Early neonatal outcome in late preterms compared with term neonates

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ABSTRACT

Introduction: Neonates born between 34 weeks and 36 weeks 6 days of gestational age (GA) are known as late preterm neonates. These late preterm neonates are the largest subgroup of preterm neonates. There have been few studies regarding the early morbidity in this cohort of neonates when compared to neonates born at term. **Objectives:** The objectives of the study were to study the incidence and various causes of early morbidities and mortality in late preterm neonates and to compare with term neonates. **Materials and Methods:** This prospective cohort study was conducted at a tertiary care teaching institution of Bengaluru. All late preterm and term neonates born between December 2016 and July 2018 were enrolled in the study. Data regarding parity, mode of delivery, sex, GA, birth weight, predefined neonatal morbidities, and maternal risk factors were all entered in the pre-designed pro forma. The morbidities and mortality of these late preterm neonates were compared with the term neonates. **Results:** A total of 408 late preterms and 1660 term neonates were enrolled in this study. These late preterm neonates were at significantly higher risk of overall morbidity due to any cause (85.3%, p<0.001, adjusted odds ratio [OR]: 1.4, 95% confident interval [CI]=0.8–2.4). They were also at higher risk of developing respiratory distress (23.5%, p<0.001, adjusted OR: 1.5, 95% CI: 1.1–2.2), need for ventilation ([Nasal continuous positive airway pressure – 8.6%] [synchronized intermittent mandatory ventilation [SIMV] – 3.7%], p<0.001), and neonatal sepsis (9.1%, p=0.003, adjusted OR: 1.3, 95% CI=0.3–3.3) when compared with term neonates. **Conclusion:** Gestational maturity is the most important determinant of the outcome in newborns. Late preterm neonates are not the same as term neonates as evidenced by the high incidence of complications in late preterm compared to term infants.

Key words: *Early neonatal outcome, Late preterm, Term neonates, Comparison, Early morbidities*

Preterm birth remains the leading cause of death and complications in the neonatal period. Since earlier times attention was more focused on premature infants born at a gestational age (GA) of 32 weeks or less, which are obviously at greatest risk. Only recently, preterm infants with GA > 34 weeks have been evaluated more carefully. In clinical practice, late preterm neonates born between 34 weeks and 36 6/7 weeks of gestation age tend to be considered, both by obstetricians and neonatologists, as having a very similar risk to those born at term [1,2].

This classification has evolved over time to help providers evaluate maternal and neonatal morbidities and mortalities. Although late preterm infants are the largest subgroup of preterm infants, there have been only a few studies regarding their outcome in India [3]. In recent times, the increase in the rate of preterm births can be attributed to increases in these late preterm births [4,5]. The reason for the rise in the late preterm birth rate during the past decade is not well understood. One theory is that it can be contributed, in part, to increased use of reproductive technologies and, as a result, an increase in multifetal pregnancies [6-9].

Another hypothesis is that advances in obstetric practice have led to an increase in surveillance and medical interventions during pregnancy [6-9]. Due to this, fetuses which are considered to be at risk of stillbirth, including those with intrauterine growth restriction, fetal anomalies, and intrapartum asphyxia, may be recognized earlier, which account for more deliveries at 34–36 weeks' gestation. Thus, late preterm neonates born between 34 and 36 weeks and 6 days of gestation are physiologically less mature and have limited compensatory responses to the extra-uterine environment, compared with term infants. This is mainly due to labeling them as "near-term," thus being looked on as "almost mature" with little need to be concerned [10-13].

While serious morbidities are rare, the late preterm group has 2–3 fold increased rates for mild-to-moderate morbidities, such as hypoglycemia, delayed lung fluid clearance and respiratory distress, poor feeding, jaundice, infection, and readmission rates after initial hospital discharge [10]. Thus, it is not surprising that the absolute number of a late preterm infant being admitted to the neonatal intensive care unit (NICU) has been increasing worldwide [10-13].

It is important to know why these neonates are being born early as well as the unique problems that this growing population of neonates may come across. Understanding the morbidities of

the late preterm neonates helps the clinician to anticipate them and also to treat accordingly, to reduce their mortality.

MATERIALS AND METHODS

This is a prospective cohort study conducted at a medical college hospital in South India. All live late preterm and term neonates born between December 2016 and July 2018 were enrolled in the study. Ethics committee consent and approval were obtained. A detailed history of parity, mode of delivery, sex, GA, birth weight, maternal risk factors, and predefined neonatal morbidities were all entered in the pre-designed pro forma. The morbidities and mortalities of these late preterm neonates were compared with the term neonates.

All late preterm neonates (34 0/7–36 6/7 weeks) and all term neonates (37 0/7–41 6/7 weeks) were included in the study. Neonates with clinically identified chromosomal anomalies were excluded from the study. Information on the following morbidities was collected.

Following respiratory complications leading to respiratory distress were enrolled. Respiratory distress syndrome (RDS) was defined as the presence of respiratory distress (tachypnea with respiratory rate >60/min, nasal flaring, grunting or retraction of chest wall) with the need of oxygen for >2 h or continuous positive airway pressure (CPAP)/ventilation. With or without radiological findings secondary to surfactant deficiency was considered. Meconium aspiration syndrome (MAS) was defined the early onset of respiratory distress in an infant with meconium-stained amniotic fluid who presents with poor lung compliance, hypoxemia, and a characteristic lung radiograph. Transient tachypnea of the newborn was defined as clinical and radiological manifestations developed during the 1st h of life and which shows complete resolution by 24–48 h.

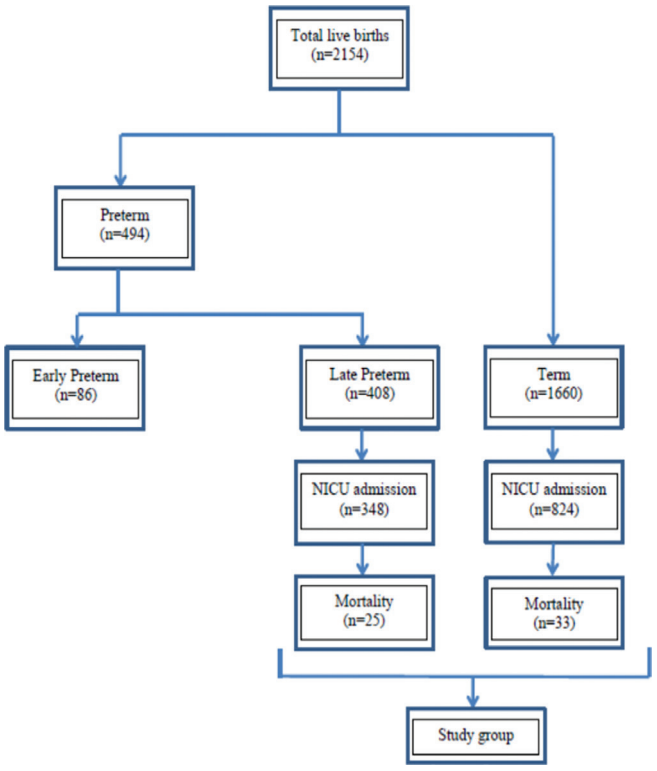

Figure 1: Flow chart for sample selection

Birth asphyxia was defined as the complete cessation of breathing, inadequate or gasping for breath with Apgar <4 at 1 min. Hypoglycemia was considered when blood sugars were <40 mg/dl in a capillary or venous blood sample. For all at risk neonates (small for GA, infant of a diabetic mother, large for GA), random blood sugar was done if clinically required. Hyperbilirubinemia was defined as visible jaundice requiring phototherapy/exchange transfusion as per hour specific nomogram by American Academy of Paediatrics.

Either proven or probable sepsis cases were considered as neonatal septicemia. Probable sepsis was considered in presence of positive septic screen (presence of two of the following five parameters: Total leukocyte count <5000/mm^3 or >20,000/mm^3, band to total polymorph ratio of >0.2, absolute neutrophil count <1800/mm^3 or >7200/mm^3, C reactive protein >0.5mg/dL, and platelets <1 lakh/mm^3). Proven sepsis was labeled in the presence of isolation of pathogens from any body fluid (blood or cerebrospinal fluid or urine). Any readmission after post-delivery discharge from hospital/NICU (within 7 days of discharge) was also recorded.

Data were entered in Microsoft Excel and analyzed using Stata version 14. A continuous variable such as GA, Birth weight, Apgar at min 1, and Apgar at min 5 was expressed as mean (standard deviation). The distribution of categorical variables such as GA, gender, NICU admissions, readmissions diagnosis, maternal risk factors, neonatal comorbidities, and interventions was expressed as proportions. To neutralize the influence of variables (e.g., overall morbidity requiring NICU admission, readmission, hypoglycemia, respiratory distress, respiratory distress requiring ventilation [nasal CPAP and SIMV], hyperbilirubinemia, and neonatal sepsis) on the outcomes evaluated, adjusted odds ratio (OR) was calculated. The associations of maternal obstetric factors and neonatal comorbidities with late preterm labor were assessed using a Chi-squared test or a Fisher's exact test. The comparison neonatal and maternal obstetric factors between late preterm and term neonates were analyzed using a Chi-squared test. The comparison of continuous variables such as GA and birth weight between late preterm and term infants was assessed using independent *t*-test. $p<0.05$ was considered as statistically significant.

RESULTS

Out of 2154 babies delivered, 408 late preterm and 1660 term babies were enrolled in this study. Of these, 1660 (77.1%) were term neonates, while 494 (22.9%) were preterm neonates. There were a total of 408 late preterm neonates who contributed to 18.9% of total live births (Fig. 1). These late preterm neonates constituted 82.59% of total preterm neonates. All the included cases were followed for the duration of 7 days. The most common maternal risk factor was pregnancy induced hypertension (PIH) (36.8%), premature rupture of membranes (16.9%) followed by oligohydramnios (15.9%).

Total 348 (85.2%) late preterm neonates required NICU admission in comparison to term neonates (824 [49.6%]). In

both the groups, neonates had more than one morbidity requiring admission to NICU. Hyperbilirubinemia (18.4%), RDS (16.7%) followed by neonatal sepsis (9.1%) were the common morbidities in these late preterm neonates. When compared to term neonates, late preterm neonates had a higher risk of developing RDS (16.7%), sepsis (9.1%), birth asphyxia (4.9%), hypoglycemia (4.4%), and necrotizing enterocolitis (NEC) (1%) which was statistically significant (p≤0.05). It was also noted that the most common cause of respiratory distress (96) in late preterm neonates was RDS (69, 71.8%) as shown in Table 1.

Table 2 shows that out of the total term neonates, 765 (46.1%) were female and 895 (53.9%) were male while out of total 408 late preterms, 183 (44.9%) were female and 225 (55.2%) were male. The rate of NICU admission was higher in late preterm neonates, than in term neonates for any morbidity ([85.3% vs. 49.6%, p<0.001, adjusted OR: 1.4; 95% confident interval: 0.8–2.4]); however, readmission rates were similar between two groups (0.9% vs. 1%, p=0.98). Late preterm neonates had higher chances of developing respiratory distress and the need for ventilation with SIMV or CPAP than the term neonates (p<0.001). Similarly, these neonates were also at greater risk for sepsis (p=0.003), hypoglycemia (p=0.002), and hyperbilirubinemia (p<0.001) than the term neonates as shown in Table 2.

Mortality rate was higher in late preterm neonates (25/348) than in term neonates (33/824), (p≤0.05). The most common cause of mortality in the late preterm neonates was RDS, and in term neonates, MAS was the most common cause as shown in Table 3.

DISCUSSION

Late preterm neonates are more prone to neonatal morbidities despite being almost mature. Out of total live births (n=2154), 1660 (77.1%) were term neonates and 408 (18.9%) were late preterm neonates. During the study period, in our hospital, every 5th birth was late preterm. This shows that these late preterm neonates contributed to a major proportion of live births. Studies have shown that there has been an increasing trend in late preterm births from 6.2% in 1995 to 7.5% in 2008 in a survey done in the USA [14]. These changes may be due to the advances in obstetric practices (such as early termination in eclampsia and other maternal and fetal morbidities) which have led to the increase in surveillance and medical interventions during pregnancy [6-9].

Among the preterm neonates, 82.5% were late preterm and the remaining 17.5% were early preterm which was higher when compared to study done in the USA in 2005 [15]. In the present

Table 1: Comparison of early morbidities between late preterm and term neonates

Early neonatal morbidities	Late preterm	Term neonates	p value
	Frequency n=408 (%)	Frequency n=1660 (%)	
NICU admissions	348 (85.3)	824 (49.6)	<0.001
Hyperbilirubinemia	75 (18.4)	457 (27.5)	<0.001
RDS	69 (16.7)	12 (0.7)	<0.001
Septicemia	37 (9.1)	86 (5.2)	0.003
TTNB	22 (5.3)	88 (5.3)	0.825
Birth asphyxia	20 (4.9)	12 (0.7)	<0.001
Hypoglycemia	18 (4.4)	30 (1.8)	0.002
MAS	5 (1.2)	77 (4.6)	0.002
NEC (G1/G2/IA)	4 (1)	1 (0.06)	0.001
Feeding difficulties	3 (0.7)	7 (0.4)	0.413

MAS: Meconium aspiration syndrome, TTNB: Transient tachypnea of newborn, NEC: Necrotizing enterocolitis, NICU: Neonatal intensive care unit, RDS: Respiratory distress syndrome

Table 2: Comparison of neonatal morbidities between late preterm and term neonates

Morbidity	Late preterm (n=408)	Term (n=1660)	Total	p value	Adjusted OR (95% CI)
Male	225 (55.2)	895 (53.9)	1120	–	–
Female	183 (44.9)	765 (46.1)	948		
Any morbidity	348 (85.3)	824 (49.6)	1172	<0.001	1.4 (0.8–2.4)
Readmission	4 (0.9)	16.1 (1)	20	0.98	1.0 (0.3–3.3)
Septicemia	37 (9.1)	86 (5.2)	123	0.003	1.3 (0.8–2)
Hypoglycemia	18 (4.4)	30 (1.8)	48	0.002	2.2 (1.2–4.1)
Respiratory distress	96 (23.5)	177 (10.7)	273	<0.001	1.5 (1.1–2.2)
Respiratory distress requiring ventilation					
SIMV	15 (3.7)	12 (0.7)	27	<0.001	2.7 (1.1–6.2)
Nasal CPAP	35 (8.6)	20 (1.2)	55	<0.001	4.3 (2.2–8.2)
Hyperbilirubinemia	75 (18.4)	457 (27.5)	532	<0.001	1.4 (1–1.9)

p≤0.05 was considered significant, CPAP: Continuous positive airway pressure, OR: Odds ratio, SIMV: Synchronized intermittent mandatory ventilation, CI: Confident interval

Table 3: Causes of mortality in the study population

Cause of mortality	Late preterm n=348 (%)	Term n=824 (%)	p value
Birth asphyxia	6 (1.7)	8 (0.9)	0.278
Septicemia	7 (2.0)	7 (0.8)	0.05
MAS	1 (0.2)	12 (1.4)	0.005
RDS	7 (2.0)	2 (0.2)	0.005
Lethal congenital anomalies	4 (1.1)	4 (0.4)	0.158
Total mortality	25	33	0.022

RDS: Respiratory distress syndrome, MAS: Meconium aspiration syndrome

study, 225 (55.2%) were male and 183 (44.8%) were females. In a study done by Gouyon *et al*. [16], male constituted 55.6% and female constituted 44.4% of the late preterm neonates. Similarly, a study done in India by Jaiswal *et al*. [3], male constituted 54.5% and female constituted 45.5%. In another Indian study by Ezhilvannan *et al.* [17], male constituted 60.47% and female constituted 39.6% of the late preterm neonates.

In our study, PIH (36.8%) and PROM (16.9%) were found to be the major maternal comorbidities. In another study by Arunagirinathan *et al.*, PROM (19.7%) and PIH (18.6%) were the major maternal comorbidities in late preterm neonates [18]. In our study, 85.2% of late preterm neonates required NICU admission during the first 7 days of life. Similarly, in a study by Arunagirinathan *et al*. [18], 83% of the late preterm neonates are required NICU admission. In other studies by Wang *et al.* [10], Leone *et al*. [19], and Jaiswal *et al.* [3] 77.8%, 70%, and 70.8% of the late preterm neonates are required NICU admissions, respectively.

The lung development of the terminal respiratory sacs and alveoli of the late preterm neonates continue through gestational weeks of 34–36 and in addition to this, some may miss the surfactant surge, which generally occurs at 34 weeks. Hence, due to the immature lung structure and functional capacity, late preterm neonates are more prone to admissions in NICU as they are at high risk of developing respiratory distress due to increased requirement of oxygen and positive pressure ventilation [10,20]. The late preterm neonates were at higher risk of developing respiratory distress ($p<0.001$) and also were more prone to assisted ventilation with SIMV ($p<0.001$) and with nasal CPAP ($p<0.001$) than the term neonates. Similarly, in a study done by Jaiswal *et al.* [3], late preterm neonates were at higher risk of developing respiratory distress (10.5% vs. 1.5%, $p<0.001$) than the term neonates.

The late preterm neonates were at higher risk of developing septicemia ($p=0.003$) than the term neonates. Similarly, in a study done by Jaiswal *et al*. [3], late preterm neonates were at higher risk of developing probable sepsis (4.1% vs. 1.1%, $p<0.001$) than the term neonates. This may be due to the fact that late preterm neonates have problems adapting from intrauterine to extrauterine life of the immune defense mechanism. Both innate and adaptive immunity are not completely developed at birth, i.e., more preterm the neonate, more immune deficiency it may have [10-13].

Hypoglycemia is inversely proportional to GA. Within the first 24 h, the enzyme concentration required for hepatic gluconeogenesis and hepatic ketogenesis increases drastically following which hypoglycemia resolves [21]. Immaturity of hepatic glycogenolysis, adipose tissue lipolysis, hormonal dysregulation and deficiency in hepatic gluconeogenesis, and ketogenesis enzyme are some of the few causes which predispose the preterm infants to hypoglycaemia [22]. The late preterm neonates were at higher risk of developing hypoglycemia ($p=0.002$) than the term neonates. Similarly, in a study done by Jaiswal *et al.* [3], late preterm neonates were at higher risk of developing hypoglycemia (8.8% vs. 1.4%, $p<0.001$). In our study, late preterm neonates were more prone to develop birth asphyxia (4.9%) than the term neonates (0.7%), ($p<0.05$), which was similar to study done by Savitha *et al.* [23].

These neonates when compared to term neonates were 2 times more prone to develop hyperbilirubinemia due to the immaturity of the liver and low concentration of uridine dephospho glucuronate and glucoronyl transferase [24]. The risk of bilirubin-induced brain injury and kernicterus is more common in late preterm neonates due to immature blood–brain barrier and low circulating bilirubin binding albumin concentration [25,26]. However, in our study, hyperbilirubinemia was more commonly seen in term neonates than the late preterm neonates. There were no attributable reasons found for the same.

Mortality in late preterm neonates was 6.1% and 7.1% in late preterm neonates ($p<0.05$). Similar results were noted in a study conducted by Mendoza *et al*. [27] In a retrospective study done by Tsai *et al.* [28], late preterm neonates had higher rates of NICU admission (36% vs. 2%) and had higher mortality rates than the term neonates. In our study, there was a higher risk of mortality with RDS (2%) and septicemia (2%) among late preterm neonates than the term neonates ($p<0.05$). Similar results were noted by Shaikh *et al.* [29] also.

Limitations of this study were that sample size was smaller due to which results might be applicable to a setting similar to our institution, and hence, these results could not be generalized. Second, as this study only emphasizes on early morbidities and does not address morbidities after 7 days of life, the long-term complications of these morbidities cannot be known.

CONCLUSION

We can conclude that the late preterm neonates are not the same as term neonates as evidenced by the high occurrence of complications in late preterm compared to term infants.

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