.09-0.92).

2.1.2. Pulmonary function (III)

At 7 years of age, flow-volume spirometry revealed lower mean FEV_1 in the BPD group compared to term controls (Figure 5). BR_{810} was more common in all VLBW groups (frequencies ranging from 79 to 100%) compared to term cases (47%). No difference was found in the frequency of positive bronchodilatation test.

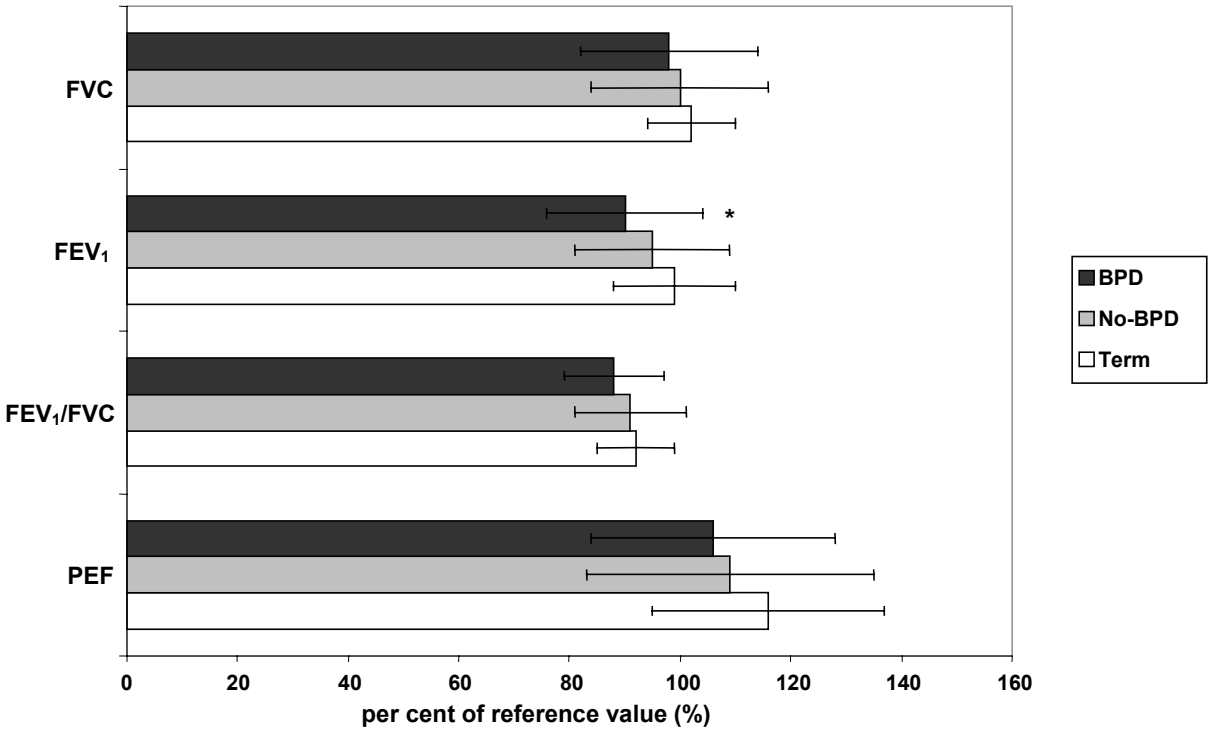


Figure 5. Flow-volume spirometric findings in BPD, no-BPD and term children. Values are presented as mean ± 1 SD. * $p<0.05$, BPD compared to term group.

The BPD children had higher RV and lower sG_{aw} than term controls, and higher R_{aw} compared to the no-BPD and term groups (Figure 6). Their mean (SD) RV/TLC ratio was also higher than that in the term group (30(8) vs 24(6)%, $p<0.05$). The frequency of high RV/TLC ratio (>30%) was 15(52%) in the BPD and 3(10%) in the term group. Both total and specific diffusing capacity of the lung were lower in all VLBW groups compared to children born at term.

Among VLBW children, administration of surfactant to treat RDS (OR 6.08, 95% CI 1.40-26.5) and longer duration of O_2 therapy emerged as risk factors for low FEV_1 at 7 years of age. A negative association was found between birth weight and high RV/TLC ratio, with an OR (95% CI) of 0.74 (0.61-0.90) for every 100 g increment in birth weight.

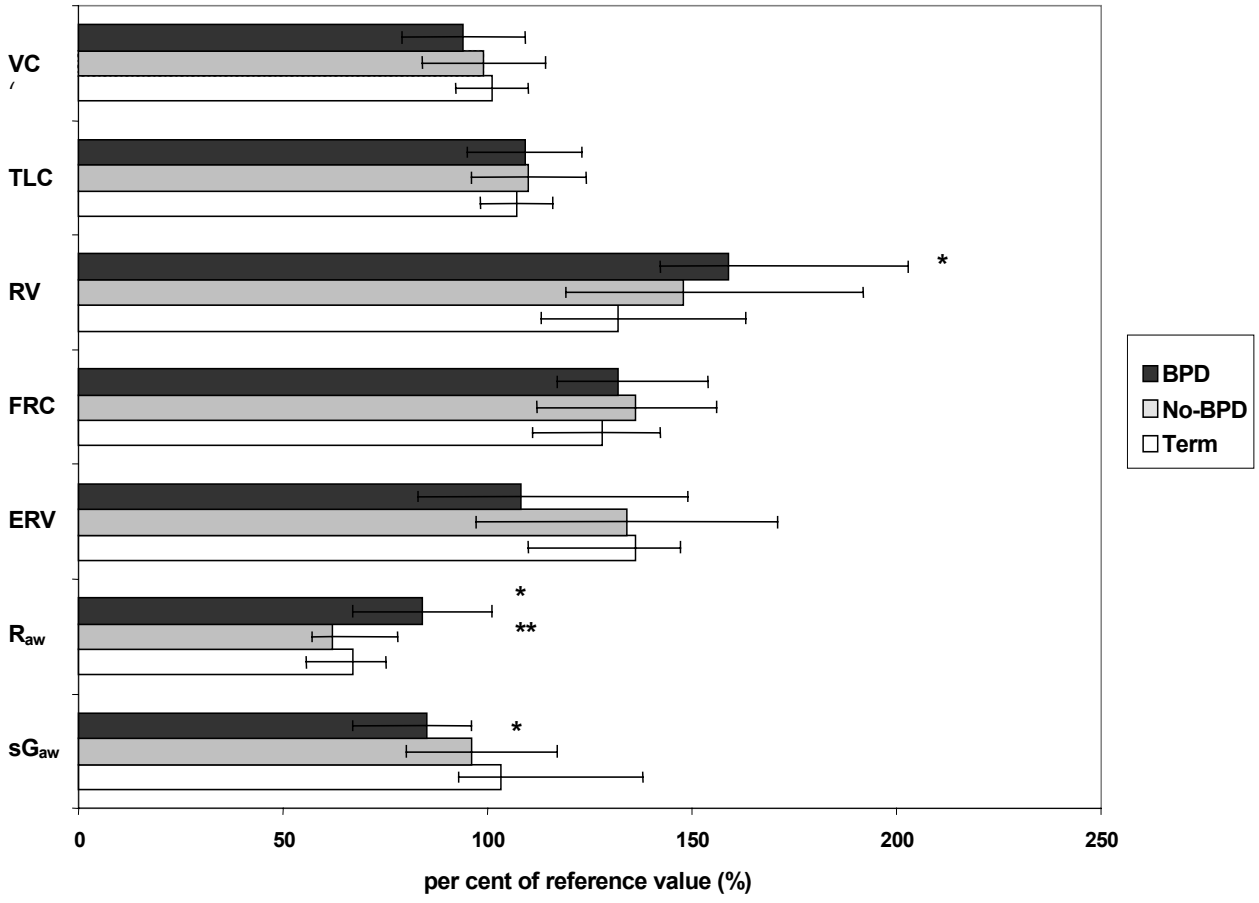


Figure 6. Results of whole-body plethysmography in BPD, no-BPD and term children. Values are median (interquartile range) except for VC and TLC (mean ± 1 SD). *p<0.05, compared to term group. ** p<0.05, compared to no-BPD group.

2.2. Neurodevelopment, rehabilitation and financial support (II)

Compared to VLBW children without BPD, the BPD cases had had lower birth weights and GAs and more often IVH (grade III-IV) and ROP. Periventricular leucomalacia had been diagnosed in none of the BPD cases but in 4(4%) of the no-BPD children. At 2-8 years of age, CP entailing a need for technical aids and regular rehabilitation had been diagnosed in 5(14%) BPD and 7(7%) no-BPD children, representing 8% of the VLBW cases.

Vision problems were reported in 10% of VLBW children, most commonly among BPD cases (28%). A squint had been detected in 14% of VLBW children (27% of BPD and 10% of no-BPD cases) compared to 1% of term controls ($p<0.001$). Three VLBW children were blind.

The need for physiotherapy, occupational therapy and technical aids was more common in VLBW than term children. Compared to the no-BPD group, BPD children more often needed physiotherapy (12(33%) vs 18(17%), $p<0.05$) and occupational therapy (11(31%) vs 15(14%), $p<0.05$), but no difference was found in the frequency of speech therapy (9(25%) vs 22(21%)). Both VLBW groups received child-care allowances more often compared to term controls, the frequencies being 42% in the BPD, 30% in the no-BPD and 6% in term cases.

2.3. Impact on family (II)

The results of the impact on family questions are presented in Table 8. Compared to the parents of term controls, those of the VLBW children were more often worried about the child's health, and felt it to have more effect on the child's everyday life and their own work and education. The parents of the BPD cases reported a greater impact of the child's health on the pastimes of other family members compared to those in the term group. The perceptions of the parents did not differ between the BPD and the no-BPD groups. However, compared to the no-BPD group, a greater number of parents in the sBPD group thought the child's health to have some or a considerable impact on the child's everyday life (6(40%) vs 16(13%), $p<0.05$).

Table 8. Number (%) of parents who thought the child's health to have some or a considerable impact on the family (See Study II/Appendix).

	BPD N= 36	No-BPD N=107	Term N=131
Worry	15(42%)*	29(27%)†	15(12%)
Fear of infections	4(11%)	12(11%)	17(13%)
Child's everyday life	8(23%)†	14(13%)†	7(5%)
Parents' education/work	8(23%)*	15(14%)†	5(4%)
Parents' pastimes	7(19%)†	11(10%)	8(6%)
Other children's pastimes	2(6%)†	1(1%)	0(0%)
Holiday	3(9%)	7(7%)	9(7%)
Leisure	2(6%)	7(7%)	4(3%)
Visiting friends	1(3%)	9(8%)	9(7%)

**p<0.001, compared to term group; †p<0.05, compared to term group.*

2.4. Cardiovascular findings (IV)

At 7 years of age, the no-BPD group had higher mean(SD) diastolic blood pressure compared to the BPD group (65(9) vs 59(8) mmHg, $p<0.05$). Slightly elevated blood pressures were detected in one BPD child, 4 no-BPD cases and 1 term child. The SGA and non-SGA cases did not differ with respect to blood pressure. ECG revealed left ventricular hypertrophy in 2 children (one BPD and one no-BPD), sinus bradycardia (verified in 24-hour-recording) in 4 children (2 no-BPD and 2 term) and 1st grade atrioventricular block in one term child.

In echocardiography, a BPD boy had PDA and one term child mild aortic valve regurgitation. Tricuspid valve gradients (range 17.3-21.1 mmHg) were measurable in 2 BPD, 3 no-BPD and 2 term cases, corresponding to PAPs of 27-31 mmHg.

No differences were found between the BPD, no-BPD and term groups in Doppler results. Low AT/ET was found in 2 BPD, 1 no-BPD and 1 term case. All M-mode recordings were within normal range. The median (range) IVSd, corrected for body surface area, tended to be higher in the no-BPD (104.8(90.5-119.5) % of ref.) compared to the BPD (95.7(83.0-117.4) % of ref., $p=0.06$) and term (98.4(86.0-124.2) % of ref., $p=0.06$) groups. The BPD group had higher mean (SD) LVSF compared to the term group (38.4(4.7) vs 35.9(3.3), $p<0.05$), and such a tendency was also detected in comparison with the no-BPD group (35.9(3.6), $p=0.05$). Otherwise the M-mode results, plotted against reference values, did not differ between the groups.

In logistic regression analysis (Table 4), higher birth weight was associated with a decreased risk of IVSd in the lowest quartile in our material. The risk of having LVPWd in the lowest quartile seemed to be reduced by surfactant administration and increased by long duration of O_2 supplementation.

Table 4. Logistic regression analysis (combined model) of M-mode echocardiographic parameters in VLBW children.

Dependent	Independent	OR	95% CI
Low IVSd	Birth weight (100 g increments)	0.67	0.45-0.99
(lowest quartile)			
Low LVPWd	Prenatal CS therapy	0.19	0.04-1.03
(lowest quartile)	Surfactant	0.16	0.03-0.94
	Duration of O_2 therapy	1.19	1.02-1.39

OR, odds ratio; CI, confidence interval; IVSd, thickness of interventricular septum at end diastole; LVPWd, left ventricular posterior wall thickness at end diastole; CS, corticosteroid; O_2, oxygen.

2.5. Growth (V)

At 7 years of age, VLBW children with and without BPD were shorter than term controls (Table 5). No difference was found between the BPD and no-BPD groups in height status, BMI or frequency of incomplete catch-up growth. However, in comparison with term controls, the BPD children had lower BMI and MUAC.

Table 5. Anthropometric data on the children at 7 years of age.

	BPD N=31	No-BPD N=33	Term N=33	P
Age (y) Median(range)	7.2(6.7-7.8)	7.3(6.9-8.1)	7.3(6.9-8.3)	0.247
Skeletal age (y)	6.7(0.7)[5.3-8.0]	6.8(0.8)[5.5-9.0]	6.7(0.8)[5.0-8.3]	0.732
Height SDs (SD) Median(range)	-1.0(-3.4-1.4)*	-0.9(-2.9-2.2)*	0.3(-1.5-1.9)	<0.001
BMI (kg/m^2)	14.8(1.7)[12.8-20.1]†	15.0(1.9)[12.4-20.5]	16.1(2.1)[13.4-21.5]	0.015
MUAC (cm) Median(range)	17.0(15.0-22.5)†	17.1(15.1-22.0)	18.4(16.1-23.6)	0.021
WHR	0.88(0.07)[0.58-0.96]	0.87(0.06)[0.63-0.98)	0.87(0.03)[0.79-0.92]	0.779

*Values are mean(SD)[range] unless indicated otherwise. SDs, standard deviation score; BMI, body mass index; MUAC, middle upper arm circumference; WHR, waist-to-hip ratio. * p<0.01, compared to term group; † p<0.05, compared to term group.*

The chronological and skeletal ages were not different in the BPD, no-BPD and term groups, nor did they differ between VLBW cases born SGA and non-SGA.

Among VLBW children, no difference was found between the SGA and non-SGA cases in height SDs, BMI, WHR, MUAC or skinfold thicknesses.

2.6. Adrenal androgens (V)

The adrenal androgen levels of the children are presented in Table 6. Compared to term controls, both the BPD and no-BPD children tended to have higher levels of androstenedione, and both groups had more often DHEAS >1.1 μmol/l. The DHEAS concentrations of the VLBW cases born SGA were higher compared to both the non-SGA and term children, and the same tendency was found in androstenedione levels.

VLBW children with androstenedione levels >1.0 nmol/l (N=18) tended to have more advanced skeletal ages compared to the rest of the VLBW cases, the median(range) differences (chronological age - skeletal age) being 0.1(-1.4-1.5) and 0.6(-0.9-1.9) years, respectively.

Table 6. Adrenal androgen levels of the children grouped either according to BPD or SGA status.

	BPD N=26	**No-BPD** N=32	***SGA*** *N=18*	***Non-SGA*** *N=40*	**Term** N=32	**p[1]**	***p[2]***
Androstenedione (nmol/l)	0.8(0-2.8)*	0.8(0-2.3)*	*1.2(0-2.8)†‡*	*0.7(0-1.8)*	0.6(0-1.4)	0.029	*0.003*
>1.0 nmo/l	8(31%)	11(34%)‡	*10(56%)‡§*	*9(23%)*	3(9%)	0.045	*0.001*
>2.5 nmol/l	1(4%)	0(0%)	*1(6%)*	*0(0%)*	0(0%)	0.289	*0.200*
DHEAS (µmol/l)	0.5(0-5.8)	0.9(0-4.1)‡	*1.2(0.2-5.8)‡§*	*0.4(0-2.5)*	0.3(0-2.3)	0.070	*0.001*
>1.1 µmol/l	9(35%)‡	11(34%)‡	*9(50%)‡*	*11(28%)*||	2(6%)	0.012	*0.002*
>1.6 µmol/l	6(23%)	5(16%)	*6(33%)‡*	*5(13%)*	2(6%)	0.185	*0.029*

*Values are expressed as median(range) or N(%). DHEAS, dehydroepiandrosterone sulfate. p^1, comparison BPD vs no-BPD vs term; p^2, comparison SGA vs non-SGA vs term; *p=0.07, compared to term group; † p=0.07, compared to non-SGA group; ‡ p<0.05, compared to term group; § p<0.05, compared to non-SGA group; || p=0.06, compared to term group.*

In the logistic regression analysis (Table 7), midparental height was inversely related to short stature at 7 years, whereas children born SGA and those with longer duration of O_2 therapy had an increased risk of short stature. High BMI of the mother appeared to lower the risk of the child's low BMI. Being born SGA appeared to predict adrenal androgen levels in the highest quartile (androstenedione > 1.0 nmol/l and/or DHEAS > 1.1 μmol/l).

Table 7. Logistic regression analysis of growth and adrenal androgen status of the VLBW children at 7 years (final model).

Dependent	Independent	OR	95% CI
Height SDs <1.2 SD	Midparental height (SD)	0.01	0.00-0.11
	SGA	73.2	3.7-1432
	Gestational age at O_2 therapy withdrawal (wk)	1.30	1.02-1.66
Low BMI	Mother's BMI (kg/m^2)	0.86	0.74-0.99
Adrenal androgens in the highest quartile	SGA	3.33	1.03-10.7

OR, odds ratio; CI, confidence interval; SDs, standard deviation score; SGA, small for gestational age; O_2, oxygen; BMI, body mass index.

DISCUSSION

1. Methodological aspects

We defined the study population according to birth weight as this can be measured more reliably than GA. This approach, however, carries risks of bias in that more mature SGA infants with less probability to neonatal lung disease are also included (reviewed by Stick 2000). On the other hand, some factors associated with foetal growth impairment may also affect lung growth (hypoxia, placental insufficiency, antenatal corticosteroids and cigarette smoke exposure).

The small sample sizes, especially in the sBPD group, weaken the power of analyses and increase the risk of type II error. It is possible that the most seriously impaired VLBW children with the greatest risk of future health problems did not participate. However, the birth weights and GAs of the children who refused did not differ from those of the participants.

A selection bias is also possible in the term control group, since parents of children with some kind of respiratory problems might have been more eager to participate. In studies III-V no current respiratory data were available on the non-participants. However, if present, this bias would probably reduce the likelihood of significant differences between the VLBW and term groups in respiratory health parameters.

2. Frequency and risk factors in BPD

The frequency of BPD at 28 days' age in our material was higher compared to the situation in the 1970s, but comparable to that in the late 1980s (Parker et al. 1992). Our sBPD frequency cannot as such be compared to previous results, because we also included radiographic findings in our diagnostic criteria. This approach seemed reasonable in that the need for O_2 therapy may be due to other reasons than BPD. Furthermore, O_2 saturation thresholds for initiating or discontinuing this therapy may vary substantially between centres (Ellsbury et al. 2002). Since the initiation of our study, radiologic BPD findings at 36 weeks' corrected GA have been reported to be good predictors of wheezing symptoms

up to 6 months of age (Thomas et al. 2003), the use of inhaled medications during the first 2 years of life and asthma up to 5 years of age (Palta et al. 1998).

Our study population dates from the first years of surfactant therapy, applied at that time mainly as a rescue therapy in VLBW cases with symptomatic RDS. Approximately 30 % of our VLBW infants (half of the BPD cases) received surfactant. In fact, surfactant therapy seemed to enhance early recovery from BPD. This emphasises the importance of risk factors other than RDS in the pathogenesis of BPD in the surfactant era. Traditional risk factors for BPD were found here as elsewhere, including male sex (Palta 1991, Darlow and Horwood 1992), low GA, low birth weight, duration of ventilator therapy and hyperoxia.

As suggested earlier (Palta et al. 1991), our SGA cases seemed to have less risk of BPD at 28 days' postnatal age. However, they evinced a tendency to late recovery from BPD. An increased risk of BPD among premature SGA infants has also been reported elsewhere (Egreteau et al. 2001, Regev et al. 2003). This risk has been attributed to significant oxidative stress associated with intrauterine growth retardation (Regev et al. 2003). The lungs of the smallest infants may be more prone to injury by mechanical ventilation than the lungs of infants with better nutritional status at birth. Furthermore, SGA infants have less chronologic time ex utero to recover from BPD than non-SGA infants of the same weight. Supporting previous data (Schiff et al. 1993), preeclampsia, a known risk factor for intrauterine growth retardation, was also associated with sBPD in our material.

Less early weight loss was found among our BPD infants who did not recover before 36 weeks' corrected GA compared to those who did. Urine output and fluid losses due to evaporation were not evaluated here. The risk of PDA may be increased in cases with excessive early fluid administration (Bell 1980), and also indomethacin treatment for PDA may lead to urine retention and weight gain. This finding emphasises the importance of early fluid therapy and strict fluid balance evaluation in the management of VLBW infants (reviewed by Tammela 1995).

Both BPD at 28 days and a late recovery from BPD had an association with the number of PRC infusions after the 1st week of life. The smallest infants with the greatest risk of BPD probably suffer more blood losses due to sampling. On the other hand, ferrous iron in PRCs may cause a burst of free radicals, known risk factors for lung injury (Hirano et al. 2001). An association between frequent blood cell transfusions during the 1st week of life and BPD development has also been suggested elsewhere (Silvers et al. 1998), while others have found no relation between PCR-induced oxidative injury and the development of BPD (Cooke et al. 1997).

3. Follow-up of respiratory health and pulmonary function

At 2-8 years of age, the BPD and no-BPD children did not differ from each other with respect to the number of respiratory infections, current cough and wheezing, use of inhaled medications or hospitalisation in the previous year. However, the BPD cases had received more antibiotics for respiratory infections than VLBW children without BPD. In keeping with previous results from the pre-surfactant era (Kitchen et al. 1992b, Elder et al. 1996, McLeod et al. 1996, Gross et al. 1998, Anand et al. 2003), respiratory symptoms were common in our 7-year-old VLBW children. A discrepancy between symptom status and use of inhaled medications was found among the no-BPD cases. Awareness of the child's neonatal pulmonary problems and BPD diagnosis may affect the parents' and doctors' attitudes so that antibiotics and inhaled medications are prescribed more easily to BPD children, and the respiratory symptoms of no-BPD children might be ignored. Another survey has detected an increasing respiratory symptom rate in VLBW children without BPD since the introduction of surfactant therapy (Palta et al. 2001).

Our BPD children did not differ from the no-BPD group in flow-volume spirometry, as previously suggested (Northway et al. 1990). Supporting earlier results (Pelkonen et al. 1997, Gross et al. 1998), children with sBPD had lower expiratory flow rates than the no-BPD group. However, duration of O_2 therapy as a continuous variable emerged as a better predictor of future respiratory medications and FEV_1 than a BPD diagnosis at 28 days' postnatal age.

BR was increased in all our groups compared to previous reports. Our metacholine challenge method might have involved too large doses of metacholine, given the young age of the participants (Le Souëf 1992). In VLBW children, a reduction in airway caliber might explain the increased risk of BR. A single estimate of BR may not be an accurate index of the overall tendency to bronchial hyperresponsiveness (Burrows et al. 1995).

Hyperinflation, defined as a high RV/TLC ratio, was detected in half of our BPD cases. BPD children from the pre-surfactant era have been reported to run a higher risk of hyperinflation compared to VLBW controls without BPD (Jacob et al. 1998). Low birth weight, not BPD, emerged as the best predictor of hyperinflation. Lungs of very premature neonates are especially prone to injury by exposure to the environment and therapy in intensive care (Galdès-Sebaldt et al. 1989). Lung injury during very early stages of lung development, alveolar underdevelopment, abnormal lung growth and obstructive airway disease may be background factors for this finding (reviewed by Eber and Zach 2001).

Lower DLCO and DLCO/VA were found in both VLBW groups than in term controls, indicating a long-lasting impact of premature birth on gas exchange in the lung (Hakulinen et al. 1996).

The lung function abnormalities detected in our study did not correlate with respiratory symptoms. Parental smoking did not emerge as a predictor of

respiratory symptoms, nor did it, as some suggest (Lewis and Britton 1998), explain the association found between SES and current respiratory symptoms. Our finding of a protective effect of increasing sibling number against respiratory symptoms is in accordance with another study on term children (Ponsonby et al. 1998). Conversely, Elder and associates (1996) found that having siblings predicted recurrent wheeze at 12 months among prematurely born infants.

4. Impact on family

In accord with previous results (Cronin et al. 1995), the parents of our VLBW children reported their child's health to have more impact on the family compared to the parents of term controls. Another study (Lee et al. 1991) found no such association. Independent of SES, our VLBW families received more financial support from society than the families of term controls.

The comparison of our study with others is restricted by different methods of impact of family evaluation. So far, no standardised and validated questionnaire has been developed for assessment of the quality of life in BPD children. In our study, good consistency was found between the impact on family questions, but only preliminary conclusions can be drawn. The need for extensive evaluation of the quality of life in these families is nonetheless obvious.

5. Cardiovascular findings

It has been suggested that infants with BPD run an increased risk of systemic hypertension, resolving within 1 year of age (Abman et al. 1984, Alagappan and Malloy 1998). In the present material, the no-BPD cases had higher diastolic blood pressure compared to the BPD group. This may be explained by their tendencies to higher DHEAS levels (Schunkert et al. 1999) and taller statures, but not their SGA status, as previously suggested (reviewed by Barker 1997). Nonetheless, no conclusions regarding clinically significant hypertension can be drawn without repetitive and/or ambulatory measurements.

In the pre-surfactant era, 5-8-year-old children with severe BPD have evinced ECG signs of right ventricular hypertrophy, increased right ventricular end-diastolic volume and increased right ventricular wall thickness in echocardiography (Smyth et al. 1981) and abnormalities of the pulmonary vascular bed in cardiac catheterisation (Berman 1982). No clinically significant echocardiographic abnormalities or signs of elevated pulmonary pressure were found in our 7-year-old VLBW children. However, only seven of our VLBW cases had had cystic radiographic findings neonatally, and none had received O_2 supplementation at home. The detected asymptomatic PDA, mild aortic valve

regurgitation and the sinus bradycardia cases were probably unrelated to the peri- and neonatal characteristics of the children.

In a recent study, Mieskonen and associates (2003) found no echocardiographic signs of hypertrophic cardiomyopathy or elevated pulmonary pressure in 7-9-year-old VLBW children with or without postnatal dexamethasone treatment. In our VLBW population, prenatal corticosteroid therapy seemed to reduce the risk of having LVPWd in the lowest quartile. However, no clinically significant long-term cardiovascular effects of prenatal or postnatal corticosteroid treatment were detected.

6. Growth and adrenarche

Despite antenatal steroids and surfactant, VLBW children still run an increased risk of short stature at school age compared to term children. In our study, VLBW children with and without BPD did not differ with respect to height SDs or BMI, but BPD children had lower BMI and MUAC compared to term controls. There are several confounding factors which hamper precise evaluation of the effect of BPD on growth (Vrlenich et al. 1995). According to our findings, the duration of O_2 therapy, a marker of neonatal pulmonary morbidity, was a significant predictor of short stature at 7 years. Children with prolonged postnatal O_2 therapy may later manifest growth impairment due to frequent infections, respiratory symptoms and corticosteroid medications. The impact of nutrition was not specifically evaluated here but is without doubt an important aspect in the growth assessment of VLBW children.

Parallel to previous data, our VLBW children born SGA did not differ from the non-SGA cases in growth parameters at 7 years (Gutbrod et al. 2000). One reason for this might be their higher adrenal androgen levels, which may have resulted in faster catch-up growth (Pere et al. 1995), and possibly also faster skeletal maturation.

In keeping with previous results on term children (Luo et al. 1998, Parsons et al. 2001), parental characteristics such as midparental height and mother's BMI predicted short stature and BMI in our VLBW cases at 7 years of age.

Intrauterine programming of adult health has received abundant attention (reviewed by Barker 1997). Previously, term-born children born SGA have been suggested to run an increased risk of premature pubarche, which, for one, may contribute to a future risk of dyslipidaemia, hyperinsulinaemia (Ibàñez et al. 1998b) or ovarian hyperandrogenism (Ibàñez et al. 1998a). According to our results, VLBW children may have more florid adrenarche than term-born children, and especially VLBW survivors born SGA carry this risk. The long-term implications of this finding, for example impact in respect of final height and future metabolic and cardiovascular health, remain to be determined.

CONCLUSIONS

1. Among VLBW infants born in the surfactant era, 31.7 % of the survivors need O_2 supplementation and yield radiological findings consistent with BPD at 28 days' postnatal age, and 13.0 % meet the same criteria at 36 weeks' corrected GA. Factors other than RDS, for example small birth weight, early weight gain and possibly intrauterine growth retardation, seem to emerge as important predictors of BPD.

2. Compared to term controls, VLBW children born in the surfactant era, regardless of BPD, suffer more respiratory symptoms, need inhaled medications, hospitalisations and regular hospital-based follow-up in the first years of life. A need for repeated antibiotic courses, physiotherapy and occupational therapy is more common in BPD children compared to VLBW children without BPD. VLBW and BPD have an impact on the family's everyday life far beyond the neonatal period and also place increasing demands on society.

3. Despite antenatal steroids and surfactant, approximately a third of VLBW infants born in the surfactant era suffer respiratory symptoms at 7 years of age. The lung function of VLBW children with and without BPD is poorer in comparison with term controls. Children who do not recover from BPD by 36 weeks' corrected GA appear to have even lower expiratory flow rates and airway conductance than no-BPD cases. However, our results suggest that birth weight and the duration of neonatal O_2 therapy, together with later environmental conditions, predict future lung function abnormalities better than a dichotomous BPD diagnosis at 28 days' age. Careful respiratory follow-up of all VLBW children is evidently warranted, regardless of the severity of neonatal pulmonary problems.

4. VLBW children with and without BPD weaned from O_2 supplementation by 1-2 months after term would not appear to evince indirect signs of clinically significant pulmonary hypertension or hypertrophy of the cardiac ventricle walls at early school age. Whether the risk of other cardiovascular findings such as late PDA in VLBW infants would warrant echocardiographic follow-up remains to be determined.

5. VLBW children, regardless of BPD, are shorter at early school age compared to term-born controls. Interventions are needed to improve growth and nutritional status among VLBW children.

6. Our results suggest that VLBW children tend to have higher adrenal androgen levels at 7 years than do term children. The presence of BPD does not increase this risk, but VLBW cases born SGA seem to have higher levels than non-SGA children. The finding of a florid adrenarche in these patient groups would imply a possible risk of short final height and future metabolic and cardiovascular problems. If the results are confirmed in further studies, interventions such as early diet counselling may be justified.

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ORIGINAL PUBLICATIONS