HK J Paediatr (new series) 2024;**29**:27-34

Original Article

Impact of Prolonged Preterm Premature Rupture of Membranes on Respiratory Support in Very Low Birth Weight Preterm Newborns

B ***Küçükali***, C ***Armağan***, F ***Erdoğan***, N ***Duman***, H ***Özkan***

Abstract

Introduction: Conflicting results have been reported regarding the impact of prolonged preterm premature rupture of membranes (P-PPROM) on morbidity and mortality in very low birth weight (VLBW) infants. Data on the difference in the respiratory support requirements of these newborns compared to other VLBW newborns are very insufficient. The aim of this study was to investigate how the presence of P-PPROM alters the need for postnatal respiratory support in VLBW infants. ***Materials and Methods:*** In this retrospective cross-sectional study, VLBW infants, followed up until discharge (or mortality) at the Dokuz Eylül University Neonatal Intensive Care Unit in the 5-year period between 2014 and 2019 were evaluated. Infants with and without P-PPROM were compared in terms of the characteristics of respiratory support applied in the first postnatal hours and the first 10 days. ***Results:*** P-PPROM was identified in 32 (22%) of 145 VLBW infants. No significant difference was found between the two groups in terms of maternal and gestational characteristics except for antenatal steroids. Apgar scores were lower in the group without P-PPROM, the need for invasive ventilation was higher during the follow-up period, and a higher percentage of fractionated oxygen and end-expiratory positive pressure were used in non-invasive ventilation. There was no difference between the two groups in terms of morbidities and mortality, except for air leak syndromes. ***Conclusion:*** Infants with P-PPROM exhibited a lesser need for respiratory support after birth, but the impact on significant morbidities could not be clearly determined due to both limited number of cases and differences in antenatal steroid treatment rates between the groups.

Key words *Mechanical ventilator parameters; Prolonged preterm premature rupture of membranes; Respiratory outcomes; VLBW*

Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, Izmir, Turkey
B **Küçükali** *MD*

Department of Pediatrics, Division of Neonatology, Dokuz Eylül University Faculty of Medicine, Izmir, Turkey
C **Armağan** *MD*
F **Erdoğan** *MD*
N **Duman** *MD*
H **Özkan** *MD*

Correspondence to: Dr B **Küçükali**
Email: batuhankucukali@gmail.com

Received July 4, 2023

Introduction

Premature rupture of membranes is defined as rupture of amniotic membranes before uterine contractions.[1] Preterm premature rupture of membranes (PPROM) occurs when this happens before 37th gestational week. The diagnosis of prolonged PPROM (P-PPROM) is accepted when there is a rupture of membranes at least 18 hours before delivery. It is unclear whether there is a significant difference in the requirement of respiratory support, ventilation parameters, and long-term respiratory outcomes between premature newborns born prematurely due to P-PPROM and those born without P-PPROM.[2-6]

Although P-PPROM is thought to be protective on the respiratory system in the early period compared to other preterm birth factors due to a prolonged inflammatory process, there is no consensus on whether it can significantly reduce the risk of respiratory distress syndrome (RDS).[4,7] In this study, very low birth weight (VLBW) preterm babies born with P-PPROM and those born without P-PPROM were compared in terms of respiratory support requirements and respiratory support parameters. It is anticipated that the data obtained will be useful in establishing trustworthy guidelines on providing best-care possible to these newborns.

Materials and Methods

In this retrospective cohort study, all VLBW infants without major congenital anomalies, born at Dokuz Eylül University Hospital between 01.01.2014 and 01.01.2019, and subsequently followed up in the neonatal intensive care unit of the same hospital until discharge (or mortality), were included. Ethics committee approval for the study was obtained from the Ethics Committee of Dokuz Eylül University, dated 18/11/2019, and assigned decision number 2019/28-30 in accordance with the Declaration of Helsinki.

Maternal clinical characteristics (including important maternal diseases, presence of P-PPROM, presence of chorioamnionitis, antenatal steroid treatment, and mode of delivery), neonatal clinical characteristics (such as gestational age, birth weight, gender, Apgar scores, the need for positive pressure ventilation (PPV) or further delivery room resuscitation, major morbidities, and mortality), and respiratory support requirements (oxygen support, invasive/non-invasive ventilation requirements and durations, and initial and maximum ventilation parameters applied) were recorded. Furthermore, the results of pathological examination of the placenta, routinely performed in premature deliveries, were reviewed to ascertain the presence of chorioamnionitis and recorded.

For the diagnosis and follow-up of RDS, intraventricular haemorrhage (IVH), early and late neonatal sepsis, necrotising enterocolitis (NEC), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), which were evaluated as significant morbidities, the recommendations in the Diagnosis and Treatment Guidelines of the Turkish Neonatology Society, aligned with international definitions, were utilised. Respiratory support in the delivery room and neonatal intensive care unit adhered to unit protocols.

Regarding the delivery room respiratory support data, 1st, and 5th minute Apgar scores, PPV and the requirement for advanced resuscitation were extracted from file records. Neonatal intensive care unit respiratory support data encompassed initial, stabilisation, and maximum respiratory support parameters. Initial respiratory support parameters included the ventilation mode applied for the longest time during the first hour of the newborn's arrival to the neonatal intensive care unit, fractional percentage of oxygen (%FiO_2), end-expiratory positive pressure (PEEP), and positive pressure reached during inspiration (Pins). Stabilisation respiratory support parameters encompassed the same parameters applied within the first 24 hours for at least 3 hours after the baby was stabilised, while maximum respiratory support parameters recorded the highest FiO_2, PEEP and Pins values applied for at least 3 hours consecutively within the first ten days of the intensive care period. If the patient was under high frequency oscillatory ventilation (HFO-V) during these periods, FiO_2, mean airway pressure (MAP), amplitude (AMP) values were documented. In summary, initial parameters refer to the longest applied ventilation settings during the first hour of the newborn's arrival at the neonatal intensive care unit, stabilisation parameters encompass ventilation settings applied for at least 3 hours within the first 24 hours, and maximum parameters denote the highest ventilation settings applied for at least 3 consecutive hours within the first 10 days of the intensive care period.

All neonates included in the study were categorised into two groups: P-PPROM (Group 1) and non-PPROM (Group 2). These groups were regarding all the aforementioned data.

Statistical Analysis

SPSS v.24 programme was used in the evaluation of the data. In descriptive statistics, categorical variables were expressed as frequency (n) and percentage (%). Chi square and Fisher's exact test were used to analyse categorical variables. Levene's test was used for normal distribution of continuous data and normally distributed data were analysed by T test and non-normally distributed data were analysed by Mann-Whitney-U. A value of $p<0.05$ was accepted for statistical significance. Logistic regression analysis was performed to evaluate possible comorbid variables.

Results

A total of 203 infants were initially enrolled in the study, with the assessment of maternal and neonatal clinical characteristics for all infants. However, only 158 infants had their respiratory support parameters evaluated. Following the exclusion of 13 patients who unfortunately passed away within the first 24 hours (8.5% in Group 1 and 8.1% in Group 2), the study proceeded with 145 patients.

Maternal and Neonatal Characteristics

Mean gestational age was 28.12±2.49 weeks, and mean birth weight was 1009.59±307.80 grams. The distribution and comparison of maternal and neonatal characteristics according to the groups are summarised in Table 1, while other characteristics related to hospital follow-up are outlined in Table 2.

Table 1 Maternal and neonatal characteristics

Clinical features	Group 1 (n:32)	Group 2 (n:113)	P value
Multiparity, n (%)	8 (25)	31 (27.4)	0.784
Antenatal corticosteroids, n (%)	27 (84.4)	75 (66.4)	**0.049**
Maternal pre-eclampsia, n (%)	12 (37.5)	40 (35.4)	0.827
Maternal diabetes, n (%)	7 (21.9)	26 (23)	0.893
C/S delivery, n (%)	28 (87.5)	94 (83.2)	0.555
Histological chorioamnionitis, n (%)*	12 (42.9)	28 (28.9)	0.162
Gestational age (weeks)**	27.45 ± 2.19	28.31 ± 2.54	0.065
Birth weight (grams)**	1048.75 ± 309.93	998.50 ± 307.67	0.421
Female gender, n (%)	19 (59.4)	62 (54.9)	0.650

*Pathological data of 125 patients were available (28 patients from Group 1 and 97 from Group 2).
**Values are given mean ± Standard deviation
C/S: C section

Table 2 Morbidity and mortality data of the patients

	Group 1 (n:32)	Group 2 (n:113)	P value
IMV requirement, n (%)	15 (46.9)	79 (69.9)	**0.016**
Total MV duration (days)*	32.75±27.33	23.82±21.22	0.111
Duration of oxygen therapy (days)*	31.67±29.48	28.35±25.43	0.578
RDS, n (%)	17 (53.1)	68 (60.2)	0.475
Surfactant treatment, n (%)	17 (53.1)	66 (53.1)	0.594
BPD (moderate-severe), n (%)	7 (21.9)	14 (15.4)	0.401
Air leakage syndromes, n (%)	0	15 (13.3)	**0.042**
PDA requiring treatment, n (%)	10 (66.7)	36 (56.3)	0.462
NEC (≥ Stage 2), n (%)	2 (6.3)	4 (3.5)	0.614
ROP (treated), n (%)	0	5 (5.2)	0.331
IVH (> Grade 2), n (%)	2 (6.3)	5 (4.4)	0.650
PVL, n (%)	5 (15.6)	8 (7.1)	0.159
Early-onset Sepsis, n (%)	12 (37.5)	47 (41.6)	0.677
Late-onset Sepsis, n (%)	22 (68.8)	60 (55.6)	0.201
Mortality	2 (6.2)	21 (18.5)	0.092

*Values are given as mean ± Standard deviation.
**Only 79 patients underwent echocardiography (15 in G1; 64 in G2). 17 patients died before ROP examination in Group 2. 5 patients in Group 2 died before the defined time of late sepsis assessment. Therefore, all statistical analysis were conducted using the remaining numbers in both groups.
IMV: Invasive mechanical ventilation, MV: Mechanical ventilation, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, PDA: Patent ductus arteriosus, NEC: Necrotising enterocolitis, ROP: Retinopathy of premature, IVH: Intraventricular Haemorrhage, PVL: Periventricular leukomalacia

Respiratory Support Features

Delivery Room Respiratory Support Period:

No significant difference was found between the two groups in terms of PPV, and further resuscitation steps, and Apgar scores at the 1st and 5th minute (Table 3).

Initial Respiratory Support Period:

Respiratory support was analysed as invasive or non-invasive mechanical ventilation. It was demonstrated that more invasive mechanical ventilation was required in cases without P-PPROM, which was statistically significant (p=0.023) (Table 3). No significant difference was found between the two groups in terms of mean PEEP and Pins values of patients who underwent invasive or non-invasive mechanical ventilation in the first hour of neonatal intensive care, whereas %FiO_2 was found to be lower in the P-PPROM group (p=0.032) (Table 3). When the non-invasive PEEP value was categorised as above and below 6 cmH_2O, no difference was found between the two

Table 3 Distribution of patients' delivery room information, initial, stabilisation and maximum respiratory support

	Group 1 (n:32)	Group 2 (n:113)	P value
PPV / Further resuscitation, n (%)	10 (31.3)	54 (47.8)	0.096
Apgar 1st minute*	7 (1-9)	6 (1-10)	0.161
Apgar 5th minute*	8 (5-10)	8 (3-10)	0.927
Initial			
Non-invasive	21 (65.6)	63 (55.7)	
• n-CPAP	9 (28.1)	38 (33.6)	
• n-IPPV	14 (43.8)	25 (21.1)	**0.023#**
Invasive	6 (18.8)	49 (43.4)	
• PCAC-VG	4 (12.5)	42 (37.2)	
• HFO-VG	2 (6.3)	7 (6.2)	
Stabilisation			
Non-invasive	17 (53.1)	56 (49.6)	
• n-CPAP	8 (25)	22 (19.5)	
• n-IPPV	9 (28.1)	34 (30.1)	0.395#
Invasive	10 (31.2)	48 (42.5)	
• PCAC-VG	9 (28.1)	36 (31.9)	
• HFOV-VG	1 (3.1)	12 (10.6)	
In-PEEP (cmH_2O)	6.39±0.89	6.54±0.88	0.475
I-nPEEP > 6 cmH_2O	7 (30.4)	27(42.9)	0.297
I-FiO_2 (%)	26.13±8.0	30.47±14.71	**0.032**
I-FiO_2 > 30%	4 (12.5)	35 (34)	**0.037**
Sn-PEEP (cmH_2O)	6.11±0.92	6.67±0.83	**0.038**
S-nPEEP > 6 cmH_2O	6 (35.3)	31 (55.4)	0.147
S-FiO_2 (%)	23.13±3.36	23.65±4.57	0.481
S-FiO_2 > 30%	0	7 (6.2)	0.149
Mn-PEEP (cmH_2O)	6.88±1.05	7.29±0.94	0.082
M-nPEEP > 6 cmH_2O	13 (52.0)	70 (75.3)	**0.024**
M-FiO_2 (%)	35.84±16.63	51.96±29.33	**0.001**
M-FiO_2 > 30%	14 (43.8)	73 (64.6)	**0.034**

*Values are given as median (min – max) (%). #: invasive and non-invasive total numbers compared.

PPV: Positive pressure ventilation, n-CPAP: Nasal Continuous Positive Airway Pressure, n-IPPV: Nasal intermittent positive pressure ventilation, PCAC-VG: Pressure Controlled Assisted - Volume Guaranteed HFOV-VG: High Frequency Oscillatory-Volume Guaranteed Ventilation, I: Initial, S: stabilisation, M: maximum. n: non-invasive, FiO_2: fractionated oxygen percentage, PEEP: end-expiratory positive pressure

groups. However, when FiO_2 value was categorised as above or below 30%, 4 (12.5%) patients in Group 1 and 35 (31%) patients in Group 2 required FiO_2 above 30%. Thus, significant difference was identified between the groups regarding the requirement for $\%FiO_2$ above 30% during the initial period (p=0.037).

Stabilisation Respiratory Support Period:

Although no significant difference was found in the distribution of stabilisation ventilation modes of the patients, the need for invasive ventilation was observed more in Group 2 (Table 3). There were no differences between groups regarding mechanical ventilator values other than, the non-invasive PEEP value, which was higher in the group without P-PPROM (Table 3). When non-invasive PEEP and FiO_2 values were categorised as in the initial respiratory support, no significant difference was found between the groups.

Maximum Respiratory Support Period:

There was no significant difference between the two groups in terms of maximum mean PEEP and Pins values in patients who received invasive or non-invasive mechanical ventilation. When non-invasive PEEP and FiO_2 values were categorised, it was found that 52.0% (n=13) in Group 1 and 75.3% (n=70) in Group 2 used a maximum PEEP value above 6 cmH_2O and this was a statistically significant difference (p=0.024). Similarly, 43.8% in Group 1 and 64.4% in Group 2 were found to have a FiO_2 requirement above 30% (p=0.034). The mean maximum FiO_2 requirement was 35.8% in Group 1 and 51.9% in Group 2 and this difference was statistically significant ($p<0.05$).

The mean maximum MAP, AMP and FiO_2 values of the patients, who were not evaluated due to an insufficient number of cases in the initial and stabilisation periods but were monitored in HFOV mode within 10 days of follow-up, did not exhibit a statistically significant difference between the two groups.

Mortality and Morbidity Data:

Surfactant-requiring RDS was identified in 58% of our patients, with similar rates in Groups 1 and 2, at 53.1% and 60.2%, respectively. There was no significant difference between the two groups in terms of major morbidities, including BPD, IVH, NEC, ROP, PVL, PDA requiring treatment, early and late sepsis. Air leakage syndrome was absent in Group 1, whereas it occurred in 13.3% (15 cases) in Group 2, exhibiting a statistically significant difference (p=0.042). Upon analysing the treated ROP cases, it was observed that all 5 cases requiring treatment were in Group 2. A total of 23 (15.8%) infants, including 2 with P-PPROM, were lost in our study (p=0.092) (Table 2).

Logistic Regression Analysis:

In our study, we examined the combined risks of P-PPROM, gestational age, and antenatal corticosteroids on two key outcomes: the ratio of invasive mechanical ventilation and FiO_2 requirement above 30% during the initial respiratory support period, as well as FiO_2 requirement above 30% and non-invasive PEEP pressure above 6 cmH_2O in the maximum respiratory support period. These parameters, showing significant differences between the two groups in conventional statistical analysis, it was found that P-PPROM and gestational age were individually influential when evaluated using logistic regression analysis (Table 4). However, the effect of these results on morbidities should be evaluated with caution due to limited number of cases.

Discussion

Preterm premature rupture of membranes remains a common challenge in preterm deliveries, and the pathophysiology has yet to be fully elucidated, with limited clarity on fetal and neonatal effects.[1]

Among the problems of prematurity, respiratory system issues pose a significant morbidity and mortality potential. Conflicting results have been reported in the studies conducted so far on how P-PPROM affects the respiratory system problems of prematurity. According to some authors, P-PPROM increases lung inflammation by affecting type 2 alveolar cells through proinflammatory cytokines. This, in turn, accelerates lung maturation, increases the production of surfactant proteins and lipids, and prevents the development of RDS by increasing lung compliance.[4,5,7] Conversely, and opposing perspective suggests that P-PPROM does not protect from RDS but elevates the risk of BPD. This is attributed to the disrupting of the complex alveolar/vascular structure with the long-term effects of inflammation, resulting in simpler vascular structure and formation of fewer but larger alveoli, dysregulation of growth factors (VEGF, Angiopoietin-1 etc.), mesenchymal structure proteins (elastin), signalling pathways and regulators in the lung.[8-10] This condition, whose pathophysiology and outcomes have not been clarified, causes inadequacy in predicting the respiratory

support requirements of these infants and determining the appropriate ventilation strategies. Optimal organisation of the respiratory support for premature infants with P-PPROM not only impacts the respiratory system but also plays crucial role in mitigating all major morbidities and mortality.

In our study, we compared the respiratory support requirements and important outcomes in terms of the presence and absence of P-PPROM in the VLBW infants in a 5-year period. The absence of differences in gestational age, labour pain and multiple pregnancy, which are the most important determinants of mortality and morbidity, was noteworthy for comparative analysis. However, pregnant women with P-PPROM received more antenatal steroid treatment (p=0.049), probably due to earlier hospital admission and more vigilant monitoring.[8] While the presence of chorioamnionitis is generally expected to have a negative effect on respiratory support requirement and other morbidities, antenatal steroids are expected to have a positive effect.[11] Therefore, different statistical tests were also employed to evaluate the effects of P-PPROM independently of other factors.

The median Apgar scores at the 1st and 5th minute, the need for PPV and advanced resuscitation, duration of oxygen treatment during intensive care, and duration of invasive and non-invasive mechanical ventilation were similar in both groups.

The need for invasive mechanical ventilation was significantly less in the P-PPROM Group 1 in our study, in contrast to Khanal et al's findings.[12] The presence of P-PPROM demonstrated a significant protective effect on the FiO_2 requirement above 30% and the maximum non-invasive PEEP of 6 cmH_2O and above. These requirements were observed in the first hour in the intensive care unit and for at least 3 hours in the first 10 days of life The pathophysiological mechanisms explaining these effects of P-PPROM on reduced requirement for invasive mechanical ventilation and lower respiratory support requirements, independently of other factors, are challenging to elucidate through clinical studies. There are experimental studies highlighting the impact of the inflammatory process on lung maturation.

A notable advantage of our study is that placental pathologies were largely studied. Although it did not reach statistical significance, the higher rate of histological chorioamnionitis in the P-PPROM Group 1 (42.9% vs 28.9%). This may be explained by changes in the antenatal management of P-PPROM over the years, especially the administration of antenatal corticosteroids and antibiotics in accordance with the guidelines.

P-PPROM may decrease the need for invasive mechanical ventilation by increasing lung maturation with the effect of inflammation. In logistic regression analyses considering factors such as antenatal corticosteroids and gestational age, which may affect the need for invasive mechanical ventilation along with P-PPROM, P-PPROM alone was found to be effective in reducing the need for invasive mechanical ventilation and PEEP and FiO_2 requirement. In summary, P-PPROM was singularly reduced PEEP pressure and FiO_2 requirement, even when other concurrent risk factors were excluded through logistic regression analyses.

The differential diagnosis for RDS, significant respiratory problem, has a broad spectrum, and the

Table 4 Logistic regression analysis results

Clinic / Factors	**Initial respiratory support period**		**Maximum respiratory support period**		**Presence of RDS**
	Invasive MV	**FiO_2 >30 %**	**FiO_2 >30%**	**PEEP >6 cmH_2O**	
Gestational age	0.484	0.774	0.600	0.781	0.666
	(0.374-0.626)	(0.656-0.914)	(0.492-0.731)	(0.634-0.961)	(0.559-0.793)
	p=0.000	**p=0.003**	**p=0.000**	**p=0.02**	**p=0.000**
P-PPROM	0.102	0.682	0.182	0.346	0.470
	(0.028-0.363)	(0.072-0.745)	(0.067-0.492)	(0.123-0.974)	(0.191-1.160)
	p=0.000	**p=0.014**	**p=0.001**	**p=0.045**	p=0.101
Antenatal steroid	0.669	0.380	1.866	0.501	1.190
	(0.259-1.730)	(0.617-3.552)	(0.782-4.453)	(0.186-1.349)	(0.524-2.704)
	p=0.669	p=0.380	p=0.160	p=0.171	p=0.678

Values are listed as odds ratio, 95% confidence interval, and p value.

PEEP: End-expiratory positive pressure, MV: mechanical ventilation, P-PPROM: Prolonged preterm premature rupture of membranes, RDS: Respiratory distress syndrome

specificity of clinical and radiological findings is low. Therefore, cases requiring surfactant were accepted as RDS. No significant difference was found in the P-PPROM and non-P-PPROM groups for RDS, consistent with the study by Kachikis et al.[13] In the same study, although a significant difference was noted in the P-PPROM group for pneumonia, neonatal sepsis and PDA requiring treatment, this significant difference disappeared in multivariate analyses. P-PPROM did not have a discernible impact on both the development and severity of BPD and the risk of RDS, aligning with our study. In a different study, the presence of P-PPROM was associated with adverse respiratory effects (excess ventilatory support, higher frequency of BPD and air leak syndromes).[14]

In other studies where P-PPROM was associated with a significant decrease in the frequency of RDS, both the birth weight and mean gestational week of the newborns included in the study were considerably higher than in our study.[12,15,16] Although the number of patients was limited, when evaluated in terms of BPD, no statistically significant difference was found, although moderate to severe BPD was more common in Group 1. These findings align with certain studies but contradict others.[3,5,8,9,13] The primary reason for the contradictory opinions in the literature is thought to be differences in the antenatal management of P-PPROM cases and limitations in the number or characteristics of the cases included in the studies. When other major morbidities of the patients were evaluated between the two groups, no difference was found, and the results in this regard have been reported contradictorily by different investigators in the literature.[14,17,18] Air leakage syndromes were found to be statistically significantly higher in Group 2. This result can be explained by the use of less invasive mechanical ventilation and lower PEEP pressures in the P-PPROM group 1. Both invasive mechanical ventilation and high mechanical ventilation pressures were associated with air leakage syndromes. Furthermore, this result advocates the hypothesis of P-PPROM's positive impact on lung maturation. However, this impact played no role in mortality, as the mortality rates were similar between the two groups.

In conclusion, it has been demonstrated that the presence of P-PPROM as an independent factor reduces the need for invasive mechanical ventilation in the first days of life and the need for high FiO_2 and PEEP during invasive or non-invasive ventilation. However, it has no significant effect on long-term respiratory support parameters and other major morbidities. Prospective studies with a large number of cases are needed to clarify the accuracy and pathophysiological mechanisms of these effects.

Declaration of Interest

The authors declare no conflict of interest.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Ethical Committee Approval

Ethics Committee of the Dokuz Eylül University approved the research project. Committee's approval page is provided in the supplementary page.

Data Availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

References

1. Kumar D, Moore RM, Mercer BM, Mansour JM, Redline RW, Moore JJ. The physiology of fetal membrane weakening and rupture: Insights gained from the determination of physical properties revisited. Placenta 2016;42:59-73.
2. Lorthe E, Ancel PY, Torchin H, et al. Impact of Latency Duration on the Prognosis of Preterm Infants after Preterm Premature Rupture of Membranes at 24 to 32 Weeks' Gestation: A National Population-Based Cohort Study. J Pediatr 2017;182:47-52.e2.
3. Muller H, Stahling AC, Bruns N, et al. Latency duration of preterm premature rupture of membranes and neonatal outcome: a retrospective single-center experience. Eur J Pediatr 2022;181:801-11.
4. Perniciaro S, Casarin J, Nosetti L, et al. Early- and Late-Respiratory Outcome in Very Low Birth Weight with or without Intrauterine Inflammation. Am J Perinatol 2020;37:S76-S83.
5. Yan C, Deng X, Hong F. Analysis of Maternal and Neonatal Outcome of Patients with Preterm Prelabor Rupture of Membranes. J Healthc Eng 2022;2022:8705005.

6. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371:164-75.
7. Lee J, Oh KJ, Park CW, Park JS, Jun JK, Yoon BH. The presence of funisitis is associated with a decreased risk for the development of neonatal respiratory distress syndrome. Placenta 2011;32:235-40.
8. Hanke K, Hartz A, Manz M, et al. Preterm prelabor rupture of membranes and outcome of very-low-birth-weight infants in the German Neonatal Network. PLoS One 2015; 10: e0122564.
9. Zanardo V, Vedovato S, Cosmi E, et al. Preterm premature rupture of membranes, chorioamnion inflammatory scores and neonatal respiratory outcome. BJOG 2010;117:94-8.
10. Nakahara M, Goto S, Kato E, Itakura A, Takeda S. Respiratory Distress Syndrome in Infants Delivered via Cesarean from Mothers with Preterm Premature Rupture of Membranes: A Propensity Score Analysis. J Pregnancy 2020;2020:5658327.
11. Metcalfe A, Lisonkova S, Sabr Y, Stritzke A, Joseph KS. Neonatal respiratory morbidity following exposure to chorioamnionitis. BMC Pediatr 2017;17:128.
12. Khanal S, Zhang W, Shrestha NR, Dahal GR. A comparative study of outcome of preterm neonate with and without history of preterm premature rupture of membrane. Nepal Med Coll J 2009;11:99-103.
13. Kachikis A, Walker CL, McAdams RM, Gyamfi-Bannerman C, Adams Waldorf KM. Phenotypic overlap in neonatal respiratory morbidity following preterm premature rupture of membranes versus spontaneous preterm labor. J Matern Fetal Neonatal Med 2021;34:1941-8.
14. Verspyck E, Bisson V, Roman H, Marret S. Adverse respiratory outcome after premature rupture of membranes before viability. Acta Paediatr 2014; 103:256-61.
15. Park CW, Park JS, Jun JK, Yoon BH. Mild to Moderate, but Not Minimal or Severe, Acute Histologic Chorioamnionitis or Intra-Amniotic Inflammation Is Associated with a Decrease in Respiratory Distress Syndrome of Preterm Newborns without Fetal Growth Restriction. Neonatology 2015;108:115-23.
16. Sims EJ, Vermillion ST, Soper DE. Preterm premature rupture of the membranes is associated with a reduction in neonatal respiratory distress syndrome. Am J Obstet Gynecol 2002;187:268-72.
17. Gezer A, Parafit-Yalciner E, Guralp O, Yedigoz V, Altinok T, Madazli R. Neonatal morbidity mortality outcomes in pre-term premature rupture of membranes. J Obstet Gynaecol 2013;33:38-42.
18. Ahn HM, Park EA, Cho SJ, Kim YJ, Park HS. The association of histological chorioamnionitis and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four weeks' gestation. Neonatology 2012;102:259-64.