Early morbidity profile of late preterm neonates in a teaching hospital in South India

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ABSTRACT

Background: Late preterm neonates although close to term neonates in weight and physical appearance, have a high risk for morbidities causing a significant health care cost. **Objective:** We undertook the study to analyze the morbidity pattern of late preterm infants to help in better management of these neonates. **Materials and Methods:** This was a retrospective analytical study conducted in a tertiary hospital of South India. The data were retrieved from admission, discharge registers, case records, and neonatal database. The rate of various morbidities during the hospital stay and subgroup analysis was performed. **Results:** About 936 late preterm neonates (32.8% of preterm deliveries) were admitted in neonatology ward for various morbidities. The mean gestational age was 35.32±0.76 (1 SD) and mean birth weight was 2.11±0.46 kg (1 SD). Male:female ratio was 1.12:1. About 50% of them were born at 36 weeks, 31% at 35 weeks, and 18% were born at 34 weeks. About 16.72% of admitted late preterm neonates were severe intrauterine growth restriction (IUGR). Neonatal jaundice requiring phototherapy 33.1%, sepsis 23.7%, birth asphyxia 8.3%, and respiratory distress syndrome 6.62%, were the most common morbidities. Around 14.2% of admitted neonates required some form of respiratory support. Sepsis occurred in a significant proportion (23.7%) and 18.7% of admitted neonates had hypoglycemia. The average duration of stay was 8.19±5.5 (SD) days. **Conclusion:** Late preterm neonates are at a high risk for various morbidities, neonatal jaundice, respiratory distress, asphyxia, sepsis, and required prolonged stay. A high proportion of severe IUGR was found in our study.

Key words: *Late preterm, Morbidity, Neonatal jaundice, Neonate, Newborn, Respiratory*

Late preterm neonates are defined as those born between 34±0 and 36±6 weeks of gestation [1,2]. Although their birth weight and size resemble term neonates, they are physiologically and metabolically immature. During this period, the lung evolves from terminal sac to alveolar period (i.e., mature alveoli lined primarily with extremely thin type I epithelial cells), pulmonary capillaries start bulging into the terminal sac, and adult pool sizes of surfactant are attained.

Because late preterm neonates born earlier, immaturity of the above lung development process may be associated with delayed intrapulmonary fluid absorption, surfactant insufficiency, and inefficient gas exchange [1]. Similarly, immaturity of the central nervous system, chemosensing receptors, liver enzymes, and brown fat metabolism may lead to increased risk of apnea, hypoglycemia, hyperbilirubinemia, and hypothermia, respectively. Late preterm infants have not been studied, making it difficult to understand the biology and mechanisms of disease in this group. In 2005, a consensus workshop by National Institutes of Health and Human Development suggested use of the terminology "late preterm" instead of "near term" to highlight that they are still immature preterm [2]. The current guidelines advocate avoiding of non-indicated elective cesarean deliveries <39 weeks to decrease the rate of complications due to late preterm. However, the rate of late preterm births is rising, due to maternal indications and the quantum and severity of morbidity profile, differs between developed and developing nations.

A recent multicentric trial reported a high risk of morbidities in late preterm neonates, namely, hypothermia, hypoglycemia, respiratory distress, poor feeding, jaundice, high rates of readmission, and a high need of monitoring under specialist care at postnatal wards, adding substantial health-care burden and costs [3,4]. A recent study, on elective cesarean neonates, showed higher respiratory morbidity in neonates who were delivered late preterm when compared to term neonates [5]. However, limited data are available from India. Since late preterm forms a sizable salvageable pool of preterm, there is a need to address the associated morbidities. Moreover, most guidelines recommend antenatal steroids up to 34 weeks only; thereby, there is a need to study the burden of respiratory morbidities in this vulnerable group. Therefore, we undertook this study to know the morbidities associated with hospitalized late preterm neonates, for anticipation and better planning of management in this group.

MATERIALS AND METHODS

The present retrospective analytical study was conducted at the department of neonatology of a tertiary teaching hospital from January to December 2019. Inborn late preterm neonates delivered and admitted during the period were eligible for the study. A convenience sampling method was used. The neonates with disparity in gestational age assessment, whose case sheet was not available, who died within 1 h of life were excluded from the study. The maternal and resuscitation details were taken using birth registers. The other data were retrieved from SNCU software database [6], old case records, birth, nominal, and discharge registers and it was anonymized. The Institutional Ethical Committee approved the study and parental consent was not appropriate since the study was retrospective and involved only case records.

Gestational age was calculated from last menstrual period (LMP) with regular cycles. The first trimester ultrasound dating was used if LMP dates were not available or menstrual cycles were irregular. If both were not available or there was a gross disparity, gestational age was estimated from New Ballard score. The neonatal admission criteria used during the period of study and the indications for admission entered in the neonatal database are shown in Table 1.

Fenton's chart was used for plotting growth parameters. Less than 3rd centile of birth weight was taken as severe intrauterine growth restriction (IUGR) [7]. BiliApp based on NICE-NHS guidelines chart for 34, 35, and 36 weeks gestation was used for deciding phototherapy and exchange transfusion for jaundice.

A standard working criteria for other major morbidities like perinatal asphyxia, sepsis, necrotizing enterocolitis (NEC), transient tachypnea of newborn, respiratory distress syndrome

Table 1: Admission criteria

Indications for admission	Criteria
Prematurity 340/7–346/7 weeks of gestation	
350/7–36 6/7 weeks of gestation with any one of the following indications –	
Abdominal distension	Visible obvious abdominal distension or persistent abdominal distension even before feeds after a period of observation for 1 h
Any other	Neonates born to mothers with risk factors for infection (any one) Premature rupture of membranes >18 h, maternal fever >38°C, leukocytosis, evidence of urinary tract infection, foul-smelling liquor, active cough, respiratory distress Neonates born to mothers with illness/medications, requiring monitoring 1. Diabetic/gestational diabetes 2. Bad obstetric history with no living child 3. Mothers received intrapartum magnesium sulfate 4. Critically ill mothers admitted at intensive care
Apnea/gasping	One or more episodes of apnea or gasping
Baby of diabetic mother	Includes known diabetic and gestational diabetic mothers
Bleeding	Except for trivial bleeding during cord fall, any other bleeding noticed at any site
Congenital malformation	Major congenital anomalies requiring intervention or observation
Cyanosis	Central cyanosis or SaO2 <95% preductal or SaO2 <92% at two different readings 15 min apart
Diarrhea	Watery stools with evidence of dehydration or with any other feature to be concerned such as vomiting feed refusal and extra lacteal feeding
Hyperthermia	Axillary temperature >37.5°C recorded over 1 min
Hypoglycemia	Capillary blood glucose <45 mg%, taken by heel prick using a glucometer
Hypothermia	Axillary temperature <35.4 recorded over 1 min
Birth weight	Large baby >4 kg or low birth weight <1800 g
Meconium aspiration	Meconium stained amniotic fluid, plus clinical evidence of respiratory distress
Neonatal convulsions	One or more episodes of seizures, after ruling out jitteriness
Neonatal jaundice	Visible jaundice at lower legs or at palms and soles and/or serum bilirubin values at phototherapy zone
Oliguria	Not passed urine until 48 h after birth, or decrease in urinary frequency <5 times/day noticed by mother or approximate urine output <1 ml/kg/day
Perinatal asphyxia	Birth asphyxia/perinatal depression with 5 min Apgar score <7 or requiring tactile stimulation/bag valve mask ventilation/chest compression/iv medications
Refusal to feed	Inability to suck at mother or swallow expressed milk on at least two occasions ½ h apart
Respiratory distress	Any one (tachypnea/apnea, grunting, and chest retractions) at 1 h of life
Shock	Tachycardia, heart rate >180 or heart rate <90 at 15 min or more of life, mean blood pressure <5th centile for GA as per Zubrow's chart, weak peripheral pulse, capillary refill time >3 s (any two)
Unconsciousness	Irritability, lethargy, weak response to deep pressure, and comatose (no response to pain) – (any one)

(RDS), and inborn error of metabolism was used. The extracted data were entered in a pre-set pro forma.

All the data were entered into Excel and statistical analysis was performed using SPSS 25.0. Data were expressed as number (with percentages) and mean values (with standard deviations). Differences between groups were analyzed with one-way ANOVA for mean and Pearson's Chi-square test for proportions. $p<0.05$ was considered statistically significant.

RESULTS

About 13,767 total deliveries and 5385 (39.12%) cesarean deliveries were conducted during the study period. A total of 20.67% (2846) were preterm deliveries and 79.32% (10921) were term deliveries. About 936 late preterm neonates (32.8% of preterm) were admitted for various morbidities. The mean gestational age was 35.32±0.76 (1 SD) and mean birth weight was 2.11±0.46 kg (1 SD). Male:female ratio was 1.12:1. Around 50% of the admitted late preterm neonates were born at 36 weeks, 31% at 35 weeks, and 18% were born at 34 weeks. The baseline maternal parity, thyroid status, course of labor, and the mode of resuscitation were not significantly different between the three gestational age subgroups (Table 2).

A total of 35.5% late preterm were small for gestational age (SGA) (<10th centile) and 16.72% of admitted late preterm neonates were severe IUGR (<3rd centile). Higher gestational age has significantly more SGA than lower gestational age (Table 2). About 136 of these neonates required some form of resuscitation and only one required chest compression.

Neonatal jaundice (36.7%), RDS (21.04%), low birth weight (LBW) (21.7%), and perinatal asphyxia (9.18%) were the most common indications for admission. A statistically significant difference ($p<0.001$) was seen between the three groups with respect to neonatal jaundice and LBW. In the final diagnosis, neonatal jaundice requiring phototherapy, sepsis, birth asphyxia, and RDS was the most common morbidities in the admitted neonates. The average duration of stay was 8.19 + 5.5 (SD) days, as shown in Table 3.

DISCUSSION

Late preterm births constitute 75% of preterm birth in the USA [8] and 55% of live preterm births in a single-center study in India [9]. They constitute 38% of preterm deliveries in our center. The percentage distribution of late preterm neonates in our ward was 18%, 21%, and 51% for 34, 35, and 36 weeks, respectively,

Table 2: Baseline characteristics of the study population

Characteristics	Gestational age (weeks)			p value
	34	35	36	
Frequency n (%)	170 (18.16%)	297 (31.73%)	469 (50.11%)	
Female	82	144	214	0.562
Male	87	149	257	
Extremely low birth weight	1 (0.6)	1 (0.3)	0	0.69
Small for gestational age <10th centile	43 (25.3)	102 (34.3)	187 (39.9)	0.002
Small for gestational age < 3rd centile	13 (7.6)	51 (17.2)	92 (19.6)	<0.001
Large for gestational age >4 kg	0	0	2 (0.4)	
Weight in kg*	1.90±(0.4)	2.03±(0.4)	2.23±(0.4)	<0.001
Head circumference, cm*	31.73±(1.6)	31.95±(1.7)	32.9±(1.9)	0.091
Length, cm*	49.60±(0.8)	46.69±4.1)	(49.3±(1.6)	0.004
Resuscitation n (%)				
Bag and mask	1 (3.2)	1 (2.0)	1 (1.8)	0.904
Chest compression	-	1 (2.0)	-	0.409
Intubation	6 (19.4)	11 (22.4)	8 (14.3)	0.553
Only oxygen	2 (6.5)	7 (14.3)	4 (7.1)	0.37
Tactile stimulation	22 (71.0)	29 (59.2)	43 (76.8)	0.145
Any one resuscitation	31/170 (18.23%)	49/297 (16.49%)	56/469 (11.94%)	0.655
Maternal details				
Tetanus toxoid doses*	(1.98±0.1)	(1.98±0.1)	(1.99±0.1)	0.767
Hemoglobin*	(10.70±1.5)	(10.87±1.6)	(10.85±1.4)	0.769
Euthyroid n (%)	114 (88.3)	203 (89.4)	325 (88.8)	0.949
Course of labor n (%)				
Obstructed	3 (1.76)	2 (0.67)	8 (1.71)	0.6
Prolonged 1st or 2nd stage	3 (1.76)	4 (1.35)	2 (0.43)	0.22
Uneventful	164 (96.47)	291 (97.98)	459 (97.870)	0.753

*** (Mean±SD). The other variables mentioned as n (%)**

Table 3: Final diagnosis (morbidities) and treatment given

Single most important morbidity	Number	Percentage
Birth asphyxia: Hypoxic ischemic encephalopathy	78	8.33
Congenital malformation	14	1.5
Extremely low birth weight (999 g or less)	2	0.21
Meconium aspiration	13	1.39
Jaundice requiring phototherapy	310	33.12
Jaundice requiring exchange transfusion	3	0.32
Suspect sepsis (clinical+positive screen)	141	15.06
Culture-positive sepsis	81	8.65
Inborn error of metabolism	2	0.21
Necrotizing enterocolitis	88	9.4
Respiratory distress syndrome of newborn (hyaline membrane disease)	62	6.62
Transient tachypnea of newborn	27	2.88
Shock	2	0.21
Any other diagnosis	23	2.46
No major morbidity, requiring monitoring for low birth weight/intrauterine growth restriction	90	9.62
Total	936	100
Maximum respiratory support		
Ventilated	69	7.37
Continuous positive airway pressure	26	2.78
Oxygen supplementation	38	4.06
Total		14.21
Comorbidities		
Hypoglycemia	175	18.7%
Duration of stay, in days, mean (SD)	8.19 (5.5)	

i.e., more mature neonates were admitted in a higher proportion. A similar trend was reported by Patil and Patil (21.78%, 34.64%, and 43.57% at 34, 35, and 36 weeks, respectively) [10].

In the present study, 16.72% of admitted late preterm neonates were severe IUGR. This is very high in comparison to other Indian studies by Femitha and Bhat and Nagalekshmi *et al*. who observed 6.8% and 10% [9,11], but similar rates were reported in a large western trial by Boyle *et al*. of 18.9% [3]. The high proportion of severe IUGR population in the present study might have contributed to the increased risk of morbidities in our study.

The most common neonatal morbidity and neonatal hyperbilirubinemia in our study was 36.32%, and this was in accordance to the other Indian studies [11], but a higher rate of 55.1% was reported by another Indian study by Jaiswal *et al*. [12]. However, a multicenter trial (LAMBS trial) reported a lower rate of jaundice (16.2%) [3]. The wide variability of neonatal jaundice was due to different criteria used in the studies. In the LAMBS trial, only the neonates who required phototherapy were taken as the morbidity criteria, whereas in the Indian study, all kinds of jaundice were included and it reported a high incidence [12]. Another recent study by Khowaja *et al*. from Karachi reported respiratory distress as the most common neonatal morbidity and jaundice developed in 17.5% of the late preterm infants [13]. The morbidities were observed for the first 72 h, only. That may be the reason for high respiratory morbidity, but in our study, overall morbidity during hospital stay was analyzed suggesting a high incidence of transfer from postnatal wards for jaundice.

The incidence of RDS is higher in late preterm infants compared to term neonates. It was 21.04% in our study, which was lower than that reported by Shaikh *et al*. [14], but was higher than that reported by Femitha and Bhat [9]. The study which reported a higher percentage had lesser coverage of antenatal steroids leading to a higher incidence of respiratory distress [14]. In our study, 14.21% of neonates received some form of respiratory support of which 7.4% received invasive ventilation and 2.8% received continuous positive airway pressure (CPAP)/non-invasive ventilation. Similar to our study, in a large multicenter trial [3], 22% of late preterm neonates received some form of respiratory support. Other Indian studies showed variable rates of invasive and non-invasive ventilation/CPAP ranging from 14.62% and 17.35%, respectively, in a government setting, to 0.5% and 2.5%, respectively, in a private hospital setting [9,12]. Similarly, Teune *et al*. in a systematic review reported 2.5% of cases which required invasive ventilation [15]. This may be due to difference in the baseline profile of admitted neonates and associated comorbid factors in different settings.

Immunological immaturity with relative deficiencies in immunoglobulin, complement levels, and innate immunity makes late preterm infants more prone to septicemia. Invasive procedures and maternal chorioamnionitis further increase the risk of sepsis [13,16]. In the present study, 23.72% of neonates admitted had a final diagnosis of sepsis. These results were in accordance with earlier studies [9,10]. In our study, 8.65% of the study population had culture-positive sepsis and 15.06% had screen positive suspect sepsis which was higher when compared to other reported studies by Boyle *et al*. and Teune *et al*. [3,15]. A majority of the organisms causing sepsis in our study were Gram negative which is in contrast to the reported Gram-positive organisms in another large cohort by Cohen-Wolkowiez *et al*. [17]. The risk of NEC in our study was 9.4%, whereas other studies reported 13.6% and 0.11% absolute risk (OR 7.5) in a systematic review when compared to term neonates [9,15].

Hypoglycemia in late preterm neonates may be due to immaturity in the enzymes involved in hepatic gluconeogenesis, glycogenolysis, ketogenesis, and lipolysis. The other contributing factors may be feeding difficulties, delayed oral feedings, and other associated comorbid factors such as respiratory distress and diabetic mother. In the present study, three neonates were direct admissions and hypoglycemia was found to be a comorbid factor in 18.7% of late preterm neonates. Femitha and Bhat reported it in 14.8% of cases and Bulut *et al*. reported hypoglycemia in 15.3% of cases [9,18], whereas low rates of 5.7% were reported in a large trial [3].

A higher incidence in our study may be due to higher prevalence of severe IUGR. It was observed that lesser the gestational age, more was the risk for hypoglycemia as 11.2%, 4.4%, and 3.2% of neonates born at 34, 35, and 36 weeks gestations, respectively, developed hypoglycemia in our study. A similar trend was seen in

the study by Femitha and Bhat [9]. There is rising evidence that late preterm neonates have a higher relative risk for intraventricular hemorrhage (RR, 4.9) [15], 1.52 times odds risk for mental and 1.56 times more risk for physical developmental delay [19], and behavioral problems at 6 years compared to term infants [20].

Our study had a few limitations. Our study being a retrospective chart study, early neonatal morbidities during hospital stay were studied. Long-term growth and neurodevelopmental outcomes in LPN were not studied. Other limitations of our study are being a state-run hospital, treatment is free, and so, health-care cost analysis could not be done.

CONCLUSION

Late preterm constitutes 33% of preterm admissions with significant morbidities causing health-care burden. Our study showed high proportion (16.72%) of severe IUGR in admitted late preterm neonates. Neonatal jaundice requiring phototherapy, sepsis, birth asphyxia, and RDS were the most common morbidities.

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