Early and Late Respiratory Complications of Late Prematurity

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Max 25 words; a brief insight into what the article is about; it should entice the reader to go

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[Example:]

Dr. Smith and Dr. Jones conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Ms. Noble and Prof. Eccleston collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Piper designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

# Abstract:

**Background**: Late preterm (LP) infants, defined as infants born at 34 to 36 6/7 weeks gestational age, experience fewer severe complications during infancy and fewer long term neurologic complications than those born before 34 weeks gestation. However, these infants are still not physiologically and developmentally mature, putting them at increased risk of developing early complications (after birth) and late complications (in childhood), especially respiratory complications.

This objective of this study was to assess whether LP infants are at greater risk than term infants of developing early and/or late respiratory complications, by collecting and reviewing postnatal discharge papers, performing lung function testing (LFT) at age 5-7 years, and completing a survey at this age.

**Methods**: The study and control population consisted of children born at term or as LP infants in the years 2006-2008 at the French Hospital in Nazareth. We collected demographic information and perinatal medical records of the children, some of whom then performed lung function testing and/or filled out a questionnaire (by the parents).

**Results**: There were no significant differences in demographic and environmental variables between the two groups; however, significantly worse outcomes were found in the preterm group in terms of both perinatal and neonatal course as well as early and late respiratory complications. LP infants suffered from more respiratory complications, greater need for oxygen, and longer postnatal hospital stays compared to term infants. Additionally, LP infants were more often treated with inhalations, diagnosed with asthma by physicians, and hospitalized with respiratory problems. Lung function testing, *~~including forced one-second expiratory volume at one second (FEV~~~~1~~~~), forced vital capacity (FVC), and forced expiratory flows at 25-75% (FEF~~~~25-75~~~~), calculated as percentage of predicted values, were significantly lowered in LP infants compared to term infants~~* revealed significantly lower flow rates and lung capacity volumes in LP infants compared to term infants.

**Conclusions**: Our data shows that late preterm infants experience higher rates of early and late respiratory complications compared to term infants, indicating that LP infants cannot be treated as term infants.

# Introduction

About 9% of all infants and 75% of all preterm infants are late preterm (LP), defined as a gestational age of 34 0/7 to 36 6/7 weeks at birth. In recent years, a rise in LP births has been reported, and has been attributed to increasing maternal age, rising use of assisted reproductive technologies with the resulting increase in the number of twin births, and increased comorbidities such as diabetes, hypertension, thrombophilia, and premature rupture of membranes.

Late preterm infants resulting from these births are generally treated similarly to mature (term) infants since they are very similar to term infants in size and weight at birth. This manifests itself in the care of infants in two major areas: the first is a low threshold for the decision to deliver the infant prematurely due to maternal or fetal risks, and the second is the care provided to the preterm infants by neonatologists, such as hospitalizing them together with low-risk infants, allowing rooming-in of infants with mothers, or earlier discharge home.

In general, preterm infants exhibit higher mortality and complication rates than term infants, including respiratory complications such as respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), respiratory tract infections, oxygen use and ventilation, apnea, hypoglycemia, jaundice of the newborn, feeding disorders, long term neurologic complications, and other complications including infections. Late preterm infants exhibit fewer severe complications in infancy and fewer long term adverse neurologic outcomes than those born before 34 weeks gestation. However, these infants are still not developmentally and physiologically mature, as described in several studies demonstrating that these infants exhibit three times greater mortality and 7 times greater morbidity during infancy than those born at term, in addition to higher rates of learning disorders in early school years.

Fetal lung development is a continuous process divided into 5 stages:

1. Embryonic stage – from 26 days to 6 weeks of fetal development
2. Pseudoglandular stage – 6 to 16 weeks
3. Canalicular stage – 16 to 28 weeks
4. Saccular stage - 28 to 35 weeks
5. Alveolar stage – 36 weeks until birth

The last stage continues through childhood, and injury to the lung at any of these stages can cause an impairment in functioning such as gas exchange, leaving the lungs more vulnerable to infection.

LP infants are born before the lungs are fully mature (in the saccular stage), when the surfactant and anti-oxidant systems are still developing. Therefore, LP infants they suffer from a deficiency of surfactant, “weak” gas exchange, and slow absorption of fluids from the lungs, resulting in higher respiratory morbidity (RDS, TTN, pulmonary hypertension, and pneumonia), more respiratory interventions (ventilation and oxygen administration), greater number of neonatal intensive care unit (NICU) admissions, and longer hospitalizations after birth.

Several factors affect the respiratory system of preterm infants: apneas, high compliance of the chest wall (which hinders maintenance of functional reserve capacity [FRC] and gas exchange), ineffective airway tethering (enlarging alveolar volume by stretching the inter-alveolar space, leading the alveoli to collapse), smaller lung volume, and thicker alveolar walls.

In addition to the neonatal period, in infancy and early childhood LP infants are at a greater risk for respiratory diseases, especially viral infections, most notably respiratory syncytial virus (RSV), and suffer a greater number of hospitalizations resulting from these diseases. These factors have negative effects on lung function at a later age.

The majority of studies to date investigated only early respiratory complications, and a small number studied LP infants’ risk for asthma; most of these studies found an increased risk for asthma and wheezing at age three (compared to term infants), while a few studies did not find an association between late prematurity and asthma.

In a study published in 2011 by Kotecha et al., studied a population of 14,000 children, out of which 6,700 children who had performed lung function testing at ages 8-9 and/or 14-17 were divided into four groups based on gestational age at birth (25-32 weeks, 33-34 weeks, 35-36 weeks, and term infants ≥ 37 weeks). Their results showed significantly lower values of lung function in the 8-9 year old group of children born in weeks 33-34, similar to those born at 25-32 weeks; LFT results were also lower in the 35-36 weeks group, though the difference was not statistically significant.

In a retrospective study from 2011, Abe et al. compared two groups of children of ages 2-83 months; one group with 537 LP infants and the other with 5650 term infants. They found no increased risk for asthma when adjusting for confounders including maternal age and education, family history of asthma, maternal smoking in pregnancy, and sex of the infants, etc.

Another study, from 2012 by Boyle et al., examined the effects of gestational age at birth on the health outcomes of infants at ages 9 months, three years, and five years; there was an inverse correlation between the gestational age and measures of health outcomes including BMI, number of hospitalizations, incidence of wheezing, diagnosis of asthma, and subjective parental assessment of the child’s health.

### Objectives

It has been established that preterm infants are at increased risk for both early (postnatal) and later respiratory complications, but most studies focused on infants born before 34 weeks gestation. In contrast, the goal of this study was to investigate whether LP infants are at increased risk of early or late respiratory difficulties, by performing lung function testing at age 5-7 years and completing parent questionnaires at this age.

### Hypothesis

Our hypothesis was that LP infants are at higher risk of developing early and late respiratory complications compared to term infants.

### Significance of study

If in fact LP infants are at increased risk for asthma and other respiratory problems, this may influence:

* decisions regarding early delivery during these weeks,
* treatment of this group as an “at risk” group, and being prepared for potential complications
* the decision to vaccinate these infants for RSV along with other high risk groups

# Methods:

### Study population:

Our study population included preterm infants born from 34 to 36 6/7 weeks in the French Hospital in Nazareth in the years 2006-2008. The control population included term infants born during those same years at the French Hospital in Nazareth.

### Variables:

The variables investigated are listed in the survey form (see Supplementary Material), collected from three sources – review of hospital records and discharge papers from pediatrics and neonatology wards, parent responses to a questionnaire (over the phone or in face to face interviews), and lung function testing at age 5-7 years

### Lung function testing

Lung function testing (spirometry): children were invited to the pulmonology institute at the French Hospital in Nazareth and tested using a KoKo® spirometer, performed by a respiratory technician experienced with testing small children. Height and weight were measured for calculation of BMI, then the child was asked to perform a number of inspiratory and expiratory loops with the help of computer software that uses games to motivate the participant. The parameters measured were FEV1, FVC, FEV1/FVC, and FEF25-75 (recorded as percentages and absolute values).

### Procedure:

The procedure can be divided into three stages:

1. First, we collected a list of all children born in the years 2006-2008; from this we extracted the majority of preterm infants born at 34 to 36 6/7 weeks, and a random selection of children born at term. We then obtained from medical records from archives, including hospitalization and discharge notes from the maternity ward and preterm/neonatal ward, reviewed them, and extracted details necessary to fill the survey form (Supplement), mainly consisting of demographic and perinatal details.
2. Next, we contacted a parent of each subject by telephone, and explained the details of the research, its methods and procedure, and in the same conversation collected data for the survey questionnaire, confirming demographic details and completing details of the child’s health up to this point (mostly respiratory morbidity, including asthma).
3. The participants whose parents consented, arrived at the Pulmonary Institute of the French Hospital in Nazareth by appointment, and once again received explanation of the study and procedure (approved by the Helsinki Committee). After signing consent forms, we measured height and weight (for BMI calculation) and performed lung function testing as described above.

### Statistical methods:

Mean values of continuous variables (e.g. age, duration of hospitalization) and standard deviations are presented in the tables, and were compared using independent samples t-tests. Nominal and categorical and variables are represented as frequencies and percentages. We compared prevalence between two groups using χ2 tests. Results were considered statistically significant if P<.05. Data was analyzed with SPSS (IBM SPSS Statistics, IBM Corporation).

# Results:

The study participants included 134 children born at 34 to 36 6/7 weeks (late preterm group); we successfully reached parents of 86 out of 134 children by telephone, and were able to complete additional details of the questionnaire, mainly related to the child’s state of health, as well as adding demographic details. Out of this group of 86 children, parents of 65 children consented to lung function testing at the pulmonology clinic of the French Hospital in Nazareth.

The control group consisted of 82 children born at term (from 37 to 42 weeks), whose data concerning perinatal course and demographic information was collected from their medical file. From this group, we successfully reached 52 by telephone and were able to complete details regarding their health. 42 participants consented to lung function testing at the pulmonology clinic of the French Hospital in Nazareth (Figure 1).

There were no significant differences in the majority of demographic characteristics between the two study groups (LP and the control group) including gender, ethnicity, father’s occupation, maternal age at birth, (28±6 in the study group vs. 29±5 in control group, P=.58), birth-order rank (P=0.08), and total number of children in the household (P=0.20).

Conversely, there were differences between the groups in religion, type of residence, and maternal occupation. The LP group consisted of more Muslims, non-Urban residents, and non-working mothers (Table 1). Likewise, the average age in the preterm group was 7.36±.55 years, compared to 6.93±0.89 years (P=.002) in the control group.

### Perinatal data

Comparison of data related to perinatal course revealed more twin births, pregnancy complications, maternal comorbidities, breech presentation, caesarean deliveries, and lower birth weight (mean 2500±470 grams in LP group vs 3300±340g in the control group, P<0.001) in the LP group vs the control group. These differences were statistically significant except for breech presentation.

There was no statistically significant difference in Apgar scores between the two groups – scores at one minute were 9±1 in the LP group and 9±0 in the control group (P=.15), and at five minutes were 10±1 in the LP group and 10±0 in the control group (P=.08). Additionally, children in the LP group were breast fed for less months on average than the control group (4.8±5.1 and 7.6±6.0 months, respectively; P=0.005). There were differences in birth season – in children in the LP group births were distributed similarly between winter, spring, and autumn (28%, 26%, and 29 %, respectively), while most children in the control group were born in winter (54%) (Table 2).

### Neonatal Data:

A comparison of neonatal course of the two groups shows that the LP infants experienced more respiratory complications; in contrast, there were no respiratory complications in the control group (20 respiratory complications in the LP group vs 0 in the control group, P<.001). Complications included mechanical ventilation (average duration of 0.66±0.13 days), need for oxygen administration (average duration of 1.25±0.38 days), or treatment with surfactant (in 15%, 3%, 16%, 0.7%, respectively) (Figure 2). Of these, the differences in respiratory complications and need for oxygen were statistically significant (Table 3). Additionally, children in the LP group were hospitalized for a greater number of days on average (10.4±9.2) compared to the control group (3.0±1.3, P<.001)

### Postnatal Data and Long-Term Outcomes:

Differences in environmental variables were not statistically significant. When compared to the control group, an insignificantly higher percentage of the LP group was exposed to animals (11% vs 9%, respectively, P=.69), passive smoking (42% vs 36%, respectively, P=.37), and maternal smoking during pregnancy (3.5% vs 0%, respectively, P=.58).

Similarly, there was a higher incidence LP group of recurrent ear infections, treatment with inhalations and systemic steroids, asthma diagnosis by a physician, and referrals to the emergency department and hospitalizations with respiratory disorders than the control group (Table 4). These differences were statistically significant only with regards to inhalation treatment, asthma diagnoses, and hospitalizations with respiratory problems. Conversely, children in the preterm group was less likely than the control group to be under the care of a pulmonologist (12% vs 11%, respectively) and/or receive prophylactic treatment for asthma (15.4% vs 15.1%), however, these differences were not statistically significant (Table 4).

Family history data showed insignificantly lower rates of asthma in fathers and siblings, and higher rates of asthma in the mother of participants of the LP group as compared to the control group. Rates of allergic rhinitis were lower in the parents and siblings of participants in the LP group compared to the control group, with no statistical significance. Additionally, there were statistically insignificant differences in family history of atopic dermatitis, with higher rates in siblings and mothers and lower rates in fathers of the LP children vs the control group (Table 5).

### Lung function testing:

As described above, each participant undergoing LFT performed several inspiratory and expiratory loops, from which the 3 best loops were selected for use and one the best result used for analysis. The best results did not differ significantly from the other results: mean difference of 0.02 (P=.34) the second best result and 0.003 (P=.76) with the third.

Results of lung function, as measured by FEV1, FVC, and FEF25-75 (as percentages), showed significantly lower values in the LP group as compared to the control group. The FEV1/FVC ratio, however, was actually lower in the control group (0.9 vs 0.91) but this did not reach statistical significance (Table 6, Figure 3). Results are displayed as percentage of predicted values for each participant.

# Discussion:

In this study, we investigated differences in early and late respiratory complications between children born late preterm and those born at term. We gathered perinatal data of 134 children in the LP group, born at an average of 35.7±0.8 weeks gestation; in this group 86 completed a survey, and 65 of those performed lung function testing at age 7.34±0.55 years. The control group consisted of 82 children born during that same period, at 39.4±1.3 weeks, 52 of which completed a survey and 42 performed lung function testing at 6.9±0.9 years. There were no significant differences in demographic and environmental characteristics; however, we found significantly worse outcomes in the LP group in measures of neonatal and perinatal course, early and late respiratory complications, and lung function test results.

Comparison of perinatal course of the two groups revealed higher rates of twin births, pregnancy complications, maternal comorbidities, breech presentation, and caesarean deliveries, but lower birth weights, younger gestational age at birth, and fewer months of breastfeeding in the LP group (Table 2), consistent with previous findings in the literature.

In our study, we performed lung function testing only at ages 5-8, which demonstrated results that were within normal range in both groups – however, the results were worse in the preterm group. This suggests that LFT performed at a later age may reveal even lower values in the LP group. As mentioned earlier, studies investigating late respiratory complications of LP infants vs term infants are sparse. Our study demonstrates statistically significant differences in lung function, worse in the LP group. From a physiological developmental perspective, these findings can be explained by the timing of lung development, which continues into the last weeks of pregnancy as well as the first years after birth. As a result, any injury to the lung environment impairs their normal development. Delivery at weeks 34 to 36 6/7 exposes the lungs to a harmful, hyperoxic environment, leading to the developmental defects of the lungs found in these children.

Despite our significant results, especially with regard to late respiratory complications in LP infants, this study has a number of limitations. These include the following: first, our sample size was relatively small, and the two groups were unequal in size. Additionally, there were some differences in baseline demographic characteristics including religion, type of residence, and maternal occupation; environmental variables such as exposure to animals, passive exposure to smoke, and maternal smoking in pregnancy; reliance on parent reporting of some environmental data instead of on medical records, which may be less reliable given parents; imperfect memory of diagnosis and treatments of the child; and parents were not asked about learning disorders which have been recognized in children at this age in the literature.

However, this study has several strengths as well. First of all, other studies mostly gathered data on health status of children only until the age of three, while we investigated outcomes until ages 5-8, and our findings were statistically significant. We were able to extract information from medical records for all study participants, while those who also completed the questionnaire did so fully, and all lung function tests were technically of high quality except for two.

# Conclusion:

In summary, in this study we found that children born late preterm (at 34 to 36 6/7 weeks gestation) suffer more from immediate respiratory complications than those born at around 39 weeks gestation. This finding conforms with existing literature on the subject. Similarly, we observed that late preterm infants were more likely in the future to suffer from late respiratory complications at around age 7 years, which was expressed as higher rate of asthma diagnoses, greater use of bronchodilation inhalation devices, and poorer results in lung function testing when compared to children born at around 39 weeks gestation. Reports on late respiratory complications of LP infants are rare in the existing literature, and mostly investigate only until two years of age. Our findings indicate that LP infants must not be routinely grouped together with term infants, because of the potential complications found in this group. Although this study is not intended to instruct obstetric physicians not to deliver during weeks 34 to 36 6/7, we do emphasize the importance of recognizing the potential risks involved with these early deliveries; LP infants have greater risk of developing complications, including the respiratory complications described in this study, and physicians must of course evaluate risk and benefits on a case-by-case basis. Likewise, neonatologists must address these LP infants as a higher risk group, with possible respiratory complications or need for oxygen, despite being born at age and weight close to term infants. Finally, it is vital for pediatricians in charge of these children’s future care to also appreciate the higher risks of developing asthma, requiring inhalations, and being hospitalized with respiratory problems. Perhaps routine follow-up with a pulmonologist including lung function testing is advisable.

References