DOI: 10.5350/SEMB.20170629124658

# Early Respiratory Outcomes Of Late Preterm Infants

**Sinan Uslu[1], Umut Zubarioglu[1], Ali Bulbul[1]**

**ABSTRACT:**

Early respiratory outcomes of late preterm infants

Late preterm infants (LPI) are defined as delivery between $34^{0/7}$ - $36^{6/7}$ weeks of gestational age. In recent years, the number of LPI has risen according to preterm births especially in developed countries. Even though the LPI are premature, they have been considered as mature infants. Respiratory problems are the most common consequences of LPI. Therefore it is important to understand respiratory problems of LPI clearly. This review presents the updated data of early respiratory problems of LPI.

**Keywords:** Early period, late preterm, newborn, respiratory problems

**ÖZET:**

Geç preterm bebeklerde erken dönem solunum problemleri

Gebelik haftası $34^{0/7}$ - $36^{6/7}$ arasında olan bebekler geç preterm bebek olarak tanımlanmaktadır. Son yıllarda özellikle gelişmiş ülkelerde geç preterm bebeklerin sayısı artan preterm doğumlarla birlikte yükselme göstermiştir. Geç preterm bebekler her ne kadar prematüre olsalar da zamanında doğmuş gibi ele alınmıştır. Solunumsal problemler geç preterm bebeklerin en sık ortaya çıkan sorunudur. Bu nedenle geç preterm bebeklerde solunum problemlerinin iyi anlaşılır olması çok önemlidir. Bu makalede geç preterm bebeklerin erken solunumsal problemleri yeni literatür bilgileri eşliğinde ele alınmaktadır.

**Anahtar kelimeler:** Erken dönem, geç preterm, yenidoğan, solunum problemleri

**Ş.E.E.A.H. Tıp Bülteni 2017;51(3):184-90**

[1]Sisli Hamidiye Etfal Training and Research Hospital, Department of Neonatology, Istanbul - Turkey

Address reprint requests to / Yazışma Adresi:
Sinan Uslu,
Sisli Hamidiye Etfal Training and Research Hospital, Department of Neonatology, Istanbul - Turkey

E-mail / E-posta:
sinanuslumd@hotmail.com

Date of receipt / Geliş tarihi:
May 8, 2017 / 8 Mayıs 2017

Date of acceptance / Kabul tarihi:
June 29, 2017 / 29 Haziran 2017

## INTRODUCTION

Late preterm delivery is a strategic term used in the definition of infants born at $34^{0/7}$ - $36^{6/7}$ gestational week or between the $239^{th}$-$259^{th}$ postconceptional days. The consequences of these infants, referred to as "near-term" previously, were discussed by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) and in June 2015, they were described as "late preterm infant (LPI)" for the first time following a workshop conducted by the National Institute of Child Health and Human Development (NICHHD) (1,2). In this study, "late preterm" was used in order to raise awareness of the specific needs of late preterms, to emphasize the need for research, to promote the development and adoption of evidence-based guidelines, and to provide resources to nurses and other health professionals.

The prevalence of cesarean delivery, intrauterine growth retardation and maternal problems are higher in LPI, who have been considered as term babies for a long period. This leads not only to maturation deficiency but also to many consequences triggered by perinatal problems. This necessitates the proper monitoring and management of a number of early neonatal problems (3-5).

When evaluated cumulatively, late preterms constitute approximately 75% of premature babies and approximately 9% of all deliveries (6). Late preterm infants have a higher risk of early mortality and morbidity (nutritional difficulties, hypothermia, hypoglycemia, hyperbilirubinemia, sepsis, etc.) than term infants (7,8). When it is thought that 30% of all

late preterm infants are hospitalized and approximately 50-80% of these babies are treated for respiratory problems, it is of utmost importance that the infant's respiratory system is managed on rational conditions. In this article early respiratory problems of late preterm infants will be addressed in the context of current literature information.

Reasons for the high number of late preterm deliveries and medical problems

Factors leading to a high number of late preterm deliveries directly or indirectly trigger the number of medical problems to be higher (9).

- Increase in medical interventions
- Increase in the number of multiple births
- Use of assisted reproduction techniques and late age maternity
- Incorrect gestational age estimates
- Assuming fetal maturity at 34 weeks of gestation
- Increase in elective cesarean section rates
- Fear of vaginal birth complications
- Changes in medical thresholds for caesarean delivery

### Lung Development and Late Preterm Labor

Late premature infants are born at late saccular or early alveolar stages of development, ie, at the third trimester of pregnancy, when the surfactant and antioxidant systems are still relatively immature (or are still developing). Capillary proliferation and saccular (sac) formation occurs in the saccular phase (24-36 weeks), terminal bronchioles become more branched and terminal branches develop to form primitive alveolar bundles. In the early alveolar phase (36 weeks-2 years), number of alveoles and bronchi increase and alveoli develop. In the lungs surrounded by capillaries and showing increase in surfactant production, the lung volume and the surface area increase as term period approaches (10). Respiratory problems such as respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), pulmonary hypertension (PH), pneumonia, apnea, respiratory failure and mechanical ventilation need are more common in infants born in these stages than term babies (11). These problems are known to be due to immature lung structure, disturbances in the clearance of fetal lung fluid, inadequate amount and structural disturbance of surfactant.

Histological studies have shown that late preterm labor is associated with structural changes in the lungs, such as bronchial muscle, collagen and elastin increase (12). It is suggested that early exposures to relatively high oxygen pressures in postnatal life and many extrauterine factors probably contribute to these effects. Since the expression of epithelial sodium channels (ENaC), which is regulated developmentally in intrauterine life, is insufficient, fetal lung fluid clearance is disturbed. The functional results of late preterm labor can be summarized as follows; functional residual capacity is difficult to protect, is vulnerable to airway collapses, airway resistance is high (13).

The results of late saccular period and early stage of alveolar phase in LPI are presented in Table-1. Factors affecting lung development in LPI are shown in Figure-1.

### Respiratory Distress in Late Preterm and Epidemiology

Many studies to date have shown that the respiratory distress symptoms and related early morbidities in LPI, respiratory support and surfactant treatment need are much higher than that of term infants (13). Respiratory problems occur more frequently and severely as gestational week decreases (6).

In a study of 35989746 live births and 21884 respiratory distress syndrome (RDS) -related deaths in the United States during the nine-year period (1987-1995) in the United States during the period when the definition "late preterm" has not yet been used, 78% of late preterm deaths were reported to be related with respiratory problems, and deaths due to RDS were reported to be 10 times higher than those of term infants (14). It was emphasized in the AWHONN workshop, that late preterms have respiratory problems 10 times more (1).

It has been shown that in a large series study conducted during a seven-year period (2002-2008), in 19 centers in the USA, with 233844 live births and 19344 LPI, logistic regression analysis revealed that respiratory risks multiplied as gestational week

**Table-1:** Results of features related to late saccular stage and early stage of alveolar stage in late preterm infants

| Features of late saccular and early alveolar stages | Results in late preterm infants |
|---|---|
| Amount of surfactant is increased especially in the last two weeks before birth. | Surfactant deficiency |
| Increasing fetal respiratory movements as the time of birth approaches are related to the development and maturation of respiratory muscles and a pressure gradient occurs between the lungs and the amniotic fluid. | Inadequacy of coordination of respiratory muscles |
| Gradual reduction in lung wall thickness and simultaneous increase in air space surface area | Parenchymal elasticity and functional residual capacity can not be maintained, airway resistance is lost |
| A period of development of epithelial sodium channels (ENaC) | Lung fluid clearance is delayed due to low ENaC expression |

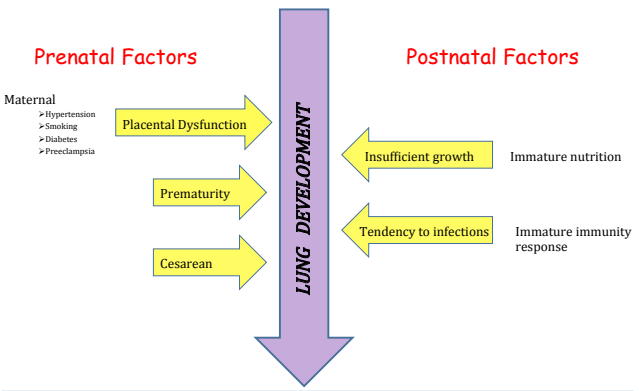


**Figure-1:** Factors affecting lung development in late preterm infants

decreased. Compared to a term infant, it was shown that preterm infants at 34$^{th}$ gestational week had 40 times more RDS risk, 15 times more chance of TTN, 10.5 times more respiratory failure, 14 times more risk of mechanical ventilation support and about 59 times more surfactant application frequency (6).

Again in a meta-analysis published in 2011, the incidences of mechanical ventilation (RR 4.9; 95% CI, 2.8-8.6), RDS (RR 17.3, 95% CI, 9.8-30.6), TTN (RR 7.5; 95% CI, 5.0-11.2), PPH (RR 4.9; %95 CI, 3.8-6.3), apnea (RR 15.7; %95 CI, 11.8-20.9), pneumothorax (RR 3.4; 95% CI, 1.8-6.4) and pneumonia (RR 3.5; 95% CI, 1.4-8.9) were emphasized as higher (15). In this meta-analysis performed with a 10-year period, including 29375675 live births and 2368471 LPI in 22 studies, in LPI, the oxygen need was found to be 24.4 times, RDS was 17.6 times, surfactant use was 16.6 times, apnea was 15.7 times, TTN was 7.5 times and frequency of PPH was 4.9 times higher.

The incidence of respiratory distress is reported to be 10.5%-28.9% in LPI and 1.13%-4.2% in term infants (16). The frequency of respiratory distress in studies performed with LPI from our country has been presented as 46.5% by Çelik et al. and as 76.7% by Atasay et al. (17,18). Binarbaşı et al. (19) found in their study that 20% of the infants had TTN, 5.5% had RDS, 2.7% had pneumonia and 3.6% had apnea in LPI, while 9.5% of the infants were in need of mechanical ventilation. In term infants, TTN was found in 1.5% while other respiratory problems were not detected. In another study, Kalyoncu et al. (20) detected respiratory distress in 44.8% of LPI, TTN in 49.6%, RDS in 20.5% and pneumonia in 13.3%. Bulut et al. (7) reported in their study in which they evaluated late preterm, that the prevalence of respiratory distress was 34.2%, that of pneumonia was 4.4% and that of late preterm deaths was 62.7% of 1179 babies hospitalized in 6741 LPI.

### Mechanisms Leading to Respiratory Problems in Late Preterm Infants

Mechanisms causing TTN, RDS, pneumonia, PPH, apnea, respiratory distress, mechanical ventilation and need of surfactant use in LPI are factors that affect each other as in a cascade.

### Delayed Clearance of Fetal Lung Fluid

In lung fluid clearance, thoracoabdominal compression and Starling forces have minimal effect. The first main step is the passive Na movement through the apical membrane from the lumen into

the cell by the permeable sodium (Na) ion channels, while in the second step, Na passes actively through the basolateral membrane into the cell, dragging the water with itself. Amiloride-sensitive epithelial sodium channels regulating the first step are the determinant of this process. ENaC expression increases at 36-37$^{th}$ weeks. This means that ENaC activity in LPI is not adequate (21).

In addition to increasing glucocorticoids and catecholamines towards the term period, Na transport proteins secreted via ENaC expression enable lung fluid clearance to occur. However, removal of lung fluid in te LPI who was not able to experience this hormonal regimen arises a problem (22).

On the other hand, a significant part of the labors of LPI to be performed with cesarean section, and the fact that these infants, not to neither have adequate hormone response, nor their thoracic cage not to have the compliance that will provide the effect of thoracoabdominal compression, may disturb lung clearance. Taking all factors into consideration, the risk of TTN is increasing in LPI.

### Disturbance in Lung Mechanics

Recent studies have also found abnormalities in the arrangements of lung mechanics of LPI. In their study, McEvoy et al. found that in the evaluation of 31 term and late preterm infants during the first 72 hours of their lives, the compliance was low, the tidal volume was low, and the resistance was high when compared with respect to tidal respiratory parameters and passive respiratory mechanics (23). Functional residual capacity in late preterm infants is low.

### Surfactant Deficiency

Although surfactant begins to be synthesized from type II pneumocytes from the 22$^{nd}$ week of gestation, it reaches to the significant level at the 36$^{th}$ week, although present in the late preterm period. The content phosphatidylcholine, which is found in the basic structure of the surfactant and constitutes 80% of the phospholipids, increases during the last trimester. On the other hand, phosphatidylglycerol level is also inadequate in late preterm infants and increases the risk and severity of RDS by causing impaired surfactant function. The uterine contractions that determine the release of surfactant into alveoli from type II pneumocytes, hormonal changes, and the processes that trigger the onset of respiration can not occur in late preterm infants (24). As a result, for infants born in late preterm period, surfactant deficiency may be mentioned in terms of both the amount and the content.

### Tendency to Infection and Pneumonia

Causes that trigger preterm labor and especially fetal infections cause pulmonary infections and sepsis in preterm infants. increased secondary pulmonary infection risk is added to the mechanism of immature lung structure of late preterm infants with especially high risk of mechanical ventilation need (25).

### Apnea and Impairment in Respiratory Control

In LPI, apnea frequency is increased due to the inadequate maturation of the brain stem that provides respiratory control. Neurological proliferation, migration, morphological and neurochemical differentiation, neurotransmitter receptors, dendritic arborization, synaptogenesis, axonal development and myelination maturation of brain stem in the last period of pregnancy are not experienced in late preterms, therefore, respiratory control may be impaired.

In preterm babies, the respiratory rate decreases after transient hyperventilation response to hypoxia. In addition, the tendency to bradycardia during sleep in late preterms who have parasympathetic system yet not matured, may lead to problems to be complicated (25).

### Disturbance in Pulmonary Vascular Adaptation

Endothelial nitric oxide synthase (eNOS) and soluble guanylate cyclase (sGC) increase as gestational age increases. As a result, the increase in NO production and sGC activity increases the intracellular calcium concentration, raising cyclic guanosine monophosphate (cGMP) concentrations, which lead to vasodilation (26). On the other hand,

estrogen concentration increases and COX-1 is regulated in the last period of pregnancy. As a result, prostacyclin (PGI) synthesis is increased, which results in increase of intracellular cyclic adenosine monophosphate (cAMP) levels that cause vasodilatation by adenylate cyclase (27).

In late preterms that are born before the basic differentiation of the NO and PGI pathways, which play a key role in particularly pulmonary vasodilatation, more frequent problems occur in pulmonary adaptation. This increases the incidence of persistant pulmonary hypertension in late preterms.

### Approach and Precautions to Respiratory Problems of Late Preterm Infants

Approaches to prevent respiratory problems of late preterm infants require a multidirectional and multidisciplinary approach.

### Prevention of Late Preterm Births and Taking Under Control of Deliveries by Cesarean Section

The American College of Obstetricians and Gynecologists (ACOG) certainly does definitely not recommend vaginal or planned cesarean delivery induced before 39$^{th}$ gestational weeks unless a clear medical indication is established (28). The USA health office and the March of Dimes demonstrated this approach before the 39$^{th}$ week of gestation and showed an approach to reduce preterm birth by 8% within two years.

### Antenatal Steroids

Antenatal steroids lead to structural and biochemical changes that increase both lung mechanics (maximal lung volume) and gas exchange by accelerating the development of type 1 and type 2 pneumocytes.

The induction of Type 2 pneumocytes (inducing the production of the enzymes necessary for making surfactant proteins and phospholipids) increase the production of surfactant.

The induction of pulmonary beta-receptors (stimulating surfactant release and alveolar fluid absorption, inducing fetal lung antioxidant enzymes, regulating ENaC gene expression) increases surfactant production and fetal lung fluid clearance, while oxygen damage is reduced.

In the meta-analysis of 2016, the efficacy of antenatal steroid administration in late preterm infants was evaluated. It was emphasized that the frequency of severe RDS (1.4% vs. 2.3%, RR 0.60, 95% CI 0.24-0.98) and TTN (8.2% vs 10.9%, RR 0.72, 95% CI 0.50-0.98) significantly decreased, there was no change in mechanical ventilation requirement and in all types of RDS, and in newborns, the frequency of hypoglycaemia increased (29).

In a study that evaluated the efficacy of betamethasone twice a day with 24 hours of interval in high risk of birth at late preterm period; it was found that the need for respiratory support treatment (especially CPAP and HFNC) decreased statistically, severe respiratory disorder, TTN, BPD frequency and the need for surfactant decreased, but in late preterms, the risk of hypoglycemia increased (30).

The proposal of some important professional organizations in this regard is as follows:

The American College of Obstetricians and Gynecologists (ACOG); recommends betamethasone administration under certain conditions in late preterm single pregnancies with inevitable preterm birth within 7 days. The antenatal corticosteroid (ACS) should not be applied to the pregnancies with chorioamnionitis. Tocolysis should not be used for postponement of labor in order to save time for ACS application in pregnancies with premature birth symptoms. If the pregnant woman has already received ACS, it should not be administered. Newborns should be monitored for hypoglycemia (31).

The Society for Maternal-Fetal Medicine (SMFM) recommends the application of 2 doses of betamethasone to the pregnancies at 34$^{0/7}$ - 36$^{6/7}$ gestational weeks with premature birth risk within 7 days under the following conditions: Tocolysis should not be performed to administer steroid in pregnancies with early onset labor symptoms, and cervical dilatation of ≥3 cm or effusion ≥75%, and until a definitive birth plan is made in pregnancies with possible medical indications for premature birth, steroids should not be administered (32).

There are two important handicaps of antenatal steroid application. Brain development and growth through cell division occur especially in the late saccular stage, and this development can be inhibited by the application of corticosteroids. Postnatal systemic glucocorticoid therapy in newborns contributes to neurodevelopmental disorders, especially as cerebral palsy (29).

### Respiratory Syncytial Virus Prophylaxis

Although not generally accepted, non-randomized studies suggest that RSV prophylaxis is beneficial in premature infants up to the 35th gestational week. Italian FLIP study (Infections associated with RSV and factors affecting hospital admission among premature infants) defined 7 variable factors that affect admission to the hospital related to RSV in infants born during the 33rd-35th weeks: gender, birth weight, being in the first 10 weeks of life during the RSV season, breastfeeding less than 2 months, older sibling more than 2 years old, family history of atopy or wheeze. It is stated that RSV prophylaxis in infants with risk factors may be effective in decreasing hospitalization due to RSV infection in the first year and the issue is still controversial (33).

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