

Late preterm infants: Week by week outcomes of morbidity and mortality

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The aim of this study was to determine the clinical outcome of late preterm infants (LPI) week by week. Our patients were divided into three groups according to gestational age (GA); group A: 34 - 34^{+6/7} weeks, group B: 35 - 35^{+6/7} weeks and group C: 36 - 36^{+6/7} weeks. Out of 10650 deliveries, 1280 (12%) were late preterm, 1004 (78.5%) of which were carried out by caesarean section. A total of 1527 infants were studied with 565 (37%) requiring admission to NICU while 5 deaths were recorded (neonatal mortality rate was estimated at 3.2 ‰). Our study demonstrates that the rate of respiratory disorders, sepsis, feeding disorders and abnormal neurological examination in LPIs was inversely proportional to their GA. Furthermore, infants of 34^{+0/7} - 34^{+6/7} weeks of GA required a longer hospitalization in the NICU than their more mature peers.

Key words: late preterm infants, neonatal preterm morbidity, neonatal preterm mortality.

Late preterm infants (LPIs) are defined as neonates born at gestational age (GA) between 34 weeks and 0 days to 36 weeks and 6 days.¹ LPIs, the largest proportion of preterm infants, correspond to 12.3% of births.² Even though LPI's size and weight are similar to term infants, mortality and morbidity are higher.^{1,3} This is attributed to physiological and metabolic immaturity and delayed adjustment from intrauterine to extrauterine life.^{4,5}

Recently, an increased incidence of LP births in United States has been observed, illustrated by the fact that LPIs represent 71-74% of all preterm births.⁶ Other studies emphasize the need for more clinical data collection.² The medical society is still raising questions on whether an LPIs, after an uncomplicated pregnancy and delivery, is at greater risk than a term infant.

The aim of this study was to determine LPI clinical outcome during hospitalization in our neonatal intensive care unit (NICU) and assess the possible correlation between LPI of different GA to morbidity and mortality.

Material and Methods

This retrospective study was undertaken in our tertiary level NICU from April 2004 until December 2011 and all inborn LPIs were included. Exclusion criteria were outborn infants and major congenital malformations. This study was approved by the Institutional Ethics Committee.

Gestational age (GA) was estimated on early second-trimester by fetal ultrasound or date of last menstrual period. Demographic data [GA, birth weight (BW)], mode of delivery [caesarean section (CS)] and morbidity [(transient tachypnea of newborn (TTN), respiratory distress syndrome (RDS), meconium aspiration (MAS), pneumothorax, persistent pulmonary hypertension (PPH), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), septicemia and feeding disorders] were recorded. Additionally, need for mechanical ventilation (MV), continuous positive airway pressure (CPAP), days on Head-Box (HBox) supply, total parenteral nutrition

(TPN) days and length of stay (LOS) were also recorded.

The minimal diagnostic criteria that we used in our research for acute pulmonary disorders were:

RDS when neonate experienced early onset of clinical signs and reticulogranular pattern on chest film or oxygenation response to surfactant.⁷

TTN if chest film was suggestive of retained fluid and oxygen requirement and spontaneous improvement over two to five days was observed.⁷

MAS was characterized by meconium in amniotic fluid and chest radiograph suggestive of aspiration.⁷

PPH when neonates met at least one criterion of right-to-left shunt and echocardiography with normal structure of cardiac anatomy and evidence of pulmonary hypertension (e.g., flattened or displaced ventricular septum).⁷

The diagnosis of patent ductus arteriosus (PDA) was based upon its characteristic clinical findings (murmur, prominent left ventricular impulse, bounding pulses and noncardiovascular findings as tachypnea, apnea, increased carbon dioxide retention, and/or increased requirements for mechanical ventilation) and confirmed by echocardiography.⁸ Definition of BPD in our infants was based on the need for oxygen supplementation, the gestational age and postmenstrual age of the patient, so as the severity of disease.⁹

NEC is a disorder characterized by ischemic necrosis of the intestinal mucosa, which is associated with inflammation, invasion of enteric gas forming organisms, and dissection of gas into the muscularis and portal venous system; its definition and treatment are based in our NICU upon Bell staging criteria.¹⁰

Our sepsis screening tests criteria based on neonatal laboratory data (blood culture) that obtained in the setting of suspicion of sepsis.¹¹

LPI due to their immaturity present at the beginning feeding disorders associated with abnormal shallow mechanisms, slow gastrointestinal transit time, delayed gastric emptying and oro-buccal incoordination.¹ Thus, we considered several factors that affect how feedings are tolerated: intestinal motility, gastric

emptying, stool output, digestive enzymes, type of milk, rapidity of feeding, volume of feeding, concentration of milk, concomitant medications, and medical conditions.¹ Administration of TPN within the first days of life in order to provide adequate nutrition and to minimize early weight loss and protein breakdown was required, mostly, in infants with severe feeding disorders or severe medical problems, like endotracheal intubation, mechanical ventilation or infection.

Finally cranial ultrasound (CUS) and neurologic examination were recorded. Disorders of periventricular white matter, flaring or other abnormal variants were considered as pathological CUS findings. Neurological findings were estimated in all infants in our NICU and distinguished in minor, moderate or severe according to New Ballard score,¹² in order to determine the severity of abnormal neurological examination.

Patients were divided into three groups according to their GA, (group A: GA between 34^{+0/7} - 34^{+6/7}, group B: GA between 35^{+0/7} - 35^{+6/7} and group C: GA between 36^{+0/7} - 36^{+6/7}).

Statistical analysis

Normality assumption was assessed using Kolmogorov-Smirnov test. Descriptive statistics (means, standard deviation and proportions) were used for data description of groups A, B and C. Categorical variables were compared with Fisher exact test or chi-square test. Continuous variables were compared by t-test or Mann Whitney U test based of distribution. Univariate logistic regression was performed between infants of group A and group B, infants of group B and group C and infants of group A and group C. P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 15, SPSS Inc, Chicago, IL).

Results

Out of 10650 deliveries, 1280 (12%) were late preterm and 1004 (78.5%) were carried out by CS. Two hundred thirty-nine deliveries (239) were of multiple –gestation [231 (18%) twins, and 8 (0.6%) triplets] while 1041 (81.4%) were singletons. A total of 1527 infants were studied (770 males) with 326 (21.3%) requiring

direct admission to NICU while 5 deaths were recorded (perinatal mortality 3.2 ‰). In our patients, sepsis due to gram negative bacteria (2 neonates), subdural hematoma (1 neonate), severe NEC (1 neonate) and birth asphyxia (1 neonate) were identified as causes of death.

As mentioned above, our patients were divided into three groups according to their GA. Group A included 340, group B 457, group C 730 neonates with 230 (67%), 192 (42%) and 143 (19.5%) being hospitalized in our NICU respectively. Median length of stay between three groups was not statistically significant.

Group A neonates were more likely to predict feeding disorders than their peers of group B ($p=0.002$), while comparison of group B and group C was also of statistical significance ($p=0.008$) (Table I).

The most common respiratory disorder was RDS, with a significant decreased rate from 34 to 36 weeks week by week, following by TTN reaching a nadir of 4.7% for group A to 11% for group C with a significant increased rate from 34 to 36 weeks week by week (Fig.1). Decreased clinical outcomes were found regarding PVL, with statistical significance

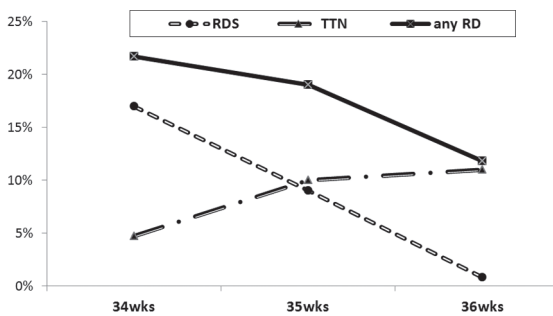


Fig. 1. Incidence of RDS, TTN and any respiratory distress among late preterm infants.

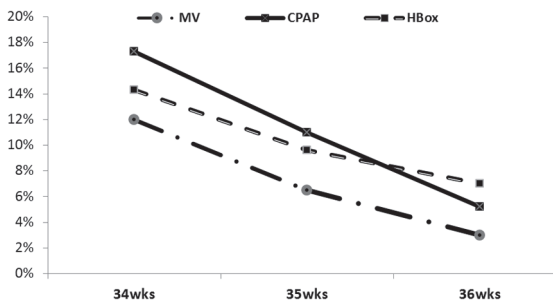


Fig. 2. Proportion of late preterm infants on MV and CPAP support and Head-Box O₂ administration.

between group A and group C ($p<0.001$). Infants of group A underwent sepsis screening tests more frequently than infants of group B and C (8.5%, 2% and 0.3% respectively). LPIs with abnormal neurological examination were more probable to belong to group A (6.4%) compared to group B (2.6%) ($p=0.007$) or to group C ($p<0.001$). Out of 340 neonates of group A, 40 required MV support (12%), while MV days were 4.4 ± 7.8 . Infants of group A needed MV more often than those of group B or group C ($p=0.008$ and $p<0.001$ respectively) and group B than those of group C ($p=0.005$) (Table II). Infants of group A required CPAP more often than infants of group B or group C ($p=0.008$; $p <0.001$ respectively) and infants of group B more often than those of group C ($p<0.001$). Need for HBox O₂ supply showed significant difference comparing group A and B ($p=0.019$) whereas for group B and C remained at the same level (Fig. 2).

Discussion

It is widely accepted that LPI's morbidity and mortality is higher than term infants'.^{3,13,14} This is attributed to immature pathophysiology and limited compensatory mechanisms exhibiting severe clinical disorders.^{1,3} The mortality of LPIs in our research remained at the rate of about 3%, similar to published data.^{1,5} Our week by week study analysis provided further information about morbidity in this specific age group. Noteworthy, literature confirms differences between infants born at 34, 35 and 36 weeks GA, suggesting that LPIs should not be regarded as a homogeneous group.¹⁵

In our study CS rate was relatively high. This finding is consistent with other authors and highlights the increasing frequency of primary emergency CS in LPIs.¹⁶⁻¹⁸ Main causes of CS at group C in our study were prior CS (about 35%), multiple gestations (20%) and failure to progress in labor and/or other maternal factors (about 10%). In infants of group A high rate of CS was attributed mainly to prior CS (23%), multiple gestations (20%) and/or other maternal factors (10%). Other clinicians believe that CS increasing rate is attributed to mother's decision to discontinue pregnancy after 34 weeks GA despite obstetricians' opposite recommendations.¹⁹ In our study the rate of this cause for CS was about 8%.

Table I. Mortality and Morbidity of LPI

	Group A	Group B	Group C
N (number of deliveries)	273	369	638
Cesarean section	237 (87%)	298 (81%)	469 (73.5%) ^
N (number of infants, % of total number of LPI)	340 (22.2%)	457 (30%)	730 (47.8%)
N (admission to NICU)	230 (67%)*	192 (42%)\$	143 (19.5%)##
Birth weight (gr.), SD	2205 (409)	2457 (449)	2706 (422)
Feeding disorders	26(7.5%)*	13 (3%)\$	6 (0.8%)##
Sepsis	29 (8.5%)*	9 (2%)\$	4 (0.3%)##
“Abnormal” brain ultrasound	24 (7%)	27 (6%)\$	7 (0.8%)##
Pathologic neurologic examinations	22 (6.4%)*	12 (2.6%)\$	3 (0.3%)##
PVL	8 (2.5%)#	3 (0.6%)	0##
TPN (d), SD	6.4 (6.3)	4.9 (3.9)	5 (4)
LOS (d), SD	14.8 (10.1)	11.8 (8)	10 (7)
Neonatal Mortality	1 (3‰)	3 (6‰)	1 (1.3‰)

* p <0.01 between groups A and B, # p <0.05 between groups A and B
 \$p <0.01 between groups B and C, ## p <0.01 between groups A and C, ^ p <0.05 between groups A and C

LPIs = Late preterm infants, PVL= Periventricular Leukomalacia, TPN = Total Parental Nutrition, LOS = length of stay, d=days, Standard Deviation

Group A: GA= 34-34^{+6/7}, Group B: GA = 35-35^{+6/7}, Group C: GA = 36-36^{+6/7}

Table II. Respiratory Morbidity of LPI

	Group A	Group B	Group C
N (number of infants, % of total number of LPI)	340 (22.2%)	457 (30%)	730 (47.8%)
RDS	58 (17%)	40 (9%)	6 (0.8%)
TTN	16 (4.7%)*	46 (10%)	81 (11%)##
Pneumothorax	3 (0.9%)	3 (0.2%)	2 (0.3%)##
Mechanical ventilation (n, %)	40 (12%)*	30 (6.5%)\$	23 (3%)##
Mechanical ventilation (d), SD	4.4 (7.8)	3 (3.7)	2.8 (1.1)
CPAP (n,%)	59 (17.3%)*	51 (11%)\$	38 (5.2%)##
CPAP (d), SD	1.5 (1.22)	1.6 (0.8)	1.7 (1.3)
Head-Box (n,%)	50 (14.3%)#	44 (9.6%)	54 (7%)##
Head-Box (d), SD	1.35 (1)	1.2 (1)	1.4 (1.5)

* p <0.01 between groups A and B, # p <0.05 between groups A and B
 \$p <0.01 between groups B and C, ##p <0.01 between groups A and C

LPIs = Late preterm infants, RDS = Respiratory Distress Syndrome, TTN = Transient Tachypnea of Newborn, CPAP = Continuous Positive Airway Pressure, SD = Standard deviation.

Group A: GA= 34 - 34^{+6/7}, Group B: GA = 35 - 35^{+6/7}, Group C: GA = 36 - 36^{+6/7}

However, a correlation of CS with respiratory disorders in LPIs seems to exist. RDS and TTN as two of the most common respiratory disorders have been well investigated.^{13,20,21} Khashu et al.²² in their study found higher prevalence of respiratory distress in LPIs (4,5-fold higher than term infants) although

no estimation specifically for RDS or TTN took place. In our study, RDS prevalence of group A infants dropped to those of group C comparable to other authors findings.^{4,13,21} This occurs due to the better maturation of closer-to-term infants' lungs. Our research showed a higher rate TTN in infants of 36^{+0/7}-

36^{+6/7} (11%) rather than for infants of 34^{+0/7}-34^{+6/7} (4.7%). This could not only be the result of delayed lung fluid clearance at 'more mature' LPIs, considering the large number of group A presenting respiratory failure,²³ but also due to increased CS incidence in neonates of group C (Table I). In clinical terms, it was difficult to distinguish which infants developed RDS or TTN as a cause of respiratory distress. RDS diagnosis was considered in neonates of group C and group B based on the need for surfactant administration. Moreover, TTN can conceivably accompany RDS in late preterm infants. However, the overall incidence of any form of respiratory distress in our research was reduced as gestational age increased (Fig. 1).

Due to immaturity, most of late preterm infants usually require clinical observation and oxygen supply after delivery with a significant fraction needing further support with CPAP or even mechanical ventilation.²⁴ The increased requirement for MV and its relation to GA has been reported in previous studies.^{3,25,26} Another study showed that LPIs were 3 to 9 times more likely for MV support than infants born at 38 weeks.²⁶

In our study, infants of group A were at greater need for MV (12%) compared to group B and C with longer MV duration (Fig. 2). This last finding is of great significance, as it could be attributed to lung maturation by GA increase.²⁰ Furthermore, days on CPAP were adversely correlated to increased GA. Apparently, this could be attributed to the fact that neonates of Group A present higher rates of RDS with a great decline at more mature infants, requiring longer duration under CPAP. On the other hand, our research revealed that the rate of decline in HBox demand by GA increase was different for MV or CPAP (Fig. 1). This is, probably, due to increased incidence of TTN at infants of 36^{+0/7}- 36^{+6/7} consequently requiring longer HBox O₂ supply. However, no significant difference regarding HBox O₂ supply was recorded among group B and group C, due to non-existence of pathophysiology differences in lung maturation process.

Wang et al.³ suggested that late preterm infants found at increased risk for sepsis due to immune system immaturity. Arnon et al.²⁷ studying 207 LPIs found that only 5% of neonates 34-35 weeks GA met sepsis

criteria. In our study sepsis prevalence was found relatively high in all groups. Moreover, our data highlight the direct relation between incidence of sepsis and GA, with a significant statistical difference.

Wang et al.³ emphasized on high rates of feeding disorders in LPIs. Our findings provide clear evidence that feeding difficulties are closely related to each GA, since group A LPIs were 8 times more likely to present feeding disorders than group C (7.5 % to 0.8%).

LPIs brain immaturity may increase its vulnerability.^{28,29} A systematic review of 22 studies reported that LPIs are at greater risk to develop neurological sequelae and even more cerebral palsy.¹⁴ Due to limited data the risk for neurological disorders in LPIs was evaluated based to abnormal neurological examination and head ultrasound findings. Group A LPIs presented abnormal neurological examination (6.4%) and CUS findings (7%) more often than group B and C. Although abnormal CUS findings were not statistically significant between neonates of group A and those of group B, neurological adverse sequelae were found statistically different between neonates of group B and C (p=0.0001). This difference might be attributed to differences brain in pathophysiology and developmental immaturity of 'more' preterm infants (group A).

Thus, gray matter injury is associated with periventricular leukomalacia. This concerns premature infants including LPIs and our results are consistent with this statement. Specifically, group B exhibits 72.6% lower possibility of PVL prevalence than group A (p=0.043), while no neonate with PVL was recorded at group C.

Kashu et al.²² and McLaurin et al.³⁰ showed increased length of stay (LOS) for LPIs. Our results are consistent, since the median LOS for group A was approximately 30 days, remaining relative high (about 19 days) for group B. LOS and diagnosis regarding each group of LPIs predict the cost for newborn care with a significant inverse relation between BW and hospital costs.³¹

Late prematurity should not be considered as a benign condition. LPIs are immature infants who often require direct admission to a NICU for close evaluation and monitoring with LOS decreasing significantly from 34^{+0/7}

to 36^{+6/7} weeks GA. Feeding disorders and sepsis rate relate directly to each GA week of LPIs. Additionally, infants over 36 week of GA exhibit more adequate neurodevelopmental outcome than their less mature peers, being more vulnerable to present brain abnormalities. In our study mortality rate were in accordance with published data. Further research on pathophysiology and morbidity risk factors could provide valuable information since LPIs represent an important workload in neonatal care units.

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