

## Early Neonatal Morbidities in Late Preterm Infants

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**Objectives:** To compare early neonatal morbidity (within first 7 days of life) in late preterm infants with term infants.

**Study design:** Prospective cohort study.

**Subjects:** All live inborn late preterm infants (34 0/7 to 36 6/7 weeks) and term infants (37 0/7 to 41 6/7 weeks).

**Outcome:** Any of the predefined medical conditions listed in the study, resulting in post-delivery inpatient hospital observation, admission, or readmission in first 7 days of life.

**Results:** 363 late preterm infants and 2707 term infants were included in study. Two hundred fifty seven (70.8%) of late preterm and 788 (29.1%) of term infants had at least one of the predefined neonatal conditions. Late preterm infants were at significantly higher risk for overall morbidity due to any cause ( $P < 0.001$ ; adjusted Odds Ratio (OR): 5.5; 95% CI: 4.2-7.1), respiratory morbidity ( $P < 0.001$ ;

adjusted OR: 7.5; 95% CI: 4.2-12.3), any ventilation (non invasive or invasive) ( $P = 0.001$ ; adjusted OR: 4.2; 95% CI: 2.8-9.9), jaundice ( $P < 0.001$ ; adjusted OR: 3.4; 95% CI: 2.7-4.4), hypoglycemia ( $P < 0.001$ ; adjusted OR: 4.5; 95% CI: 2.6-7.7), and probable sepsis ( $P < 0.001$ ; adjusted OR: 3.2; 95% CI: 1.6-6.5). The incidence of morbidities increased from 23% at 40 weeks to 30%, 39.7%, 67.5%, 89% and 87.9% at 38, 37, 36, 35 and 34 weeks, respectively ( $P < 0.001$ ).

**Conclusion:** Compared with term infants, late preterm infants are at high risk for respiratory morbidity, need of ventilation (non invasive or invasive), jaundice, hypoglycemia, sepsis, and probable sepsis. All gestations except 39 weeks were at significantly higher risk for morbidity with 40 weeks as reference term.

**Key words:** India, Late preterm infants, Neonatal morbidity, Outcome.

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Late preterm infants (34 0/7 through 36 6/7 weeks of gestation) are physiologically less mature and have limited compensatory responses to the extra-uterine environment, compared with term infants. Although late preterm infants are the largest subgroup of preterm infants, there has been little research on this group until recently. This is mainly because of labeling them as “near-term”, thus being looked upon as “almost mature,” with little need to be concerned. However, recent research has revealed a contrary trend [1-4]. While serious morbidities are rare, the late preterm group has 2 to 3 fold increased rates for mild to moderate morbidities, such as hypothermia, hypoglycemia, delayed lung fluid clearance and respiratory distress, poor feeding, jaundice, infection, and readmission rates after initial hospital discharge [1]. As the late preterm

subgroup accounts for nearly 10% of all births, even a modest increase in any morbidity will have a huge impact on the overall health care resources. Thus, it is not surprising that the absolute number of late preterm infant being admitted to NICUs has been increasing worldwide. Only few studies have been conducted to assess the neonatal morbidity and mortality in late preterm infants [1-4]. These were done in developed countries and were retrospective in nature.

Understanding morbidity risk among late-preterm infants is not only important for helping newborn care providers to anticipate and to manage potential morbidity during the birth hospitalization and earlier follow-up after hospital discharge, but also may possibly assist in guiding non-emergency obstetric intervention decisions. The present study is

an attempt to obtain actual data on incidence, pattern of early neonatal morbidities, and to compare it with term infants.

## METHODS

This hospital-based prospective cohort study was conducted at the Fernandez Hospital, Hyderabad, an urban private tertiary care women and newborn hospital. The study was approved by the hospital ethics committee. All live inborn late preterm infants (34 0/7 to 36 6/7 weeks) and term infants (37 0/7 to 41 6/7 weeks) [5] born between February 2009 to September 2009 were eligible for enrollment in the study. Informed parental consent was obtained prior to enrolment in the study. Infants with major congenital anomalies and those with clinically identified chromosomal syndromes were excluded. Gestational age was assessed by maternal last menstrual period and by first trimester ultrasound scan.

A suitable case reporting form (CRF) mentioning infant's particulars, risk factors, and neonatal morbidity was developed for the study. It was pre-tested on 25 infants and modified. All infants enrolled in study were followed daily till first 7 days of life for any morbidity by clinical evaluation and reviewing hospital records. Infants who were discharged before 7 days were called for mandatory follow up evaluation in the outpatient clinic on 5<sup>th</sup> and 7<sup>th</sup> day of life. Infants who did not come for follow up were called on telephone and status of the baby was enquired.

## Outcome

Any of the following predefined medical condition resulting in post delivery inpatient hospital observation, admission or readmission in first 7 days of life: (i) Post Resuscitation care: Requirement of post-resuscitation care as per NRP 2005 guidelines. (ii) Hypoglycemia: Blood glucose of less than 40 mg/dL. Blood sugars were monitored at 12 hourly intervals in all late preterm, IUGR (intrauterine growth restriction), IDM (Infant of diabetic mother) and LGA (Large for gestation, birth weight >2SD) infants. Random blood sugar estimation was also done in all symptomatic infants as per the clinician's discretion. (iii) Jaundice: Clinically visible jaundice requiring phototherapy/exchange transfusion as per

hour specific total serum bilirubin (TSB) nomogram (AAP chart). Criteria for 35 weeks were used for infants with 34 weeks gestation. (iv) Respiratory distress: Presence of at least 2 of the following criteria: Respiratory rate >60/min, Subcostal/intercostal recessions, Expiratory grunt/roaning, and requiring oxygen therapy. (v) Sepsis: Probable sepsis: Positive septic screen (two of the five parameters namely, TLC <5000/mm<sup>3</sup> or >15000/mm<sup>3</sup>, band to total polymorph ratio of >0.2, absolute neutrophil count less than 1800/mm<sup>3</sup> or >7200/mm<sup>3</sup>, C reactive protein >0.5mg/dL, platelets <1 lakh/mm<sup>3</sup>); or Proven sepsis: Isolation of pathogens from Blood or CSF or Urine. (vi) Weight loss: If weight loss >10% of birth weight. (vii) Readmission: Any readmission after post-delivery discharge from hospital.

## Statistical analysis

Assuming 5% prevalence of morbidities in term infants with relative risk of 2 times in late preterm compared with term infants and allowing standard  $\alpha$  (0.05) and  $\beta$  (0.2) error, 275 late preterm infants were to be recruited. Expecting 30% lost to follow up, 363 infants were enrolled in the study. All data thus collected were than analyzed using SPSS software. Neonatal morbidities were compared between late preterm and term infants. Chi-square test and student 't' test were used for discrete and continuous variables, respectively. Logistic regression analysis was done with neonatal morbidity as the dependent variable, and late preterm, mode of delivery, IUGR and multiple pregnancy status as the covariates. *P* value <0.05 was considered significant. Chi-square for trends was done for comparing morbidities across gestational age groups.

## RESULTS

There were 3300 live births in hospital during study period. Of these, 371 (11.24%) were late preterm and 2725 (82.58%) were term births. Three hundred sixty three (98.65%) of late preterm infants and 2707 (99.33%) of term infants were included in the study. Twenty two infants were excluded due to congenital anomalies and in 4 cases parental consent was refused. All included infants were followed for 7 days of life for outcomes. On comparing the two

groups, there was significant difference in mean gestation, mean birthweight, weight for gestation, mean Apgar score, mode of delivery, and multiple pregnancy status (**Table I**).

257 (70.8%) of late preterm and 788 (29.1%) of term infants had at least one of the neonatal morbidities requiring inpatient hospital observation, admission or readmission during the first 7 days of life. On comparing the neonatal morbidity after adjusting for mode of delivery, intrauterine growth, and multiple pregnancy status; late preterm infants were at significantly higher risk for overall morbidity due to any cause, respiratory morbidity, any ventilation (non invasive or invasive), jaundice, hypoglycemia, probable sepsis, and confirmed sepsis (**Table II**). Thirty six (9.9%) late preterm infants and 199 (7.4%) term infants required readmission in the first 7 days of life (**Table III**). As 40 weeks is considered an ideal gestation age for delivery, neonatal morbidities at each of the lower gestations was compared with morbidities of neonates born at 40 weeks. The incidence of morbidities increased from 23% at 40 weeks to 30%, 39.7%, 67.5%, 89% and 87.9% at 38, 37, 36, 35 and 34 weeks, respectively (**Fig. 1**).

## DISCUSSION

In the present study, 70.8% of late preterm and 29.1% of term infants had at least one neonatal

morbidity requiring inpatient hospital observation, admission or readmission during the first 7 days of life. Neonatal jaundice requiring phototherapy (55.1%) followed by respiratory morbidity (10.5%) and hypoglycemia (8.8%) were the frequently identified morbidities in late preterm infants while neonatal jaundice (24.8%) was the most frequently identified morbidity in term infants. Cesarean delivery, IUGR and multiple pregnancy status significantly contribute to neonatal morbidities. Compared with term infants, these variables are more common in late preterm infants. In order to neutralize the influence of these variables on the outcomes evaluated, adjusted odds ratios were calculated and were significantly higher in late preterm group. Compared with term infants, late preterm infants were at 5.5 times higher risk for overall morbidity due to any cause, 7.5 times higher risk for respiratory morbidity, 4.2 times higher risk for ventilation (non invasive or invasive), 3.4 times higher risk for jaundice, and 4.5 times and 3.2 times higher risk for hypoglycemia and probable sepsis, respectively.

Similar to our findings, in a retrospective study by Wang, *et al.*[1], 77.8% near term infants compared with 45.3% of term infants had at least one clinical problem and nearly all clinical outcomes differed significantly between near-term and full-term neonate *viz.* temperature instability, hypo-

**TABLE I** BASELINE VARIABLES OF THE STUDY POPULATION

Variable		Late preterm (n = 363)	Term (n = 2707)	P value
Gestation (wks) mean (SD)		35.39 (±0.78)	38.64 (±1.11)	
Birth weight (Kg) mean (SD)		2.35 (±0.48)	3.04 (±0.43)	
Female sex		165 (45.5)	1325 (48.9)	0.116
Weight for Gestation	AGA	304 (83.7)	2305 (85.1)	
	SGA	37 (10.2)	132 (4.9)	
	LGA	22 (6.1)	270 (10)	
Mode of delivery	Vaginal	117 (32.2)	1554 (57.4)	<0.001
	Cesarean	246 (67.8)	1153 (42.6)	
Singleton pregnancy		297 (81.8)	2693 (99.5)	
APGAR at 1 min		7.43 (±0.8)	7.72 (±0.7)	<0.001
APGAR at 5 min		8.49 (±0.6)	8.77 (±0.5)	<0.001

AGA: appropriate for gestational age; SGA: small for gestational age; LGA: large for gestational age.

**TABLE II** COMPARISON OF MORBIDITY IN LATE PRETERM AND TERM INFANTS

Variable	Late preterm (n= 363) (%)	Term (n= 2707) (%)	P value	Adjusted OR (95% CI)
Any morbidity	257 (70.8)	788 (29.1)	<0.001	5.5 (4.2-7.1)
Readmission	36 (9.9)	199 (7.4)	0.056	1.9 (1.2-2.8)
Hypoglycemia	32 (8.8)	39 (1.4)	<0.001	4.5 (2.6-7.7)
Respiratory morbidity	38 (10.5)	41 (1.5)	<0.001	7.5 (4.2-12.3)
Ventilation				
Any	11 (3)	23 (0.8)	0.001	4.2 (2-8.9)
CPAP	9 (2.5)	15 (0.5)		
IPPV	2 (0.5)	8 (0.3)		
Jaundice	200 (55.1)	671 (24.8)	<0.001	3.4 (2.7-4.4)
Probable sepsis	15 (4.1)	30 (1.1)	<0.001	3.2 (1.6-6.5)
Confirmed sepsis	4 (1.1)	1 (0.04)	0.001	

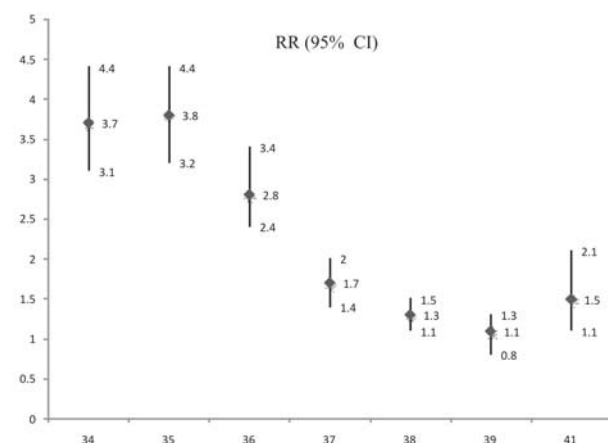
glycemia, respiratory distress, and jaundice. They found that during the initial birth hospitalization, late preterm infants were 4 times more likely than term infants to have at least one medical condition diagnosed and 3.5 times more likely to have two or more conditions diagnosed [1]. Melamed, *et al.* [6] also found that compared with full-term infants, spontaneous late preterm delivery was independently associated with an increased risk of neonatal morbidity, including respiratory distress syndrome, sepsis, intraventricular hemorrhage, hypoglycemia, and jaundice requiring phototherapy. Another study Tomashek, *et al.* [7] found that late preterm infants were 1.5 times more likely to require hospital-related care and 1.8 times more likely to be readmitted than term infants. In another study, newborn morbidity was 7 times more likely in late preterm compared with term infants (22% vs 3%)

**TABLE III** NEONATAL MORBIDITY IN THE READMISSION GROUP

Variable	Late preterm n=36 (9.9%)	Term n=199
Mean age at readmission (d)	5.53 ± (1.4)	4.7 ± (1.2)
Hypoglycemia	2 (5.5%)	7 (3.5%)
Respiratory morbidity	2 (5.5%)	5 (2.5%)
Weight loss >10%	4 (11%)	21(10.5%)
Jaundice	32 (88.8%)	160 (80.4%)
Probable sepsis	5 (13.8%)	12 (6%)

[8]. The higher risk for neonatal morbidity in our study may be attributed to the inclusion of neonates of 34 weeks gestation in our data, difference in definition of morbidities, and a more precise follow-up due to it being a hospital based prospective study than previous studies, which are either retrospective or were based on population data.

The incidence of morbidity increased from 24% at 40 weeks to 90% at 34-35 weeks showing an inverse relationship with gestational age. There was a 10% increase from 38 weeks to 37 weeks, 20% increase from 37 weeks to 36 weeks and 30% from 36 weeks to 35 weeks. With 40 weeks as reference standard, all gestations except 39 weeks were at



**FIG. 1** Neonatal morbidity: Individual gestation vs reference term (40 weeks).

**WHAT IS ALREADY KNOWN?**

- Late preterm infants are physiologically less mature than term infants.

**WHAT THIS STUDY ADDS?**

- In comparison with term infants, late preterm infants are at high risk for early neonatal morbidities especially respiratory morbidity, need of ventilation, jaundice, hypoglycemia and probable sepsis.

significantly higher risk for morbidity. Bradley, *et al.* [9] concluded previously that clinically significant respiratory morbidities are least common at 39-40 weeks. Roberta De Luca, *et al.* [10] similarly found that mortality and morbidities had a strong GA-related trend with the lowest incidences consistently found between 38 and 40 weeks of gestation. Shapiro-Mendoza, *et al.* [8] found that the newborn morbidity rate doubled in infants for each gestational week earlier than 38 weeks.

The present study is one of the first attempts to obtain actual data on late preterm births and associated neonatal morbidities from India. A major limitation of present study is inability to assess feeding difficulties and breastfeeding status. This was because of existing policy of the unit to give supplementary feeding to all at risk infants. As the present study was designed to assess early neonatal morbidities, it did not address morbidities after 7 days of life, and also whether outcomes studied had long-term implications. Among the neonatal units, often there is as a wide variation in antenatal use of steroids, intrapartum monitoring, feeding policy, asepsis protocols and management of jaundice/respiratory distress and hence the results of this study may be more applicable to settings similar to ours and may not be generalizable.

The results show that late preterm infants have 5.5 times higher risk for overall morbidity due to any cause relative to term infants. All gestations except 39 weeks were at significantly higher risk for morbidity with 40 weeks as reference term.

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