The repercussions of reduced energy and protein intake during the early neonatal period of very-low-birth-weight infants on their lung function during childhood

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Abstract

Background Prematurity and bronchopulmonary dysplasia can modify lung function in children and adults. Postnatal nutrition and rapid growth catch-up may influence the long-term development of lung function. Methods This prospective observational study was based on a cohort of 334 very-low-birth-weight (VLBW) neonates, born between 1 January 2008 and 12 December 2015. Patients with severe neurological damage, death or incomplete data record were excluded. When these infants reached a mean age of 7.7 years, a spirometry evaluation was performed, to determine FEV1, FEF25-75%, FVC and the FEV1/FVC ratio. The relation between these parameters and nutritional intake in the early neonatal period was determined by regression analysis. Results In total, 40 spirometry tests were performed. The results obtained, after adjusting for age and sex by Z-scores for the spirometry variables, showed that the schoolchildren who had been VLBW recorded significantly lower spirometry results (FVC, FEV1, FEF25-75%) than the reference values. Furthermore, there was a significant association between the FEV1/FVC ratio and the intake of macronutrients and energy in the first week of life. It is hypothesised that increasing energy intake and achieving a higher protein/energy ratio in the first week of life would improve the FEV1/FVC ratio by the time these VLBW infants reach school age. Conclusions Active nutritional management in the early neonatal period is associated with improved lung function, as reflected by the spirometry findings obtained.

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Short title: Nutrition and lung function.

Abbreviations: BPD - bronchopulmonary dysplasia; CRIB - clinical risk index for babies; EN – enteral nutrition; $FEF_{25\text{-}75\%}$: mean expiratory flow; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IUGR - intrauterine growth restriction; NICU - neonatal intensive care unit; PN – parenteral nutrition; VLBW - very low birth weight

ABSTRACT

Background

Prematurity and bronchopulmonary dysplasia can modify lung function in children and adults. Postnatal nutrition and rapid growth catch-up may influence the long-term development of lung function.

Methods

This prospective observational study was based on a cohort of 334 very-low-birth-weight (VLBW) neonates, born between 1 January 2008 and 12 December 2015. Patients with severe neurological damage, death or incomplete data record were excluded. When these infants reached a mean age of 7.7 years, a spirometry evaluation was performed, to determine FEV_1, $FEF_{25-75\%}$, FVC and the FEV_1/FVC ratio. The relation between these parameters and nutritional intake in the early neonatal period was determined by regression analysis.

Results

In total, 40 spirometry tests were performed. The results obtained, after adjusting for age and sex by Z-scores for the spirometry variables, showed that the schoolchildren who had been VLBW recorded significantly lower spirometry results (FVC, FEV_1, $FEF_{25-75\%}$) than the reference values. Furthermore, there was a significant association between the FEV_1/FVC ratio and the intake of macronutrients and energy in the first week of life. It is hypothesised that increasing energy intake and achieving a higher protein/energy ratio in the first week of life would improve the FEV_1/FVC ratio by the time these VLBW infants reach school age.

Conclusions

Active nutritional management in the early neonatal period is associated with improved lung function, as reflected by the spirometry findings obtained.

Key words. Infant; Premature; Bronchopulmonary dysplasia; Lung function; Nutrition.

INTRODUCTION

Preterm neonates constitute approximately 10% of all deliveries, and approximately 12 million are born annually [1]. In recent years, the rate of preterm births has increased in developed countries, and this fact, together with improvements in perinatal care, has reduced mortality but at the same time is associated with increased morbidity during childhood and adulthood [2]. Respiratory pathologies derived from prematurity, such as bronchopulmonary dysplasia (BPD), are frequent in premature newborns and may subsequently affect the lung function of children and adults [3, 4].

Strategies for protecting the lungs of preterm infants are limited and mainly involve reducing the prevalence and intensity of BPD lesions. In this respect, studies have reported that the prevalence of BPD may be reduced by avoiding invasive ventilation and oxygen therapy and/or improving early nutritional intake, observing that BPD has a multifactorial aetiology that alters the normal development of the immature lung [5-7]. Compared with their full-term counterparts, preterm infants have fewer energy reserves. In consequence, the existence of antenatal and/or postnatal malnutrition can aggravate any lung damage resulting from ventilatory therapy during the neonatal period [8]. Infants with BPD have up to 25% greater energy requirements than full-term infants, in part due to the greater respiratory effort needed [9]. When newborns suffer energy restriction, this is associated with more severe forms of BPD in later infancy [7, 10] and these repercussions of early macronutrient intake on lung function in childhood or even adulthood are still insufficiently understood. Although the clinical manifestations of neonatal lung disease tend to improve, with the optimisation of treatment and with growth, significant decreases in lung function may persist among adolescents [4, 11]. Furthermore, growth and nutritional status may be associated with changes in FEV_1 during childhood, suggesting that appropriate nutritional intervention at an early stage may enhance lung function both in children and in adults [12].

In the present study, we consider the nutritional intake of very-low-birth-weight (VLBW) newborns during the early neonatal period and its association with the spirometry parameters of lung function when these

same infants are of school age.

SUBJECTS AND METHODS

This longitudinal prospective observational study was carried out of a cohort of children born at the San Cecilio Clinical Hospital (Granada, Spain) between 1 January 2008 and 12 December 2015. The study protocol was approved by the Provincial Ethics Committee, and all applicable rules and regulations on confidentiality and data protection were respected.

Inclusion and exclusion criteria. All newborns weighing <1500 g admitted to the hospital's neonatal intensive care unit during the study period were included in our analysis. Subsequently, each child was followed up in pulmonology, neonatology and neurology consultations. Infants who died in the first 28 days of life and those transferred to other hospitals were excluded from the analysis, as in these cases it was not possible to establish the degree of bronchopulmonary dysplasia (BPD). Those who presented severe neurological alterations were also excluded from the study, as it was assumed that this would make it impossible to perform the spirometry test. Also excluded were newborns for whom data were not available on total nutritional intake during the first week of life. The flow diagram in Figure 1 illustrates the process applied for patient recruitment and inclusion.

Anthropometry. Table 1 shows the anthropometric variables and z-scores obtained at birth and during the first week of life and in childhood during the spirometry study. Fenton tables were used to calculate the z-scores [13]. Intrauterine growth restriction is defined as inadequate weight gain, i.e. weight below the 10th percentile for gestational age [14].

*Nutritional management.*In the Neonatal Unit, the nutritional strategy and the liquid intake supplied were in accordance with the Unit's standard protocol and with the recommendations of the Nutrition and Metabolism Group of the Spanish Neonatology Society [15].

For these infants, the normal procedure during the first days of life is to complement enteral nutrition (EN) with parenteral nutrition (PN) when complete EN cannot be established. The daily requirements of liquids, proteins and lipids are calculated daily. At our hospital, breast milk composition is determined according to the Standardised Reporting of Neonatal Nutrition and Growth checklist, and formula composition is assessed according to commercial notifications [16]. In all cases, the aim is that during the first week of life the minimum nutritional requirements to ensure growth should be met, according to standard recommendations [1, 17, 18]. For the purposes of the present study, the inputs of liquids, energy, proteins, carbohydrates and lipids during the first week of life were recorded.

*Morbidity***.** In accordance with the thresholds proposed by NIHCD [19] and by Jobe and Bancalari [20], BPD is defined as a need for supplemental oxygen >21% at 28 days of life and/or a need for supplemental oxygen >21% or for positive airway pressure at 36 weeks corrected gestational age.

The clinical risk index for babies (CRIB II score) for each newborn was performed using the following variables: sex, gestational age (in weeks), birth weight (in grams) and excess base. The total CRIB II score (range 0 to 27) was calculated [21].

Lung function

Spirometry is a non-invasive test that evaluates lung function by measuring the amount of air mobilised in the lungs during maximum inspiration and expiration, in both normal and forced expiration. In our tests, forced spirometry was performed with a Jaeger Type MSC Power-Unit Flow Pneumotachograph, of approximately 230 V, 50/60 Hz, 0.1 A, IP 20.

In the spirometry tests performed, disposable mouthpieces were used, with forceps to cover the nostrils and thus prevent the exhaled flow from escaping. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and mean expiratory flow ($FEF_{25\text{-}75\%}$) were measured and the FEV_1/ FVC ratio was determined. FEV_1 is the volume of air expelled during the first second of forced expiration. Although it is expressed as volume (L), since it is related to time, in practice FEV_1 is a measure of flow. The FEV_1 result is

considered normal if it is >80% of the theoretical value. This is the most important parameter considered to assess whether there is obstructive airway pathology, and in normal conditions it must be >75%. FVC is the maximum volume of expired air, with the maximum possible effort, starting from maximum inspiration. It is expressed as a volume (L) and is considered normal when it is >80% of the theoretical value. The maximum mid-expiratory flow velocity ($FEF_{25-75\%}$) is the airflow velocity during the middle half of the FVC test (i.e. 25-75% of the FVC) and should be [?]65% of the theoretical value.

The parameters of the lung function tests present great interindividual variability and depend on the patients' anthropometric characteristics (sex, age, height, weight and race). Interpretation of the spirometry results is based on comparing the values produced by the patient with those that would theoretically correspond to a healthy individual with the same anthropometric characteristics. This theoretical value or reference value is obtained from a school-age prediction equation [3].

The spirometry results are expressed as the z-score ($z=\frac{x-\mu}{\sigma}$, where x is the value obtained, μ is the population mean for the anthropometric characteristics of the subject and σ is the standard deviation) [4].

Statistical analysis. The descriptive data were summarised using medians (p50) and the interquartile range (p25 - p75) for the continuous values, and frequency distribution for the categorical ones. Univariate comparisons of the continuous variables were performed using the Mann-Whitney test, and of the categorical ones by the chi-square test. The association between nutritional parameters in the first week of life and spirometry variables at school age were estimated by linear regression analysis.

RESULTS

During the study period, 334 VLBW infants were admitted to our Neonatal Intensive Care Unit. Of these, 44 died and 58 had severe neurological disorders and therefore were excluded from the study. Of those remaining, and initially considered for inclusion, nutritional data corresponding to the first week of life were available for 105 school-age children, whose parents were telephoned, inviting them to participate in the study. However, 55 could not be located and another ten did not attend the first appointment. Finally, 40 spirometry tests were performed for our analysis. Table 1 shows the characteristics of the newborns included in the study. In summary, 42.5% had mild BPD, 35% had moderate BPD, 17.5% had severe BPD and 5% did not present BPD. The spirometry test was performed when the children had an average age of 7.7 (6.9 - 9.6) years.

After adjusting for age and sex, using the Z-score for spirometry variables, the results obtained showed that these preterm newborns presented significantly lower spirometry results for FVC, FEV_1 and $FEF_{25-75\%}$ in relation to the reference values (Table 2). The poorest parameter in this respect was $FEF_{25-75\%}$ (Z-score -0.43). The FEV_1/FVC ratio was significantly above the reference values, due mainly to a more marked decrease in FVC than in FEV_1.

The results also showed that at school age there was a decrease in the weight gain curve, with a mean weight Z-score of -0.61 (-1.73 to 0.91), in contrast to the birth weight Z-score of -0.30 (-1.18 to 0.38).

Table 3 details the infants' macronutrient intake during the first week of life, and Table 4 reveals a significant association between the FEV_1/FVC ratio and the macronutrient and energy intakes during the same period. Our analysis shows that an increased energy intake and a higher protein/energy ratio both improve the FEV_1/ FVC ratio at school age.

DISCUSSION

Achieving an adequate energy intake and protein/energy ratio in the first week of life improves the FEV_1 spirometry results of children who were VLBW infants. Although in our sample FEV_1, FVC and $FEF_{25-75\%}$ were all significantly below the reference values, the parameter that was most significantly reduced in these preterm infants was that of mean flow rate (FEF25-75%), which was approximately 19% below the reference values, and thus an indicator of fine airway obstruction. It is important to note that abnormal lung function in childhood is a precursor of chronic obstructive pulmonary disease in the adult.

The question arises of whether respiratory dysfunction after preterm delivery is: 1) due to the disruption of normal lung development after premature exposure of an immature lung to unfavourable extrauterine conditions; 2) related to factors that contribute to or foster preterm birth; 3) subsequent to lung injury caused during resuscitation, subsequent ventilatory support or the deficient intake of nutrients at critical moments of development. Research has provided clear evidence of altered lung development after preterm delivery per se, in which respiratory morbidity and reduced lung function are both much more severe in preterm infants with prior BPD [22].

Therefore, extreme prematurity and BPD may be risk factors for the future development of chronic obstructive pulmonary disease. In this respect, Halvorsen et al. [11] observed a substantial decrease in FEV_1, an increase in bronchial hyperresponsiveness and a more pronounced decrease in lung function among adolescents who had been preterm, in comparison with controls. Similarly, Anand et al. [23] found evidence of obstruction in the flow of the small and medium airways, which paralleled our own findings of reductions of nearly 20% in $FEF_{25\text{-}75\%}$. Fawke et al. [24] warned of an increased risk of respiratory morbidity, airway obstruction and bronchial hyperresponsiveness among premature infants, and for such cases proposed strategies to prevent or reduce the severity of BPD, such as reducing the duration of invasive ventilation, favouring non-invasive ventilation strategies or applying postnatal surfactant therapy or antenatal steroids. In contrast, Doyle et al. [25] found that decreased invasive ventilation in a cohort of VLBW infants was not associated with an improvement in lung function at school age.

Hirata et al. [26] evaluated the spirometry variables of lung function in preterm infants now of school age and observed that lung function did not improve after the age of 8-12 years; in comparison with the general population, lung function tends to be poorer among those with a history of prematurity. Furthermore, a history of severe BPD is associated with greater deterioration in lung function at school age. In an earlier study [7], our group observed that energy restriction during the early postnatal period is directly associated with the severity of BPD. Current data confirm the association between higher protein and energy intake in the first week of life and the proportion of FVC that is expelled during the first second of forced expiration. After birth, nutrition plays a critical role in the respiratory development of preterm infants, especially those who are VLBW, whose saccular-alveolar stage of lung maturation occurs mostly or entirely in post-natal life. Pulmonary alveolation continues until at least the age of two, and therefore malnutrition at very early stages of postnatal life could plausibly have repercussions on future lung function [5].

VLBW infants may suffer malnutrition for several reasons, including the interruption of transplacental nutrition following delivery, or a delay in the start of enteral nutrition, due to poor clinical status and/or haemodynamic and respiratory instability, generally related to the infant's lower gestational age. It is normally recommended that parenteral nutrition should not be initiated too quickly for VLBW infants, whose energy reserves are limited, in order to avoid energy catabolism [9, 27]. Finally, it has been reported that preterm infants with BPD tend to grow more slowly than their peers, and that this delay persists beyond the period of hospital stay [9, 28].

The main limitation of our study is the relatively high proportion of eligible participants who did not perform the spirometry test, an absence that signals a potential selection bias. Most of those who were recruited were BPD patients who were already under follow-up in paediatric pulmonology clinics, while many of the children who were healthy and had been discharged from the paediatric pneumology clinic several years previously did not accept the invitation to participate.

In conclusion, we find that early postnatal nutrition and subsequent lung function of the child are related. Active nutritional management in the early neonatal period can improve the lung function in the child and possibly in the adult.

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Contributors' statement page

JU designed the data analysis and interpretation , wrote the article and critically reviewed it for important intellectual content. He approves the version to be published and agrees to be responsible for all aspects of the work to ensure that questions related to the accuracy or completeness of any part of the work are properly investigated and resolved. Y.G.J., A.C.M. and E.B.J. made substantial contributions to the conception, design and writing of the article and critically reviewed it for important intellectual content. They approve the submission of this manuscript for publication. They agree to be responsible for all aspects of the work to ensure that questions related to the accuracy or completeness of any part of the work are properly investigated and resolved.

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Figure 1. *Flow diagram for the VLBW newborns included in the study (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097).*

Table 1. Pregnancy and neonatal characteristics.

Characteristics		
Maternal	**Maternal**	
IVF	IVF	8 (20.0)
PIH	PIH	0 (0)
Chorioamnionitis	Chorioamnionitis	7 (17.5)
Antibiotics	Antibiotics	18 (45.0)
Glucocorticoids	Glucocorticoids	36 (90.0)
PPROM	PPROM	10 (25.0)
Gestation (w)*	Gestation (w)*	27 (26, 29)
Gestation [?] 27 w	Gestation [?] 27 w	23 (57.5)
Twin birth	Twin birth	15 (37.5)
Caesarean section	Caesarean section	33 (82.5)
Neonatal	**Neonatal**	
Birth weight (g) *	Birth weight (g) *	996 (844, 1096)
Birth weight (z-score) *	Birth weight (z-score) *	-0.30 (-1.18, 0.38)
Weight 7 days (z-score) *	Weight 7 days (z-score) *	-0.94 (-1.57, -0.36)
Days stay at UCIN *	Days stay at UCIN *	42.5 (31, 57)
CRIB score	CRIB score	2 (1, 4)
Male gender	Male gender	21 (52.5)
Apgar <7 at 5 minutes	Apgar <7 at 5 minutes	18 (45.0)
IUGR	IUGR	8 (20.0)
Human milk feeding * §	Human milk feeding * §	23 (57.5)
Mechanic ventilation (days)*	Mechanic ventilation (days)*	5 (1, 10)
CPAP (days)*	CPAP (days)*	11 (3, 17)
BPD	BPD	
No	No	2 (5)
Mild	Mild	17 (42.5)
Moderate	Moderate	14 (35)
Severe	Severe	7 (17.5)
Childhood	**Childhood**	
Age (y) *	Age (y) *	7.7 (6.9 – 9.6)
Weight (Kg) *	Weight (Kg) *	22.8 (18.4, 31.5)
Weight (Kg) (z-score) *	Weight (Kg) (z-score) *	-0.61 (-1.73, 0.91)
Length (cm) *	Length (cm) *	124 (116, 133)
Length (cm) (z-score) *	Length (cm) (z-score) *	-1.0 (-1.65, 0.29)
Body mass index (Kg/m^2) *	Body mass index (Kg/m^2) *	15.4 (13.5, 18.7)

Counts and percentages. *Median (IQR). §Supplemented by less than 25% of the weekly volume with premature formula milk

CRIB: Clinical risk index for babies, IUGR: Intrauterine growth restriction, IVF: In vitro fertilisation, PIH: Pregnancy induced hypertension, PPROM: Preterm pre-labour rupture of membranes, BPD: Bronchopulmonary dysplasia.

Table 2. Mean values and interquartile range of the spirometric variables.

	Reference values	**Measured values**	**Z score**	**P**
FEV_1 (L)	1.32 (0.89, 1.77)	1.25 (0.93, 1.82)	-0.08 (-0.21, 0.02)	0.014
FVC (L)	1.60 (1.17, 2.01)	1.49 (1.12, 2.00)	-0.16 (-0.32, 0.04)	0.001

	Reference values	Measured values	Z score	P
FEF $_{25\text{-}75\%}$ (L/s)	1.62 (1.27, 2.34)	1.29 (0.77, 2.00)	-0.43 (-0.90, -0.04)	0.001
FEV_1/FVC	0.81 (0.79, 0.84)	1.02 (0.95, 1.13)	1.69 (0.94, 2.14)	0.001

$FEF_{25\text{-}75\%}$: Mean expiratory flow; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

Table 3. Median (p50) and interval interquartile (IQR) of liquids and nutritional supports (enteral and parenteral) in the first week of life (w) in VLBW newborns with BPD.

Characteristics *	**Week-1 postnatal**	
Liquids (mL/Kg/w)	Liquids (mL/Kg/w)	914 (757, 1100)
Energy (Kcal/Kg/w)	Energy (Kcal/Kg/w)	444 (365, 534)
Carbohydrates (g/Kg/w)	Carbohydrates (g/Kg/w)	70.3 (63.3, 84.6)
Proteins (g/Kg/w)	Proteins (g/Kg/w)	16.1 (10.5, 19.9)
Lipids (g/Kg/w)	Lipids (g/Kg/w)	10.9 (6.8, 14.3)
Protein/energy (g/100Kcal)	Protein/energy (g/100Kcal)	3.43 (2.71-3.82)

*Median (IQR).

Table 4. Regression analysis week-1 nutritional intake and infanthood spirometric variables.

Infanthood period	**Week 1 postnatal**	**b (SE)**	**p**	**Partial R^2**
FEV_1				
	Energy (kcal/kg/week)	0.001(0.001)	0.41	0.019
	Protein (g/kg/week)	0.008 (0.007)	0.24	0.039
	Carbohydrates (g/Kg/week)	0.001 (0.002)	0.60	0.008
	Lipids (g/Kg/w)	0.009 (0.01)	0.35	0.026
	Protein/energy (g/100Kcal)	0.067 (0.051)	0.19	0.048
FVC				
	Energy (kcal/kg/week)	0.001 (0.001)	0.35	0.004
	Protein (g/kg/week)	0.008 (0.008)	0.31	0.030
	Carbohydrates (g/Kg/week)	0.001 (0.003)	0.85	0.001
	Lipids (g/Kg/w)	0.011 (0.011)	0.31	0.030
	Protein/energy (g/100Kcal)	0.105 (0.157)	0.07	0.091
FEF $_{25\text{-}75\%}$				
	Energy (kcal/kg/week)	0.001 (0.001)	0.28	0.035
	Protein (g/kg/week)	0.017 (0.015)	0.27	0.036
	Carbohydrates (g/Kg/week)	0.005 (0.005)	0.39	0.022
	Lipids (g/Kg/w)	0.020 (0.022)	0.38	0.023
	Protein/energy (g/100Kcal)	0.073 (0.119)	0.54	0.011
FEV_1/FVC				
	Energy (kcal/kg/week)	0.004 (0.002)	0.01	0.160
	Protein (g/kg/week)	0.114 (0.028)	0.001	0.330
	Carbohydrates (g/Kg/week)	0.034 (0.011)	0.004	0.222
	Lipids (g/Kg/w)	-0.004 (0.049)	0.93	0.000
	Protein/energy (g/100Kcal)	0.668 (0.240)	0.009	0.186