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Surfactant Therapy in Late Preterm Infants with Respiratory Distress in Türkiye: An Observational, Prospective, Multicenter Study

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What is already known on this topic?

- *Late preterm infants are at an increased risk of respiratory morbidity due to their immature lung structure and reduced surfactant production.*
- *Exogenous surfactant is widely used to treat respiratory distress in LPT infants, yet there are no established guidelines to direct its use.*

What this study adds on this topic?

- *We observed significant variability in the treatment practices for respiratory pathologies in LPT infants. This finding highlights an urgent need for standardized protocols regarding the use of surfactants in LPT infants suffering from various respiratory diseases.*

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ABSTRACT

Objective: Surfactant therapy (ST) is commonly used in late preterm (LPT) infants with respiratory distress despite a lack of definitive recommendation for these infants. Our aim was to establish a national prospective database to evaluate the use of surfactants in LPT infants.

Materials and Methods: A multicenter, prospective observational cohort study was conducted among LPT infants treated with surfactant between January 1, 2022, and December 31, 2022. Twenty neonatologists from 16 neonatal intensive care units (NICUs) participated in the study.

Results: During the study period, a total of 3327 LPT infants were admitted to the participating NICUs. Among them, 1866 infants experienced respiratory distress, and 288 received surfactant treatment. In this study, respiratory distress syndrome (RDS) was the most common indication for surfactant administration, affecting 158 infants (54.8%), followed by congenital pneumonia in 79 infants (27.4%) and transient tachypnea of the newborn (TTN) in 32 infants (11.1%).

Conclusion: We demonstrated that ST is administered with significant variability among LPT infants experiencing respiratory distress. Additionally, respiratory issues in LPT infants beyond RDS, such as congenital pneumonia and TTN, are also frequently treated with surfactant.

Keywords: Respiratory distress of newborn, surfactant therapy, late preterm infant, observational cohort study

INTRODUCTION

Late preterm (LPT) infants, born between 34 0/7 and 36 6/7 weeks of gestation, account for approximately 75% of all preterm births.[1,2] Due to their increased maturity and physical appearance, they are typically managed similarly to term infants. However, they have

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a higher risk of morbidity and mortality compared to term infants because of their relative physiologic immaturity.[3-5] They are also more susceptible to respiratory problems at birth as a result of immature lungs, decreased surfactant production, and a delayed transition to extrauterine life.[6]

While respiratory distress syndrome (RDS) due to pulmonary surfactant deficiency is the most common cause of respiratory distress in preterm infants, LPT infants are also at an increased risk.[6,7] Exogenous surfactant is widely used, and there are established guidelines for its treatment of RDS in preterm infants.[8,9] In addition to RDS, several other respiratory disorders, such as neonatal pneumonia, meconium aspiration syndrome (MAS), pulmonary hemorrhage, and acute respiratory distress syndrome (ARDS), can affect LPT infants, leading to surfactant inactivation and subsequent dysfunction.[10-12] Surfactant therapy (ST) may be associated with a reduced risk of mortality and lower rates of short-term respiratory morbidities in LPT infants. Recently, higher rates of respiratory morbidity and increased need for respiratory support have been reported in LPT infants, who are also more likely to require ST.[13-15] However, there is currently no standardized protocol for ST regarding optimal dosage, timing, and criteria for administration in LPT infants.[16] Experience with ST for respiratory problems in LPT infants is limited, relying primarily on retrospective data from a few centers. A recent meta-analysis reported that the rate of ST in both LPT and term infants with RDS was 46%, indicating a highly heterogeneous group of infants.[16] Therefore, it is important to define the clinical characteristics of LPT infants treated with surfactant in order to develop an evidence-based approach to their management.

Current evidence suggests that ST in LPT infants may be associated with a potentially decreased need for respiratory support. However, the thresholds for determining the need for surfactant replacement in LPT infants vary widely. Therefore, we aimed to establish a national prospective database to evaluate the use of surfactants in LPT infants. We investigated the clinical and therapeutic characteristics of LPT infants with respiratory distress who were deemed suitable for surfactant treatment.

MATERIALS AND METHODS

Study Design and Data Collection

A multicenter prospective observational cohort study was conducted involving LPT infants treated with surfactant from January 1, 2023, to December 31, 2023. Neonatologists were invited to participate via email, and a total of 20 neonatologists from 16 neonatal intensive care units (NICUs) agreed to take part in the study. Clinical directors of the NICUs and hospital directors provided written consent for participation in the research. The study was approved by the local ethics committee of Etlik Zübeyde Hanım Women's Health and Research Hospital, where the project manager is based (approval number: 2021/6, date: March 18, 2021)). Written informed consent was obtained from parents or guardians prior to participation in the study.

This study evaluated LPT infants, defined as those born between 34 weeks 0 days and 36 weeks 6 days of gestation, who were admitted to the NICU with respiratory distress and received surfactant treatment. A prestructured data form regarding surfactant use in LPT infants was prospectively completed by trained neonatologists. The records of infants from 16 NICUs were pooled and analyzed at the end of the study. The total number of LPT infants, as well as those with respiratory distress admitted to NICUs during the study period, was obtained from the participating centers. Neonates with major congenital anomalies and genetic syndromes were excluded from our analysis. However, patients with congenital diaphragmatic hernia were included in the study to demonstrate the use of ST in this population. The benefits of ST remain a topic of discussion for neonates with congenital diaphragmatic hernia who experience severe respiratory distress.

Clinical Data and Definitions

The documented antenatal and natal variables included gestational age (GA), birthweight (BW), sex, maternal age, multiple gestation, antenatal steroid administration (2 doses of 12 mg betamethasone given intramuscularly before delivery), maternal preeclampsia/eclampsia, diabetes, preterm prelabor rupture of membranes (PPROM), chorioamnionitis, systemic diseases, mode of delivery, Apgar score at 5 minutes, and the need for resuscitation in the delivery room.

Clinical data recorded for each neonate treated with surfactant included postnatal age (in hours of life) at admission, diagnosis, timing of surfactant administration, type of respiratory disease, type and dose of surfactant, number of surfactant doses, method of surfactant administration, and any complications. During neonatal follow-up, the duration of respiratory support (including noninvasive and invasive mechanical ventilation, as well as supplemental oxygen), occurrences of early and late-onset sepsis, administration of systemic antibiotics, and the presence of neonatal morbidities such as hemodynamically significant patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH) (according to Papile criteria),[17] and bronchopulmonary dysplasia (BPD) (defined as oxygen requirement at 36 weeks postmenstrual age)[18] were also recorded.

Management and Treatment

Treatment of LPT infants with respiratory distress and administration of surfactant were performed according to local protocols at all participating centers. The Silverman Andersen Respiratory Severity Score (RSS) was utilized to quantify respiratory distress in neonates.[19] This scoring system evaluates 5 parameters of respiratory effort, assigning a total score where a patient breathing comfortably scores "0" and a patient in severe respiratory distress scores "10." A score of 0-3 indicates no or mild respiratory distress, 4-6 indicates moderate respiratory distress, and 7-10 indicates significant respiratory distress. The type of respiratory support, fractional inspired oxygen concentration (FiO_2), mean airway pressure (MAP), positive end-expiratory pressure (PEEP), and arterial blood gas analysis just before and 6 hours after ST was recorded. The changes in FiO_2 and PEEP measured before and 6 hours after surfactant treatment were calculated. The timing of surfactant administration was classified as "early treatment" if it was administered before 2 hours of life and "late treatment" after the second hour of life.

The type of respiratory support, FiO_2, MAP, PEEP, and arterial blood gas analysis were recorded just before and 6 hours after ST. Changes in FiO_2 and PEEP measured before and 6 hours after ST were calculated. Surfactant administration was classified as "early treatment" if it occurred before 2 hours of life and as "late treatment" if it occurred after the second hour of life.

Outcome Measures

The primary outcome measure was the frequency of ST administered to LPT infants in our country. Secondary outcome measures included the indications for ST in LPT infants based on clinical findings and the threshold FiO_2 at which therapy was initiated.

Statistical Analysis

Statistical analyses were conducted using SPSS for Windows, Version 15.0. (SPSS Inc.; Chicago, IL, USA). Categorical data are presented as numbers (n) and percentages (%). The chi-square test was used to compare categorical variables. Non-parametric tests were used to analyze continuous variables. The distribution of numerical variables was investigated and compared between 2 groups by the Mann–Whitney *U*-test or independent samples *t*-test, where appropriate. The normal distribution test of continuous variables was performed using the Shapiro–Wilk test. The Wilcoxon signed-rank-sum test for pairwise comparisons was used. Normally distributed continuous data were presented as mean ± SD (minimum-maximum), and the nonnormally distributed continuous data were reported as median {interquartile range (IQR)}. Statistical significance was accepted if the *P*-value ≤ .05.

RESULTS

Patient Characteristics

In this study, data were collected from 16 NICUs. During the study period, a total of 3334 LPT infants were admitted to the participating NICUs, of which 1866 presented with respiratory distress. Among these, 288 LPT infants (15.4%) received ST. The rate of surfactant use in LPT infants varied significantly among the centers, ranging from 2.5% to 46.1% (Table 1). The number of patients eligible for the study and the number of infants included are illustrated in Figure 1.

Data from 288 LPT infants (135 females and 153 males) treated with surfactant were analyzed. The median time to NICU admission was 1 hour (IQR: 0-2 hours). The mean BW and GA for the total cohort were 2480.4 ± 381 g (range: 1535-3460 g) and 34.9 ± 0.8 weeks (range: 34-36 weeks), respectively. Of the total cohort, 98 infants (34%) were at 34 weeks GA, 102 infants (35.4%) were at 35 weeks GA, and 88 infants (30.5%) were at 36 weeks GA. Additionally, 22 infants (7.6%) were classified as small for gestational age (SGA). The rate of resuscitation in the delivery room was 35.4%, and the median Apgar score at 5 minutes was 8.

Antenatal steroids were administered to 9% of mothers. The rates of antenatal steroid administration were 16.3% (16/98) at 34 weeks, 5.8% (6/102) at 35 weeks, and 4.5% (4/88) at 36 weeks. The cesarean delivery rate was 82%, with cesarean sections (CSs) performed in only 29.5% of patients after the onset of labor. Additionally, 11% of mothers had preeclampsia, 6.6% had gestational diabetes, 13.8% had PPROM, and 5.2% had chorioamnionitis. Perinatal and natal baseline characteristics are presented in Table 2.

Table 1. Description of LPT Infants Admitted to NICUs During the Study Period

Participating NICUs	Number of LPT Infants Admitted to NICU	Number of LPT Infants with Respiratory Distress	Number of LPT Infants Received Surfactant (%)*
1	398	191	42 (21.9%)
2	154	34	11 (32.3%)
3	368	288	25 (8.6%)
4	367	250	10 (4%)
5	110	39	18 (46.1%)
6	83	28	11 (39.2%)
7	101	79	7 (8.8%)
8	161	122	47 (38.5%)
9	132	89	20 (22.4%)
10	143	32	10 (31.2%)
11	179	88	16 (18.1%)
12	125	55	10 (18.1%)
13	517	199	21 (10.5%)
14	78	52	20 (38.4%)
15	316	240	6 (2.5%)
16	102	45	9 (20%)

LPT, late preterm; NICU, neonatal intensive care unit.
*The ratio of LPT infants with respiratory distress who received ST.

Respiratory Morbidities of the Patients and Management

In this study, RDS was the most common indication for surfactant administration, affecting 158 infants (54.8%), followed by congenital pneumonia in 79 infants (27.4%) and TTN in 32 infants (11.1%). Notably, the proportion of surfactant treatment in non-RDS patients was 45.2%.

The median time for surfactant administration was 4 hours of life (IQR: 2-10). In this cohort, 113 infants (39.2%) received surfactant within the first 2 hours of life (early treatment group). The late treatment group consisted of 175 infants (60.7%), with 76 receiving surfactant between 2 and 6 hours of life and 99 receiving it after the sixth hour. Among those with RDS, 83 infants (73.4%) were treated early. In contrast, 72.2% (n = 57) of patients with congenital pneumonia received surfactant late.

Natural surfactant preparations were administered to all patients. Beractant (Survanta®, Abbott Laboratories, USA, 4 mL/kg) was used in 159 infants, Poractant alfa (Curosurf, Chiesi

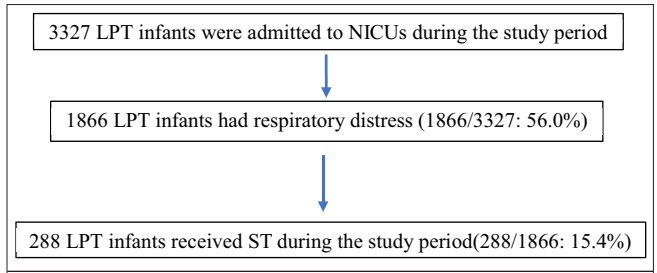

Figure 1. Flow chart of patients included in the study.

Table 2. Perinatal and Natal Characteristics of the Study Population

Characteristics	
Mothers	N = 288
Antenatal steroids, 2 doses, n (%)	26 (9%)
Antenatal steroids, 1 dose, n (%)	31 (10.7%)
Cesarean section (CS), n (%)	237 (82.2%)
Urgent CS	115 (48.5%)
After labor	70 (29.5%)
Elective	52 (21.9 %)
Pregnancy associated conditions, n (%)	
Preeclampsia	32 (11.1%)
Gestational diabetes	18 (6.2%)
PPROM	40 (13.8%)
Chorioamnionitis	15 (5.2%)
Infants	
Gestational age	34.9 ± 0.8 (34-36)
34 weeks, n (%)	98 (34%)
35 weeks, n (%)	102 (35.4%)
36 weeks, n (%)	88 (30.5%)
Birth weight (g)	2480.4 ± 381 g (1535-3460)
Sex F/M	135/153
Multiple pregnancy, n (%)	24 (8.3%)
Small for gestation (SGA), n (%)	22 (7.6%)
Apgar score (fifth minute)*	7.64 ± 1 (3-9)
Resuscitation details	
Positive pressure ventilation, n (%)	69 (23.9)
Intubation, n (%)	30 (10.4)
Chest compression/adrenaline, n (%)	3 (1.04)
Perinatal asphyxia, n (%)	13 (4.5%)

F/M, female/male; PPROM, premature prelabor rupture of membranes; SGA, small for gestation.

Table 3. Clinical Characteristics of the Study Population

Respiratory morbidity, n (%)	
RDS	158 (54.8%)
Congenital pneumonia	79 (27.4%)
TTN	32 (11.1%)
Meconium aspiration syndrome	12 (4.1%)
Congenital diaphragmatic hernia	7 (2.4%)
Postnatal time admission to NICU, hours	1 (0-2)
Respiratory Severity Score before surfactant administration, n (%)	
0-3 points no/mild respiratory distress	63 (21.8%)
4-6 points: moderate respiratory distress	130 (45.1%)
7-10 points: significant respiratory distress	95 (32.9%)
Respiratory support before surfactant administration, n (%)	
Non-invasive mechanical ventilation	
n CPAP	60 (20.8%)
NIPPV	99 (34.3%)
Invasive mechanical ventilation	
SIMV	83 (28.8%)
Assist control	35 (12.1%)
HFOV	11 (3.8%)
Blood gas analysis before surfactant administration, n (%)	
Acidosis (pH <7.2)	54 (18.7%)
Hypercarbia ($PaCO_2$ >50 mm Hg)	98 (34%)
Time of surfactant administration, hours	4 (2-10)
Early treatment group, n (%)	113 (39.2%)
Late treatment group, n (%)	175 (60.7%)
Method of administration of surfactant, n (%)	
Endotracheal intubation	180 (62.5%)
INSURE	57 (19.7%)
LISA	51 (17.7%)
Dosing of surfactant	
≥2 doses	76 (26.3%)
Threshold FiO_2 to administer surfactant*	45 (40-60)
Duration of non-invasive mechanical ventilation (days)*	3 (2-4)
Duration of invasive mechanical ventilation (days)*	2 (0-4)
Duration of oxygen treatment (days)*	3 (2-5)
Neonatal morbidities during hospitalization, n (%)	
Persistant pulmonary hypertension	11 (3.8%)
Culture-positive sepsis	11 (3.8%)
PDA requiring treatment	13 (4.5%)
ARDS	3 (1.04%)
Complications, n (%)	
Pneumothorax	12 (4.1%)
Endotracheal tube complications	9 (3.1%)
Pulmonary hemorrage	4 (1.3%)
Duration of hospitalization*	12 (9-18)
Mortality, n (%)	10 (3.4%)

Values are presented as mean ± SD (minimum-maximum), for continuous variables according to normality. ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; NICU, neonatal intensive care unit; NIPPV, nasal intermittent positive pressure ventilation; RDS, respiratory distress syndrome; SIMV, synchronized intermittent mandatory ventilation; TTN, transient tachypnea of the newborn; INSURE, intubation, surfactant administration, extubation; LISA, less-invasive surfactant administration; PDA, patent ductus arteriosus.
*Nonnormally distributed continuous data were reported as median [interquartile range (IQR)].

Pharmaceuticals, Italy, 2.5 mL/kg) in 116 infants, and Calfactant (Infasurf; ONY, Inc., Amherst, NY) in 13 infants. Most participants (95%) received the manufacturer's recommended dose. Regarding surfactant dosing, 76 infants received 2 or more doses. The most common indications for surfactant treatment requiring 2 or more doses were RDS (n = 37) and congenital pneumonia (n = 31), followed by TTN (n = 5) and MAS (n = 3).

The most common type of respiratory support immediately before surfactant administration was non-invasive ventilation, with nasal intermittent positive pressure ventilation (NIPPV) used in 34.3% of cases and nasal continuous positive airway pressure (nCPAP) in 20.8%. However, the most frequent method of surfactant administration was invasive, accounting for 62.5% of cases. Intubation followed by surfactant administration and extubation (INSURE) was employed in 20.1% of infants, while less-invasive surfactant administration (LISA) was used in 17.3%.

In this study, the most common complications following surfactant treatment included pneumothorax in 12 patients and endotracheal tube obstruction in 9 patients. The majority of infants (92.4%) received antibiotics upon admission. Hemodynamically significant PDA requiring medical treatment was identified in 13 cases (4.5%). Additionally, 11 infants (3.8%) developed culture-proven sepsis. Persistent pulmonary hypertension (PPH),

Table 4. Oxygen and Pressure Requirements of LPT Infants Before and After ST

	Before ST	After ST 6 Hours	*P*
FiO_2	45 (40-60)	30 (25-40)	<.001
PEEP	6 (6-6.5)	5 (5-5.5)	<.001

FiO_2, fractional inspired oxygen concentration; PEEP, positive-end expiratory pressure; ST, surfactant therapy.

managed with inhaled nitric oxide (iNO) and ST, was diagnosed in 11 patients (3.8%). Acute respiratory distress syndrome due to congenital pneumonia and perinatal asphyxia occurred in 3 patients (1%). The clinical characteristics of the study population are presented in Table 3.

Overall, the mortality rate in the study was 3.4% (n = 10). Among those who died, 5 infants had congenital pneumonia, 4 had RDS, and one had congenital diaphragmatic hernia. The clinical features of the infants who had fatal outcomes are presented in Table 6.

The median FiO_2 and positive end-expiratory pressure (PEEP) just before surfactant administration were 45% and 6 mmHg, respectively. As expected, the infants' oxygen and pressure requirements decreased following surfactant treatment (Table 4).

When comparing the clinical characteristics of infants based on the timing of surfactant administration, those in the early treated group had a lower birth weight (*P* = .004) and a higher need for resuscitation in the delivery room (*P* = .000).

Respiratory severity before surfactant administration was significantly higher in the early-treated group (*P* = .002). While the rate of invasive respiratory support and the FiO_2 threshold for surfactant administration were both higher in the early-treated group, the differences were not statistically significant. In contrast, when evaluating the clinical characteristics of infants in the late ST group, a greater number of infants with congenital pneumonia received late surfactant (*P* = .000). Although the rate of pneumothorax was higher in this group, it did not reach statistical significance, and the mortality rate was also higher among infants receiving late surfactant treatment (*P* = .02) (Table 5).

Table 5. Comparison of Clinical Characteristics of LPT Infants: A Comparative Analysis of Early vs. Late Surfactant Administration

	Early ST n = 113	Late ST n = 175	*P*
Gestational age (weeks)*	34.7 ± 0.9	34.7 ± 0.7	.142
Birth weight (g)*	2487 ± 354	2510 ± 332	.004
Resuscitation at delivery room, n (%)	54 (47.7%)	47 (26.8%)	<.001
Apgar score (fifth minute)*	7(6-8)	8 (7-8)	.384
Perinatal asphyxia, n (%)	7(6.1%)	6 (3.4%)	.601
NICU admission time after birth, h**	1(0-1)	1 (1-2)	.000
RDS, n (%)	83 (73.4%)	75 (42.8%)	.073
Congenital pneumonia, n (%)	18 (15.9%)	61 (34.8%)	<.001
Respiratory Severity Score before surfactant administration**	6 (1-9)	5 (2-7)	.002
Invasive respiratory support before surfactant administration, n (%)	68 (60.1%)	77 (44%)	.484
Threshold FiO_2 to administer surfactant**	40 (40-45)	50 (40-60)	<.001
≥2 doses, n (%)	24 (21.2%)	50 (28.5%)	.296
Pneumothorax, n (%)	3 (2.6%)	6(3.4%)	.745
Duration of hospitalization**	11.5 (8-17)	13 (10-18)	.212
Mortality, n (%)	8 (7%)	2 (1.1%)	.02

NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; ST, surfactant therapy. *Values are presented as mean ± SD (minimum-maximum), for continuous variables according to normality. **Nonnormally distributed continuous data were reported as median [interquartile range (IQR)].

DISCUSSION

We conducted the first multicenter study on surfactant treatment in LPT infants in our country. Our results indicate that, despite advances in obstetric care, LPT infants continue to be at risk for respiratory failure that necessitates surfactant support. Late preterm neonates are at a higher risk of neonatal morbidity and mortality compared to term neonates, particularly due to respiratory issues. This vulnerability is often attributed to their physiological immaturity, including underdeveloped lungs and insufficient surfactant production, which can lead to complications such as RDS and other respiratory disorders.

Table 6. The Clinical Features of the Infants Who Had Fatal Outcomes

	Diagnosis	Respiratory Support Before ST	Time of ST	Dosing of Surfactant	Cause of Death	Death Time in Days
1	RDS	IMV	ET	2	Persistent pulmonary hypertension	2
2	RDS	IMV	ET	2	Persistent pulmonary hypertension	2
3	RDS	IMV	ET	3	ARDS	3
4	RDS	IMV		2	Pulmonary hemorrage	6
5	Congenital pneumonia	IMV	LT	2	Late-onset sepsis	15
6	Congenital pneumonia	IMV	LT	2	Late-onset sepsis	25
7	Congenital pneumonia	IMV	ET	2	Pneumothorax	2
8	Congenital pneumonia	IMV	LT	3	ARDS	7
9	Congenital pneumonia	IMV	ET	1	Pneumothorax	2
10	Congenital diaphragmatic hernia	IMV	LT	1	Persistent pulmonary hypertension	2

ET, early treatment; IMV, invasive mechanical ventilation; LT, late treatment; RDS, respiratory distress syndrome; ST, surfactant therapy.

Surfactant therapy significantly improves survival rates and reduces respiratory-related morbidities in neonates with RDS. The use of exogenous surfactant is widely recommended in guidelines for the treatment of RDS in preterm infants.[20-22] However, the efficacy of surfactant replacement therapy for other respiratory disorders remains controversial, and to date, there are no evidence-based recommendations for its use in LPT infants.[16] An ongoing trial, SURFON (SURFactant Or Not), is investigating the early use of surfactant in LPT infants, which is expected to shed light on this issue.[23] Recent reports from the United Kingdom and Belgium indicate that the thresholds for determining the need for surfactant replacement in both LPT and term infants vary widely.[21,24] The results of our study are consistent with findings from other countries, indicating that the use of ST in LPT infants with respiratory distress varies significantly among different centers.

In our study, 15.4% of LPT infants with respiratory distress were treated with surfactant. Similarly, an observational study from Italy reported a surfactant use rate of 16.2% in LPT infants with respiratory distress.[13] In a recent meta-analysis evaluating the efficacy of surfactant treatment in LPT and term infants with RDS, it was found that 46% of infants received ST.[16] According to the results of this study, the ratio of surfactant use in LPT infants with respiratory distress ranged between 2.5% and 46.1%. This meta-analysis also suggests that this wide range is largely due to the absence of clear criteria and inconsistencies in definitions. Consequently, this variability is reflected in our own results.

A lower risk of mortality, air leakage, persistent pulmonary hypertension of the newborn (PPHN), and reduced duration of respiratory support in LPT and term infants with RDS have also been reported.[16] Similarly, in our study, oxygen demand and airway pressure decreased within 6 hours after ST in LPT infants, with 28.2% of infants on invasive mechanical ventilation successfully extubated after this period.

For preterm infants born at less than 32 weeks of gestation, international guidelines recommend early ST when the FiO_2 exceeds 0.30.[8] However, no specific FiO_2 threshold for ST has been established for LPT and term infants. Previous studies have reported a generally higher FiO_2 requirement in surfactant-treated LPT infants.[6] Consistent with these findings, the median FiO_2 threshold just before ST in our cohort was 45%.

Notably, according to the results of this study, 63 patients (21.8%) who received surfactant treatment had a RSS of 0-3 points, indicating no or mild respiratory distress. This finding suggests that, in addition to the FiO_2 level, factors such as physical examination findings and lung ultrasound scores should be incorporated into the diagnostic criteria to determine whether surfactant administration is warranted for LPT infants with respiratory distress.

Due to their increased respiratory capacity and larger lung surfactant pool, LPT infants can remain stable on non-invasive respiratory support for longer periods during the first hours of life. In this study, the most common type of respiratory support prior to ST was non-invasive ventilation. The median timing for surfactant administration was 4 hours, with 60.7% of infants receiving treatment after 2 hours of life. Similarly, Surmeli et al reported a "late" median timing for ST in LPT infants,[25] which may reflect variations in treatment protocols across different centers.

The majority of participants in this cohort preferred the invasive method of surfactant administration. In contrast, a Belgian study[24] found that the less invasive method was the most commonly used. Currently, it appears that non-invasive methods of surfactant administration may be the most appropriate treatment approach, given the ongoing developments in neonatal care practices.

In our study, RDS was identified as the most common indication for surfactant administration in LPT infants. The high CS rate of 82.2%, coupled with only 29.5% of these procedures being performed after the onset of labor, may contribute to the elevated rates of RDS observed in this cohort. Additionally, the low rate of antenatal steroid administration further poses a risk factor for the development of RDS.

There are varying recommendations regarding antenatal steroid administration for LPT infants. The European Consensus Guidelines on the Management of RDS do not advocate for antenatal steroid administration in this population.[8] In contrast, the American College of Obstetricians and Gynecologists recommends administering a single course of betamethasone to pregnant women between 34 0/7 and 36 6/7 weeks of gestation who are at risk of preterm birth within the next 7 days.[26] Consequently, policies in perinatology units differ regarding the administration of antenatal steroids during this gestational period.

Surfactant therapy is generally considered for infants with congenital pneumonia, as this condition often leads to surfactant deficiency or dysfunction.[10,27,28] In our cohort, congenital pneumonia was the second most common indication for surfactant requirement. A single-center study from Türkiye also found that sepsis/pneumonia was the most frequent indication for ST in neonatal respiratory disorders, following RDS.[29] In our study, the majority of infants diagnosed with congenital pneumonia received surfactant after the second hour of life. Similarly, previous research has reported significantly later timing for ST in LPT infants with non-RDS lung disease.[6,27]

This prospective multicenter study demonstrates that surfactant is commonly used in the treatment of LPT infants with respiratory distress. To the best of our knowledge, this is the first prospective study in Türkiye to investigate the clinical characteristics of LPT infants who received ST. The administration of surfactant and the management of LPT infants with respiratory distress were conducted in accordance with local protocols across all centers, reflecting general clinical practice. These factors represent significant strengths of our study.

Our report is an observational study that has several limitations. Notably, we did not include all LPT infants with respiratory distress, resulting in the absence of a control group of patients who did not receive ST. Additionally, there were diagnostic limitations, such as the lack of evaluation of X-ray and lung ultrasound results from the participating NICUs. Furthermore, we were unable to assess the outcomes of respiratory distress across all LPT infants in the study.

Nevertheless, this multicenter cohort study included 16 NICUs, which enabled us to prospectively gather data on surfactant use in LPT infants with respiratory distress. These participating NICUs are high-volume centers, providing valuable insights into current practices within our country. Our findings indicate that surfactant is widely utilized in LPT infants for treating respiratory morbidities beyond just RDS.

Treatment with surfactant is associated with a reduced risk of invasive ventilation. However, follow-up data from clinics indicate disparities in the treatment approaches for LPT infants with respiratory distress. There are uncertainties concerning the appropriate threshold for FiO_2, the assessment of respiratory distress severity, the type of respiratory support needed when administering surfactant, and the optimal timing and dosing of ST in this population.

These results indicate that predicting which infants will derive the most benefit from ST while on non-invasive or mechanical ventilation is challenging. Therefore, developing an algorithm to help identify LPT infants who are most likely to benefit from ST could be highly beneficial.

In conclusion, ST is applied with significant variability in LPT infants experiencing respiratory distress. Respiratory issues in LPT infants, other than RDS, such as congenital pneumonia and TTN, are also commonly treated with surfactant. The findings of this study underline the urgent need for standardized protocols to guide best practices regarding ST in this population. To establish a consensus on the use of surfactant in LPT infants, randomized controlled multicenter trials are essential.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Etlik Zübeyde Hanım Women's Health and Research Hospital (approval no.: 6/2021, date: March 18, 2021).

Informed Consent: Written informed consent was obtained from the patients' parents or guardians who agreed to take part in the study.

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