Respiratory Medicine 136 (2018) 83–87

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Pulmonary function in former very low birth weight preterm infants in the first year of life

Daniela de Melo Miranda Gonçalves[a], Gustavo Falbo Wandalsen[b], Ana Sílvia Scavacini[a], Fernanda Cordoba Lanza[b], Ana Lucia Goulart[a], Dirceu Solé[b], Amélia Miyashiro Nunes dos Santos[a,*]

[a] Department of Pediatrics, Neonatal Division of Medicine, Federal University of São Paulo, São Paulo, SP, Brazil
[b] Department of Pediatrics, Division of Allergy, Clinical Immunology and Rheumatology - Federal University of São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Keywords:
Child
Infant
Premature
Pulmonary function
Plethysmography
Risk factors

ABSTRACT

Background: Pulmonary function in former preterm infants may be compromised during childhood.
Objectives: To assess pulmonary function in very-low-birth-weight preterm infants at 6–12 months of corrected age and analyze the factors associated with abnormal pulmonary function.
Methods: Cross-sectional study with preterm infants at 6–12 months of corrected age with birth weight < 1500 g. Children with malformations or affected by neuromuscular and respiratory diseases were excluded. Forced expiratory flows were assessed using the chest compression technique, and volumes were measured by total body plethysmography. Pulmonary function parameters in preterm infants were compared to a control group of same-aged children born at term.
Results: We studied 51 preterm and 37 infants born at term. Preterm infants had: gestational age at birth (30.0 ± 2.5 weeks), birth weight (1179 ± 247 g), 27.5% had bronchopulmonary dysplasia, and 45% received mechanical ventilation. Preterm infants had lower median z-scores in comparison to term infants for the following parameters ($p < 0.05$): FVC (−0.3 vs. 0.7), $FEV_{0.5}$ (−0.5 vs. 0.9), $FEV_{0.5}$/FVC (−0.6 vs. −0.5), FEF_{50} (−0.4 vs. 0.9), FEF_{75} (−0.3 vs. 0.8), FEF_{85} (−0.1 vs. 0.6) and FEF_{25-75} (−0.5 vs. 1.1). No term child had abnormal lung function, compared to 39.2% of preterm infants ($p = 0.001$). Factors associated with abnormal pulmonary function were lower gestational age at birth, small for gestational age, need for mechanical ventilation and presence of recurrent wheezing.
Conclusions: Preterms had a high prevalence of abnormal pulmonary function and lower pulmonary function in comparison to term infants. Prematurity, intrauterine growth restriction, respiratory support and recurrent wheezing were associated with abnormal pulmonary function.

1. Introduction

The pulmonary function of infants born prematurely may be compromised during childhood and adolescence, especially for extremely preterm infants, infants with intrauterine growth restriction or those who develop bronchopulmonary dysplasia or have been subjected to mechanical ventilation in the neonatal period [1–3]. As the pulmonary parenchyma grows, there may be a progressive improvement in parameters related to pulmonary volume due to alveolar multiplication. However, alterations in pulmonary flow may persist until adolescence or adulthood [4,5].

One study comparing very low birth weight preterm infants with and without a history of bronchopulmonary dysplasia at 9.5 years average age showed a significant difference between groups in z-score values for FEV_1 (1.27 vs. 0.40; $p = 0.008$), FVC (1.39 vs. 0.71; $p = 0.022$), and FEF_{50} (2.21 vs. 1.04; $p = 0.048$) [2].

Even with the advent of exogenous surfactant for treating respiratory distress syndrome, the impairment of pulmonary function in extremely preterm infants persists [6,7]. Hacking et al. [7] compared two cohorts of extremely preterm infants with gestational age at birth below 28 weeks at an age of 8 years old; one group was born between 1991 and 1992, the other between 1997 and 1998, finding similar results for both groups, including a significant reduction in the values of FEV_1 and FEF_{25-75} in extremely preterm children.

However, even preterm infants who had no serious respiratory diseases during the neonatal period may later develop impairments in

* Corresponding author. Rua Diogo de Faria, 764. CEP: 04037-002, São Paulo, SP, Brazil.
E-mail address: ameliamiyashiro@yahoo.com.br (A.M.N. dos Santos).

https://doi.org/10.1016/j.rmed.2018.02.004
Received 2 November 2017; Received in revised form 29 January 2018; Accepted 5 February 2018
Available online 08 February 2018
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their pulmonary function. Friedrich et al. [8] compared the pulmonary function of 62 healthy preterm infants who needed mechanical ventilation for at most 48 h with 27 term newborns during the first month of life, and observed that 31% of preterm infants had a pulmonary flow lower than the 50th percentile, 32% had a flow between the 25th and 75th percentiles, and 10% had a flow below the reference 5th percentile.

Within this context, the objective of this study was to assess pulmonary function in very low birth weight preterm children with corrected ages between 6 months and 1 year and analyze the factors associated with impairment of pulmonary function in these infants.

2. Methods

A cross-sectional study was conducted on infants with corrected ages between 6 months and 1 year, after approval by the Ethics Committee of the Federal University of São Paulo, SP, Brazil (CEP UNIFESP: 1864-08) and signature of a Declaration of Consent by the parents of all children included in the study.

The study included infants aged 6 months to 1 year of corrected age, born at gestational age < 37 weeks and birth weight < 1500 g and followed up at the institution's premature outpatient clinic. Infants with congenital malformations or affected by neuromuscular diseases were excluded from the study, as well as those with respiratory symptoms during the 15 days preceding the pulmonary function test.

The demographic and clinical background of all children included in the study were assessed by consulting their medical records; history of wheezing was assessed using the questionnaire developed by the International Study of Wheezing in Infants (EISL) [9].

Pulmonary function tests were performed after sedation with chloral hydrate (60–80 mg/kg); patients' heart rate and peripheral oxygen saturation were continuously monitored during the tests.

Pulmonary volumes were measured by total body plethysmography using a 90-L plethysmograph (Infant Pulmonary Lab, Collins-nSpire, USA). Measurements were performed according to existing recommendations [10], after daily calibration. In brief, functional residual capacity (FRC) was calculated using the variations in mouth pressure and plethysmograph pressure measured during spontaneous respiratory movements against the occluded airway. At least 3 technically acceptable sequences were obtained for each patient, each with 3 inspirations; the FRC was registered using the average values of the technically acceptable curves obtained.

Forced expiratory flows were obtained using the raised volume rapid thoracic compression technique with Infant Pulmonary Lab equipment, following international recommendations [11]. In short, flow-volume curves were obtained by compression of an inflatable jacket positioned around the thorax and abdomen. Positive pressure inflation of the lungs (30 cm H_2O) was done prior to compression. Thoracic and abdominal compression continued until the end of expiration (identified visually), or for 4 s at most. The thoracic and abdominal compression pressure was raised until no further increase was noted in flow and forced volume values (flow limitation). The best curve among those considered technically acceptable was chosen based on the sum of forced vital capacity (FVC) and forced expiratory flows between 25% and 75% of the FVC (FEF_{25-75}) [11]. The following parameters were registered: FVC, forced expiratory volume during the first half second ($FEV_{0.5}$), forced expiratory flow (FEF) at 50% of the FVC (FEF_{50}), FEF at 75% of the FVC (FEF_{75}), FEF at 85% of the FVC (FEF_{85}), and FEF_{25-75}.

Given that thoracic and abdominal compression continued until the residual volume (RV) was reached, the expiratory reserve volume (ERV) was calculated as the volume difference between the FRC and the volume at the end of thoracic compression. RV was calculated as the difference between FRC and ERV, and total lung capacity (TLC) was calculated as the sum of FVC and RV [12].

Pulmonary function parameters were registered as their z-scores or as the percentage of predicted values according to available reference values [12,13]. Values were considered altered when they were < 80% of predicted values, or when their z-score was < −2 [12,14]. Patients with z-scores < −2 for $FEV_{0.5}$, $FEV_{0.5}$/FVC or FEF were considered to have obstructive pulmonary disease, while patients with TLC < 80% the predicted value were considered to have restrictive pulmonary disease [12,14].

3. Data and statistical analysis

This study used a convenience sample of very low birth weight preterm infants monitored in the institution's preterm outpatient clinic whose parents accepted their participation in the study.

Preterm infants were compared to a control group of same-aged children born at term, without chronic or respiratory disease and having had at most one episode of wheezing prior to their inclusion in the study. Control infants were subjected to pulmonary function tests carried out by the same team, in the same laboratory and using the same methodology and equipment employed for the preterm infants included in this study. Pulmonary function was performed after approval of the Ethic Committee of the Institution and signature of the Informed Consent Form by the parents of all children included in the study (CEP 1345/09).

Numerical variables were initially analyzed using Kolmogorov-Smirnov test. Normal distributed variables were expressed as mean and standard deviation and compared by t-student tests. Numerical variables with non-normal distribution were expressed as median and minimum – maximum values an compared by Mann-Whitney tests. Categorical variables were compared with χ^2 tests or Fisher's exact tests. Linear regressions were used to analyze the factors associated with reduced percentages of predicted values or reduced z-score values for pulmonary function parameters. Statistical analyses were performed using the software *SPSS for Windows/v.17.0* (*IBM SPSS Statistics, Somers, NY, USA*), considering p-values < 0.05 as significant.

4. Results

We studied 51 preterm infants and 37 infants born at term for which adequate pulmonary function curves were obtained. At birth, the preterm infants included in the study had a gestational age of 30.0 ± 2.5 (25–34 weeks), weighed 1179 ± 247 (605–1495 g), measured 36.5 ± 2.5 (31–42 cm) and had 5 min Apgar scores of 9 (3–10); 18 of them (35.3%) were small for their gestational age. Thirty-eight (38, or 74.5%) of the preterm infants were delivered via caesarean section, and 24 (47.1%) were male. During the time spent in the neonatal ICU, 26 infants (51.0%) presented with respiratory distress syndrome, 1 (2.0%) with pneumonia, 13 (25.5%) had patent ductus arteriosus, 10 (19.6%) had early-onset sepsis, 10 (19.6%) had late-onset sepsis, 20 (39.2%) presented with peri-intraventricular hemorrhage, 9 (17.6%) had retinopathy of prematurity, 14 (27.5%) were oxygen dependent 28 days after birth, while 7 (13.7%) were oxygen dependent at a corrected age of 36 weeks, and 23 (45.1%) were subjected to mechanical ventilation for a median period of 5 days (range: 1–35 days). The median time of hospitalization in the neonatal unit was 55 days (range: 25–128 days).

After discharge from the neonatal unit, 34 preterms (66.7%) had at least one wheezing episode, 18 term infants (46.6%) had one wheezing episode. The number of wheezing episodes was higher in preterm infants [median 2 (0–4) vs. 0.0 (0–1), Mann-Whitney test p < 0.001]. Moreover, 10 (19.6%) preterm infants had recurrent wheezing, with three or more episodes, 18 (35.3%) presented with bronchiolitis, and 9 (17.6%) with pneumonia. While no infant born at term was hospitalized, 20 (39.2%) preterms needed hospitalization and the median number of hospitalizations varied between 1 and 5 for these infants.

Both groups (preterm and term infants) were similar in their familial history of asthma (33.3 vs. 43.2%, χ^2 test, p = 0.343), rhinitis (58.8 vs. 62.2%, χ^2 test, p = 0.752) and atopic dermatitis (15.7 vs. 13.5%, χ^2

Table 1
Parameters of lung function in former preterm and term children, in percentage of predicted or z-score, values expressed in median (minimum – maximum).

	n	Preterm	n	Term	p
TLC %	47	92.0 (71.0–145.0)	34	95.4 (75.7–118.3)	0.518
FRC %	47	105.0 (64.0–158.0)	35	104.0 (79.0–138.0)	0.718
FVC z-score	51	−0.3 (−2.8–2.9)	37	0.7 (−1.0–1.5)	< 0.001
$FEV_{0.5}$ z-score	51	−0.5 (−4.2–1.5)	37	0.9 (−0.8–1.7)	< 0.001
$VEF_{0.5}$/CVF z-score	51	−0.6 (−3.9–1.7)	37	0.4 (−1.1–2.0)	0.008
FEF_{50} z-score	51	−0.4 (−4.3–2.0)	37	0.9 (−0.6–2.4)	< 0.001
FEF_{75} z-score	51	−0.3 (−4.4–2.4)	37	0.8 (−1.5–2.0)	< 0.001
FEF_{85} z-score	51	−0.1 (−3.9–1.9)	37	0.6 (−1.4–2.4)	0.001
FEF_{25-75} z-score	51	−0.5 (−4.7–2.3)	37	1.1 (−0.9–2.3)	< 0.001

TLC: Total lung capacity, FRC: functional residual capacity; FVC: forced vital capacity, $FEV_{0,5}$: Forced expiratory volume in 0.5 s, FEF_{50}: forced expiratory flow at 50% of FVC, FEF_{75}: forced expiratory flow at 75% of FVC, FEF_{85}: forced expiratory flow at 85% of FVC, FEF_{25-75}: forced expiratory flow at 25–75% of FVC. p value: Mann-Whitney test.

test, p = 0.777), as well as in the presence of pets in the home (39.2 vs. 24.3%, χ^2 test, p = 0.142) and exposure to smoking at home (45.1% vs. 40,5%, χ^2 test, p = 0.670).

At the time of their inclusion in the study, preterm infants had a corrected age of 8.2 ± 1.9 months and similar chronological age to the term infants (10.9 ± 2.2 vs. 10.6 ± 3.8 months, *t*-test, p = 0.758), but lower weight (7.2 ± 1.2 vs. 8.4 ± 1.3 kg, *t*-test, p < 0.001) and size (67.8 ± 3.8 vs. 71,7 ± 5.3 cm, *t*-test, p < 0.001) than term infants.

The comparison of evaluated pulmonary function parameters of term and preterm infants, presented as percentages of expected values or z-scores, is shown in Table 1.

The proportions of preterm infants with parameters < 80% of predicted values were 8.5% for TLC and 6.4% for FRC. The percentage of preterm infants with z-scores < −2 for pulmonary function parameters were: 9.8% for FVC, 11.8% for $FEV_{0.5}$, 9.8% for FEF_{50}, 7.8% for FEF_{75}, 7.8% for FEF_{85} and 11.8% for FEF_{25-75}, corresponding to a total of 20 (39.2%) preterms with altered pulmonary function, of which 15 (29.4%) had obstructive disease, 4 (7.8%) had restrictive disease, and 1 (2.0%) had mixed respiratory disease. None of the infants born at term had pulmonary alterations, compared to 39.2% of preterms (Fisher exact test, p = 0.001).

Preterm infants with birth weight < 1000 g had lower median z-score (minimum-maximum) values for $FEV_{0.5}$/FVC [-1.2 (−2.1–0.7) vs. −0.4 (−3.9–1.7), Mann-Whitney test, p = 0.004] when compared to those with higher birth weight. Children who had recurrent wheezing had lower predicted FRC values [104.0% (64.0–158.0) vs. 112.0% (90.0–139.0), Mann-Whitney test, p = 0.024].

Preterm infants who developed bronchopulmonary dysplasia, compared with those without this diseases, had lower median z-scores (minimum-maximum) values of FEF_{50} [−1.0 (−2.8–0.5) vs. −0.3 (−4.3–2.0), Mann-Whitney test, p = 0.013)], FEF_{75} [−0.7 (−2.7–0.6) vs. −0.1 (−4.4–2.4), Mann-Whitney test, p = 0.029], FEF_{85} [−0.6 (−2.2 - 1.2) vs. 0.3 (−3.9–1.9), Mann-Whitney test, p = 0.025], FEF_{25-75} [−1.0 (−3.2–0.3) vs. −0.4 (−4.7–2.3), Mann-Whitney test, p = 0.011].

Preterm infants who used Continuous Positive Airway Pressure (CPAP) had lower median z-scores (minimum-maximum) for FEF05/FVC [-0.6 (−3.9–1.5) vs. −0.3 (−1.7–1.7), Mann-Whitney test, p = 0.039] FEF_{50} [−0.5 (−4.3–1.9) vs. −0.1 (−0.9–2.0), Mann-Whitney test, p = 0.025], FEF_{85} [−0.1 (−3.9–1.9) vs. 0.2 (−0.8–1.4), Mann-Whitney test, p = 0.031].

Infants submitted to mechanical ventilation while in the neonatal unit showed significantly lower median scores (Mann-Whitney test p < 0.05) of expiratory flow parameters, when compared to non-ventilated infants, compared to their opposite pairs (Fig. 1).

Children who were oxygen dependent at 36 weeks of corrected age had a higher frequency of alterations in pulmonary function (30.0% vs. 3.2%, Fisher exact test, p = 0.011). The prevalence of pulmonary alterations was also higher, but without statistical significance, in children who were oxygen dependent for 28 days after birth (42.1 vs. 20.0%, χ^2 test, p = 0.095) and in those who have undergone mechanical ventilation (68.4 vs. 46.7%, χ^2 test, p = 0.155).

The multiple linear regressions of gestational age at birth, small size for gestational age, oxygen dependence at 36 weeks of corrected age, use of mechanical ventilation and presence of recurrent wheezing on pulmonary function parameters showed associations of pulmonary parameters with gestational age at birth, small size for gestational age, neonatal mechanical ventilation and presence of recurrent wheezing (Table 2).

5. Discussion

This study showed that very low birth weight preterm infants aged 6–12 months of corrected age had a high prevalence of alterations in pulmonary function, predominantly due to obstructive process. Predicted values for pulmonary function parameters were significantly lower in preterm infants when compared to children born at term for FVC, $FEV_{0.5}$, $FEV_{0.5}$/FVC, FEF_{50}, FEF_{75}, FEF_{85} and FEF_{25-75}, no differences being found for TLC and FRC. This study also showed an association of altered pulmonary flows with lower gestational age at birth, small size for the infant's gestational age, neonatal mechanical ventilation and recurrent wheezing during the first year of life.

The high prevalence of altered pulmonary function in preterm infants found in this study has already been described by other researchers. A cohort study that compared 49 extremely preterm and 52 term children at age 11 showed that 78% of extremely preterm children had altered pulmonary function, with airway obstruction, hyper responsiveness and altered ventilation [15]. Factors such as the high incidence of respiratory diseases during the first year of life, with 67% of children experiencing at least one episode of wheezing, 20% having recurrent wheezing and 18% presenting with pneumonia, as well as complications during the neonatal period such as respiratory distress syndrome, bronchopulmonary dysplasia and the need for mechanical ventilation, must have contributed to increase the risk of pulmonary impairment in the children studied here [16].

Another research with 84 children and adolescents aged 6–14 born at a gestational age of 31.8 ± 2.4 weeks found a 43% prevalence of altered pulmonary function, with a predominance of altered pulmonary flows. The same study found the following frequencies of parameters < 80% the expected values: 8.3% for FVC, 22.6% for FEV_1; 16.7% for FEV_1/FVC ratio; and 32.4% for FEF_{25-75} < 70% of predicted value [5].

In our study, pulmonary flow parameters showed greater alteration in extremely preterm infants, those submitted to mechanical ventilation and those who developed bronchopulmonary dysplasia, similarly to what is described in the literature. One study has shown that very low birth weight preterm infants with a history of bronchopulmonary dysplasia evaluated at 50, 70 and 100 weeks after birth had lower values for tidal volume, respiratory minute volume, respiratory compliance and FRC, when compared to a control group without pulmonary disease [17].

The linear regression analysis has shown that the factors associated with impaired performance in pulmonary function tests were low gestational age, intrauterine growth restriction, use of mechanical ventilation and recurrent wheezing. In all of these situations, impairment in pulmonary function appears to be related to obstruction of small airways and bronchial hyper responsiveness [18]. Regarding prematurity and intrauterine growth restriction, it seems that, besides changes in pulmonary flow, lung growth is also impaired, as shown by altered pulmonary volume measurements [19,20].

A prospective cohort study has shown that, in children born preterm with an mean gestational age of 25.6 weeks, evaluated at 6, 12 and 24

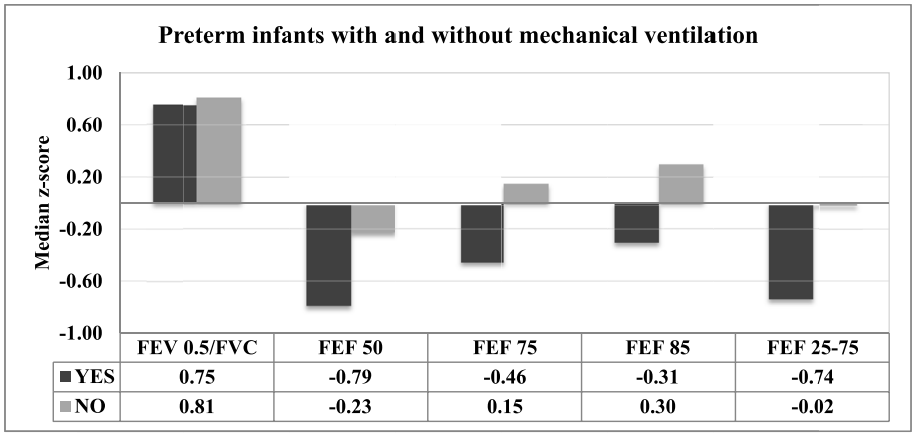

Fig. 1. Median z-score of pulmonary function parameters in preterm children who were submitted or not to mechanical ventilation during stay in the neonatal unit (Mann-Whitney test, $p < 0.05$).
$FEV_{0.5}$: forced expiratory volume in 0.5 s; FVC: forced vital capacity; - $FEV_{0.5}$/FVC ($p = 0.015$); FEF_{50}: forced expiratory flow at 50% of FVC ($p = 0.001$); FEF_{75}: forced expiratory flow at 75% of FVC ($p = 0.022$); FEF_{85}: forced expiratory flow at 85% of FVC ($p = 0.047$); FEF_{25-75}: forced expiratory flow at 25–75% of FVC ($p = 0.005$).

Table 2
Multivariate logistic regression analysis for factors associated with pulmonary function parameters, adjusted for confounders.

		Beta	CI 95%	p
FVC z-score	Small for gestational age	−1.005	−1.718 to −0.291	0.007
	Gestational age (weeks)	0.215	0.046 to 0.014	0.014
$FEF_{0.5}$ z-score	Small for gestational age	−0.643	−1.227 to −0.059	0.032
	Mechanical ventilation	−0.659	−1.220 to −0.098	0.022
% predicted FRC	Gestational age (weeks)	−2.205	−4.392 to −0.018	0.048
	Recurrent wheezing	16.925	4.160 to 29.690	0.011
$FEF_{25–75\%}$ z-score	Mechanical ventilation	−0.602	−1.143 to −0.062	0.030

FVC: forced vital capacity; $FEV_{0.5}$: Forced expiratory volume in 0.5 s; FRC: functional residual capacity; FEF_{25-75}: forced expiratory flow at 25–75% of FVC.

months after discharge from the neonatal unit, pulmonary flows were persistently limited during the first two to three years of life, with an increase in functional residual capacity in children who used a bronchodilator, suggesting an obstructive component and bronchial hyperreactiveness in these children [21]. Another study found an association between histories of wheezing in childhood and reduced pulmonary flows and volumes, similar to what we observed in the present study [15]. Bronchial hyperreactiveness seems to be a factor common to preterm-born and asthmatic children [22], although some authors question whether the physiopathology of bronchial hyperreactiveness in preterms is similar to that of asthma, as some studies could not find, in preterms, markers of airway eosinophillic inflammation seen in asthma [18]. In this context, it should be noted that preterms in the present study had a similar proportion of familial history of asthma and atopic diseases to that seen in term infants; however, they had higher frequency and a greater number of wheezing episodes and greater alteration of pulmonary flow parameters.

Another factor observed in our results was the association between altered pulmonary flow and the use of mechanical ventilation in the neonatal unit. Despite many advances in assisted ventilation in preterm babies in neonatal ICUs, this procedure is still an aggravating factor for the development of pulmonary disease after the neonatal period. It has been observed in the present study that children exposed to both invasive and non-invasive ventilation have shown impaired pulmonary flow. Likewise, a recent study comparing the development of preterms born at gestational age below 28 weeks during three periods, 1991–1992, 1997 and 2005, has shown that despite the use of less invasive mechanical ventilation techniques, the duration of oxygen therapy and the occurrence of bronchopulmonary dysplasia were higher during the last period. Furthermore, when children were evaluated at 8 years of age, no improvement in pulmonary flow parameters was identified over time, with significantly lower FEV_1 values in 2005 (z-score: -1.19 ± 1.17) when compared to 1997 (z-score: -0.65 ± 1.30, $p < 0.05$), significantly lower FEV_1/FVC in 2005 (z-score: -0.06 ± 1.49) when compared to the first and second periods (1st period: -0.30 ± 1.33 vs. 2nd period: 0.77 ± 1.20, $p < 0.005$) and similar $FEF_{25–75\%}$ during all three periods (z-score: -1.45 ± 1.04 vs. -1.30 ± 1.06 vs. -1.27 ± 1.08) [23].

Some publications call attention to the role of intrauterine growth restriction in the pulmonary development of affected fetuses [16,20,24–26], pointing out an association of this gestational condition with development of chronic pulmonary disease [24], impaired pulmonary function [20] and wheezing at age 3 years [26]. To explain this association, some authors refer to a lower expression of mRNA for surfactant proteins in animal models with restricted intrauterine growth [25], reduced pulmonary vascularization and alveolarization [19] and bronchial hyperreactiveness [3,27]. We likewise observed a significant association between small size for gestational age and reductions in FVC and $FEV_{0.5}$.

A limitation of this study is the small sample size analyzed, which resulted from the difficulty in obtaining acceptance from parents to allow pulmonary function tests needing sedation to be conducted on asymptomatic children, or on children for whom the indication of these tests is questionable from the clinical point of view. The use of chloral hydrate is not without risk, especially in preterm infants with reports of bradycardia, oxygen saturation drops and prolonged sedative effects [28,29]. A further limitation is related to this being a cross-sectional study and therefore not allowing the inference of causal relationships for the risk factors found for alterations in pulmonary function.

In conclusion, it can be stated that very low birth weight preterm infants had a high prevalence of impaired pulmonary function, particularly in pulmonary flow measurements, the worst results having been found in preterms with lower gestational age, intrauterine growth restriction, exposed to mechanical ventilation in the neonatal period, and presenting with recurrent wheezing during infancy. Furthermore, preterms had lower pulmonary flow parameters when compared to infants born at term.

Authorship

DMMG, ASS and FCL: contribute to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and approved the final approval to be submitted.

GFW: contribute to the conception and design of the study, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and approved the final the version to be submitted.

ALG and DS: contribute to the conception and design of the study, revising the article critically for important intellectual content and approved the final the version to be submitted. AMNS: contribute to the conception and design of the study, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and approved the final the version to be submitted.

Confict of interest

none.

Financial support

none.

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