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Original Article

Evaluation of pulmonary functions in preschool children born late-preterm

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Abstract

Aim: The aim of this study was to evaluate the pulmonary functions of preschool children born late-preterm.

Material and Methods: Children aged between 3-7 years who were born at $34^{0/7}$-$36^{6/7}$ weeks' gestation represented the target sample. Patients with a diagnosis of congenital cardiac, pulmonary and/or muscle diseases were excluded. Respiratory symptoms were evaluated using the modified asthma predictive index and International Study of Asthma and Allergies in Childhood criteria for children aged under and over 6 years, respectively. Skin prick tests were performed. Age-matched healthy controls were chosen according to the criteria proposed by the American Thoracic Society. Lung functions were evaluated using impulse oscillometry study in both groups. Data were recorded in the SPSS program.

Results: A total of 139 late-preterms and 75 healthy controls participated in the study. The mean gestational week of the late-preterms was 35.3±0.9 weeks. The main admission diagnosis to neonatal intensive care unit was respiratory distress. In the postdischarge period, 54.1% were hospitalized for pulmonary infections at least once, and 57.8% were passive smoking currently. Aeroallergen sensitivity was detected as 25.8% in the late-preterm group; 34.5% and 15.1% were diagnosed as having asthma and non-asthmatic atopy, respectively. Impulse oscillometry study parameters of R5, R10, and Z5 were higher and X10 and X15 were lower in late-preterms than in controls ($p<0.05$). Late-preterms with and without respiratory distress in the postnatal period revealed no statistical differences for any parameters.

Conclusions: Our findings suggest that presence of increased peripheral airway resistance in late-preterms as compared to term-born controls. (Turk Pediatri Ars 2017; 52: 72-8)

Keywords: Impulse oscillometric study, late-premature, pulmonary functions, preschool period.

Introduction

Babies born between $34^{0/7}$ and $36^{6/7}$ gestational weeks were named "late preterm" with a consensus made in 2005 in terms of emphasizing that they were preterm and reminding of the presence of related medical risks, with the aim of standardizing applications related with different definitions and therapies for late preterms (1).

There are no sufficient data related with long-term lung functions in late preterms, who have more respiratory problems compared with term babies, in the perinatal period and who seem to be healthy. The fact they were born in the saccular stage of lung development renders these babies vulnerable to trauma and infections and it is thought that this may have negative effects on future respiratory findings (2). In studies conducted in recent years, the association of late

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preterm delivery and asthma has been emphasized frequently (3, 4).

The traditional methods used in the evaluation of lung functions cannot be applied in young children because problems with noncompliance. Impulse oscillometric study (IOS) is an easily applied method in pre-school children because it requires passive participation (5).

Therefore, we aimed to evaluate lung functions in children aged between 3 and 7 years who were born in our hospital as late preterm babies using the IOS method and investigate respiratory findings.

Material and Methods

This prospective study was conducted by Kocaeli University Division of Neonatology between 2013 and 2014. Children aged between 3 and 7 years who were born at the $34^{0/7}$-$36^{6/7}$th gestational age and hospitalized in Kocaeli University Neonatal Intensive Care Unit between January 2006 and December 2010 were selected as the study group. Children who had congenital cardiac, lung and/or muscle disease were not included in the study. Perinatal data were recorded from the hospital files. Respiratory symptoms were evaluated using guidelines, which specify the risk of development of asthma in children aged below 6 years (modified Asthma Predictive Index-mAPI) and according to the International Study of Allergy and Asthma in Children (ISAAC) in children aged above 6 years (6, 7). Age-matched healthy controls were selected according to the American Thorax Society study criteria from healthy children who had no asthma or any familial history of asthma, no allergic rhinitis or eczema, no history of mechanical ventilation and preterm delivery (<37 GW), who were born with a birth weight above 2500 g, whose family members were non-smokers, non-obese, and had no muscle disease (8).

Children from either group who had respiratory tract infections in the last 2 weeks were not included in the study. Impulse oscillometric study was performed following height and weight measurements, and a physical examination. A skin prick test was performed using an aeroallergen kit that contained house dust mite, tree pollen, a mixture of herb-grain pollen, fungus, and animal epithelium-dander, and a food allergen kit containing milk and egg. A blood sample was obtained for total serum immunoglobulin (Ig) E and and eosinophil count. The study was approved by the Kocaeli Univeristy Ethics Committee (2013/138) and informed consent was obtained from the families who participated in the study.

Impulse oscillometer

Impulse oscillometer is a type of oscillacion technique. It measures entrance impedance in the respiratory tract and shows the difference in airway resistance between the central and peripheral parts. It can detect pathologic changes in the small airways in the early stage, and can be applied easily in all age groups without difficulty.

In the impulse oscillometer, the impedance (Z) used in the measurement is the sum of the forces required to form a pressure wave along the respiratory tract. The two main factors that constitute impedance are resistance (R) and reactance (X). It is measured between certain frequencies (5-20 Hz). When R and X are measured at 5 Hz, they are named R5 and X5. These values are recorded simultaneously in each respiration during measurement.

Resistance (R) is the energy required for the pressure wave to be transferred in the airway and for the lung parenchyma to become strained. Low frequency waves give information about the whole pulmonary system because they advance to the peripheral part of the lung, and about the distal airways in particular. High frequency waves remain in the upper airways and give information about the main airways. For example, the increase in R5 is higher compared with the increase in R20 in the distal airway pathologies. In main airway obstructions, R5 and R20 increase equally.

The property of reactance (X) is constituted by the movement in the airways, which provide transfer of pressure waves and the power of the lung tissue to expand. At low frequencies, the lung expands passively, its elasticity is high and its ability to expand is low. As the frequency increases, the amount of energy distributed in the lungs increases and the lung switches to active straining from passive expansion. This event is similar to inflating a balloon. A small amount of air given at the beginning enables the balloon to expand easily. Straining is observed with the increase in power of expansibility in response to continuing air flow. However, the air given leads to resistance and repulsion in time. At the frequency at which the lungs switch from passive expansion to active straining, the pressure required for this event and the power of elastic expansibility are balanced at one point. This frequency at which the power of expansibility is zeroized is called the resonance frequency (Resfreq). It is related with the size and tissue structure of the thorax (5).

"Coherence" is the congruity between air flow and pressure. This value reflects the reliability of IOS measurements. If there is incongruity between the air flow transferred into the lungs and the pressure wave formed as reflex, "coherence" will be low. Although there are no values specified for pre-school children, 0.6 or above at 5 Hz and 0.8 and above at 10 Hz are considered congruent as a standard for a 30-second test where 120 samples are obtained (9).

In our study, the device was introduced to the child before the test was performed. The child was made to relax and sit straight holding their head in a natural or slight extension position. It was ensured that the lips grasped the mouthpiece of the device tightly. The nose was closed with a clip and measurement was initiated by applying pressure to the cheeks. Recordings were initiated when regular respirations were observed and a 20-30-second measurement was performed. The best test was selected after 3-5 measurements were recorded according to the compliance to the test (Figure 1).

There are no clear standard values for normal reference values of IOS in the childhood age group. In our study, the data of the measurements specified by the IOS device according to weight and height were used as used in previous studies (5, 9).

Statistical analysis

Statistical analysis was performed using the IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program. Compatibility with normal distribution was tested using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean +/- standard deviation and categorical variables are expressed as frequency (percentages). The differences between the groups were evaluated using Kruskal-Wallis one-way variance analysis (ANOVA), and Dunn's post hoc test and the Mann-Whitney test were used for continuous variables that did not have a normal distribution. A p value of <0.05 was considered significant. One hundred nine of 685 children who were born late preterm and hospitalized in Kocaeli University Neonatal Intensive Care Unit between January 2006 and December 2010 accepted to participate in the study and these children were specified as the study group. Seventy-five healthy children who were born at term, who were in the same age range, and who met the American Thorax Society study criteria were included as the control group. The power value that we aimed for could not be reached because the condition of 400 subjects per group required to reach an α value of 0.05 and a 1-β value of 0.86 could not be achieved because of the above mentioned reasons.

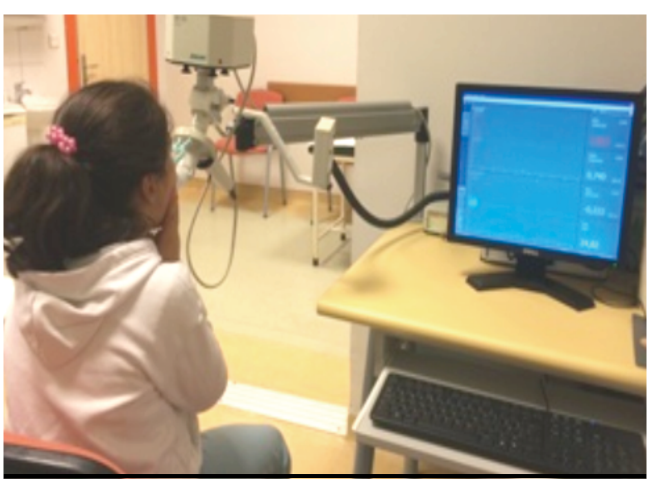

Figure 1. Lung function test with the impulse oscillometric method

Results

Six hundred eighty-five (22.4%) of 3079 patients who were hospitalized in Kocaeli University neonatal Intensive Care Unit between January 2006 and December 2010 were late preterms. Six hundred fifty of these patients could be contacted and 139 accepted to participate in the study. Fifty (36%) of the participants were female and 89 (64%) were male. Seventy-five children were included in the control group. The weight and height percentiles of the late preterm and control groups were within the normal limits by age and there was no statistically significant difference (p>0.05).

The mean gestational week in the preterm group who participated in the study was 35.3±0.9 weeks. The main diagnoses at hospitalization mostly included transient tachypnea of the newborn (TTN), neonatal pneumonia, meconium aspiration, indirect hyperbilirubinemia, early neonatal sepsis, hypoglycemia, and difficulty in feeding. The characteristics of the other perinatal periods are shown in Table 1. In the follow-up visit at the age of 3-7 years after discharge, it was learned that 46.8% of the subjects received treatment with diagnoses of asthma and non-asthmatic atopy (allergic rhinitis, eczema). Some 54.1% of the subjects were found to have been hospitalized at least once because of lung infection and 57.8% were found to have been exposed to cigarette smoke at home. Just under half (48.6%) of the subjects

Table 1. Perinatal period characteristics in the late preterms

Late preterms	n=139
Sex, n (%)	
Female	50 (36%)
Male	89 (64%)
Gestational week (Mean±SD)	35.3±0.9
Mode of delivery, n (%)	
Cesarean section	111 (79.9%)
Birth weight (g) (Mean±SD)	2386±515.7
Intrauterine development, n (%)	
Appropriate for gestational week	120 (86.3%)
Apgar score at the 5th minute (Mean±SD)	9.3±0.7
Gestational age (Mean±SD)	29.3±4.9
Maternal smoking status during pregnancy, n (%)	32 (23.2%)
Maternal history of asthma during pregnancy, n (%)	7 (5.1%)
Subjects with postnatal respiratory distress, n (%)	77 (55.4%)
Need for mechanical ventilation, n (%)	46 (33.1%)
Subjects who were given surfactant, n (%)	17 (7%)
Period of hospitalization (days), (Mean±SD)	5.9±5.2

Mean±SD: mean±standard deviation

Table 2. Evaluation of the late preterms in the 3-7–year age period

Late preterms	n=139
Hospitalization because of lung infection, % (n)	75 (54.1%)
Passive smoking, % (n)	78 (57.8%)
Familial history of asthma-atopy, % (n)	67 (48.6%)
Aeroallergen sensitivity, % (n)	36 (25.8%)
Total IgE, (Mean±SD)	125.7±58.1
Eosinophil percentage, (Mean±SD)	2.7±2.2
Diagnosis of asthma, % (n)	48 (34.5%)
Non-asthmatic atopy (allergic rhinitis and eczema), % (n)	21 (15.1%)
Food sensitivity, % (n)	26 (19.1%)

Mean±SD: mean±standard deviation

Table 3. Impulse oscillometry study measurements in the study and control groups

	Study group (n=139)		Control group (n=75)		
	Mean	SD	Mean	SD	p
R5kPa/(L/s)	0.97	0.29	0.88	0.25	0.014
R10kPa/(L/s)	0.81	0.20	0.75	0.19	0.035
R15kPa/(L/s)	0.76	0.19	0.72	0.18	0.163
R20kPa/(L/s)	0.70	0.17	0.67	0.17	0.236
X5 kPa/(L/s)	-0.26	0.12	-0.26	0.11	0.973
X10kPa/(L/s)	-0.15	0.10	-0.12	0.07	0.030
X15kPa/(L/s)	-0.10	0.10	-0.07	0.06	0.022
X20kPa/(L/s)	-0.00	0.08	0.01	0.05	0.137
Resfreq 1/s	20.37	7.6	18.52	4.69	0.078
Z5kPa/(L/s)	1.01	0.29	0.91	0.27	0.017

IOS: impulse oscillometric study; R: resistance; Resfreq: resonance frequency; X: reactance; Z: impedance

had a familial history of asthma-atopy. In the screening performed in our hospital, aeroallergen sensitivity was found in 25.8% of the late preterm group. The mean total IgE value was 125.7±58.1 IU/m, and the mean eosinophil percentage was found as 2.7±2.2% (Table 2).

Respiratory function test measurements performed by IOS were compared between the two groups and statistical analysis was performed. The mean R5, R10, and Z5 IOS values were significantly higher in the study group compared with the control group ($p<0.05$). No significant difference was found between the other R values ($p>0.05$). Among the mean IOS X values, X10 and X15 were significantly lower in the study group compared with the control group ($p<0.05$). No difference was observed between the other X values ($p>0.05$) (Table 3).

The data of the late preterms who were divided into two groups; those with and without respiratory distress in the postnatal period were compared with the control group. The mean R5 value was significantly higher in both groups compared with the control group ($p<0.05$). There was no difference in terms of the other values ($p>0.05$) (Table 4).

When the IOS measurements were compared between the subjects with and without postnatal respiratory distress, no statistically significant difference was observed ($p>0.05$). The data after discharge that could affect respiratory function were investigated in these two groups. It was observed that poor environmental factors including presence of lower respiratory infection and exposure to cigarette smoke were found with a higher rate in the group without postnatal respiratory distress, and genetic factors that could lead to a predisposition to asthma were found with a higher rate in the group with postnatal respiratory distress. However, no statistically significant difference was found in terms of these factors ($p>0.05$).

When clinical and laboratory data were evaluated, a diagnosis of asthma was made in 34.5% of the late preterm group and non-asthmatic atopy was diagnosed in 15.1% (total rate of atopy: 49.6%). The rate of food sensitivity was 19.1%.

Table 4. Impulse oscillometry study measurements in subjects with and without respiratory distress in the postnatal period and in the control group

	Respiratory distress positive (n=77)		Respiratory distress negative (n=61)		Control (n=75)		
IOS	Mean	SD	Mean	SD	Mean	SD	p
R5kPa/(L/s)	0.95	0.24	0.99	0.35	0.88	0.25	0.048
R10kPa/(L/s)	0.81	0.19	0.82	0.21	0.75	0.19	0.106
R15kPa/(L/s)	0.75	0.18	0.77	0.19	0.72	0.18	0.350
R20kPa/(L/s)	0.69	0.18	0.71	0.16	0.67	0.17	0.410
X5 kPa/(L/s)	-0.26	0.10	-0.27	0.14	-0.26	0.11	0.962
X10kPa/(L/s)	-0.14	0.07	-0.16	0.13	-0.12	0.07	0.088
X15kPa/(L/s)	-0.09	0.07	-0.11	0.13	-0.07	-0.06	0.067
X20kPa/(L/s)	-0.01	0.08	-0.00	0.09	0.01	0.05	0.214
Resfreq 1/s	20.86	9.4	19.76	4.4	18.52	4.69	0.164
Z5kPa/(L/s)	0.98	0.21	1.04	0.36	0.91	0.27	0.057

IOS: impulse oscillometric study; R: resistance; Resfreq: resonance frequency; SD: standart deviation; X: reactance; Z: impedance

Discussion

The prevalence of late preterm delivery has increased by 20% since 1990 to the present time and late preterms constitute 70-75% of premature deliveries (10). Although late preterm babies are born near term, they are not as healthy as term babies, as expected. The rates of perinatal morbidity and mortality are high in late preterm babies as compared with term babies. In recent studies, the association of late preterm delivery and childhood asthma has been frequently emphasized. It is thought that incompletely matured lungs at the time of delivery and physiologic insufficiency in protective mechanisms affect future respiratory functions negatively in late preterms (2-4). However, screening of the literature shows that most studies that evaluated lung function in children were conducted with very-low and low-birth-weight newborns. It is noted that the number of studies conducted with late preterm newborns is limited and these studies addressed recent respiratory problems encompassing the first 3 years at most (2, 11, 12). Therefore, in our study, we evaluated lung function using the IOS method in pre-school children who were born late preterm in our hospital and investigated respiratory findings. As a result of our study, we found that small airway resistance was present in children who were born late preterm when compared with children born at term. In our previous study by Er et al. (13) in which the respiratory findings of children who were born late preterm in the same age group but with no asthma were compared with healthy controls, the same conclusion was made. In both of our studies, the effect of late preterm birth on long-term respiratory findings and its importance was emphasized.

In the literature, the number of studies evaluating lung functions in children born late preterm is limited and these studies were conducted with children aged older than the pre-school age group. In these studies, children who were born late preterm and age-matched controls born at term were evaluated using spirometry and no difference was reported in terms of respiratory findings (the mean age was 11.6 years in one of these studies and another study was conducted with children aged between 8 and 9 years and 14 and 17 years) (14, 15). In contrast to traditional respiratory function tests, IOS can be applied easily in pre-school children who may have difficulty with cooperation because it requires passive participation (5). The first study to evaluate respiratory findings in pre-school children who were born late preterm using the IOS method was our study by Er et al. (13). We aim to continue performing longitudinal studies with our study group in future years and investigate similarities or differences in lung functions compared with term peers.

As a result of our data, it was observed that respiratory distress and its treatment in the postnatal period had no negative effect on lung function in the pre-school period in children born late preterm. However, it is known that respiratory distress in the postnatal period including mainly TTN is an independent risk factor for a diagnosis of asthma in childhood; atopy is observed more frequently in children who had been diagnosed as having TTN with the impact of genetic predisposition, and respiratory function tests are most frequently affected by asthma (16). When we examined the characteristics of our late preterm group, we observed that poor environmental factors including passive smoking, lung infections that required hospitalization, and receiving treatment for asthma were found with a higher rate in the 3-7–year period after discharge in the group that had no postnatal respiratory distress, though there was no statistically significant difference. On the other hand, we found that genetic factors including male sex, aeroallergen sensitivity, a diagnosis of non-asthmatic atopy, and increased eosinophil count, which may lead to a predisposition to asthma, were found with a higher rate in the group that had postnatal respiratory distress. When evaluated as a whole, it was thought that genetic factors and poor environmental factors acquired in a period of 3-7 years may negatively affect lung function in both groups in different aspects and even equalize them. Studies conducted in this context have shown that late preterms born before completing lung development are at risk in terms of recurrent bronchiolitis and pneumonia caused by viruses, mainly including respiratory syncytial virus in infancy and early childhood (17-19). It has been reported that frequent infections at early ages may lead to reduced lung functions at advanced ages in children who were born late preterm (20, 21). The direct and indirect effects of cigarette smoke on lung functions are already known.

The association of asthma and late preterm delivery has been emphasized frequently in recent years. In the study conducted by Harju et al. (4), it was reported that early preterms (37-38 weeks) and late preterms carried a significantly higher risk for asthma compared with term babies, and the increase in the prevalence of asthma in recent years was related with the increase in the birth rate of these babies. In our study, aeroallergen sensitivity was found in 25.8% of our late preterm born patients, a diagnosis of asthma was made in 34.5%, and non-asthmatic atopy was diagnosed in 15.1%. The rates we found are higher compared with the Turkish and world literature. For example, Goyal et al. (3) found the rate of atopy as 16% in children who were born in the 34-36th gestational weeks. Although Turkish data related with late preterms are lacking, the prevalence of cumulative asthma was reported as 13.7-15.3% in childhood in Turkey according to the modified ISAAC study (22). Considering the fact that the city in which we live is the industrial city of Kocaeli, our hospital is a reference center, and that subjects who were willing to participate in our study were mostly late preterm born children who had symptoms, we think that these rates were high and comprehensive epidemiologic studies are needed for clearer data.

In conclusion, peripheral airway obstruction was shown in late preterm born children aged between 3 and 7 years compared with a control group that comprised healthy term-born children in the same age range. We think that lung infections that require hospitalization, exposure to cigarette smoke, late preterm birth might have negatively affected lung function in these children. Therefore, respiratory function tests should be included in the outpatient follow-up of children who were born late preterm for early diagnosis and treatment of respiratory problems.

Ethics Commitee Approval: Ethics commitee approval was received for this study from Kocaeli University School of Medicine Ethic Committee (KOU KAEK 2013/138 Date: 21.05.2013).

Informed Consent: Informed consent was optained from the parents.

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