RESEARCH PAPER

Physical Growth, Morbidity Profile and Mortality Among Healthy Late Preterm Neonates

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Received: April 01, 2016; Initial Review: July 14, 2016; Accepted: May 19, 2017.

Objective: To compare the physical growth outcomes, morbidity profile and mortality at an age of 12 months among late preterm (34 $^{0/7}$to 36 $^{6/7}$) neonates to term (37 $^{0/7}$to 41 $^{6/7}$) neonates.

Study design: Prospective cohort study.

Setting: A tertiary care center of Northern India during 2014-2015.

Participants: 200 apparently healthy late preterms and term infants, followed up to 12 months of age.

Main outcome measures: Physical growth parameters, morbidity profile and mortality.

Results: At mean age of 12 months, mean (SD) weight, length and head circumference of late preterms were 7.4 (0.8) kg, 69.2 (2.5) cm and 43.0 (1.1) cm, respectively; which were significantly lower than that of the full term infants [8.7 (1.6) kg, 72.2 (3.1) cm and 44.2 (1.1) cm] (P< 0.001). On univariate analysis, late preterm group was associated with higher odds (95% CI) of being underweight [5.6 (3.4, 5.5)], stunted [3.5 (2.1, 5.8)] and wasted [3.6 (1.9, 6.9)]. On multivariate analysis, only adjusted odds of late preterms becoming underweight by one year was significant [OR 4.1; 95% CI (1.6, 10.4)]. Feeding difficulties, jaundice and re-hospitalization rates were significantly higher in the late preterm group. The median (IQR) episodes per baby for late preterms as compared to terms for diarrhea [1.84 (0,3) *vs* 1.14 (0,2) (P <0.001)], and fever [1.33 (0,2) *vs.* 0.95 (0,2) (P = 0.01)] were higher.

Conclusion: Healthy late preterms are at significantly higher risk of being underweight in the first year of life, in addition to having significantly higher morbidity.

Keywords: *Prematurity, Prognosis, Stunting, Underweight, Wasting.*

Published online: June 04, 2017. PII:S097475591600062

Late preterm (LPT) infants accounts for nearly 8% of all births and almost 74% of all preterm births [1]. They are at increased risk for having higher morbidities and mortality in the neonatal period as well as adverse neurodevelopmental outcomes as compared to full term (FT) infants [2-4]. Late preterms have also been shown to have higher health care utilization rates [5], re-hospitalization rates and mortality by 1 year of age [6,7]. However, majority of them do not require admission in neonatal intensive care unit (NICU) soon after birth. Such infants are often left out from the ambit of follow-up and growth monitoring. Few retrospective studies from developed countries have reported that even such apparently healthy looking late preterms have higher morbidity and mortality in the initial years of life [3]. A recent study from India has compared the short term outcomes of late preterms, [8] but there is no Indian data on longer follow-up of such infants. With this background, we designed this cohort study with the objective of follow-up of apparently healthy asymptomatic late preterm infants till 1 year of age and assess them for physical growth, morbidity and mortality.

METHODS

This cohort study was conducted after obtaining approval from Institutional Ethical Committee of the LLRM Medical College, Meerut, Uttar Pradesh in Northern India. All neonates born between April 2014 and August 2014 were assessed for eligibility, and enrolled neonates were followed till 1 year of age. Informed written consent in local language (Hindi) was obtained from mother and/or father of the enrolled infant. Healthy late preterms (born between 34$^{0/7}$to 36$^{6/7}$ gestational age) [9] appropriate for gestational age (AGA) neonates delivered in the hospital, who did not require resuscitation or admission in the NICU for more than 48 hours and resided within 20 km radius of institution premises were included as cases. We excluded multiple births, those with major congenital anomalies, and those with families who were reluctant for institutional follow-up for any reason. Control group constituted the next born healthy term

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infant ($37^{0/7}$to $41^{6/7}$weeks) who did not require resuscitation or admission in NICU for more than 48 hours, and consented for follow-up.

Gestational age was documented in completed weeks from the date of mother's last menstrual period (LMP) or antenatal ultrasonography of first trimester. If LMP or ultrasonography were not available, gestational age was estimated using New Ballard Score [10]. AGA, SGA and large for gestational age were defined by standard growth charts [11]. Follow-up of infants in the two groups was planned at the time of all routine immunizations and at 12 months of age. We telephonically reminded all parents for their visit to hospital and for routine immunization and follow-up. For study purpose, detailed physical growth parameters were recorded only at 12-month visit. Morbidities were recorded at every immunization visit, and finally at 12 months. Similar standard of care was provided to infants in both groups.

The primary outcome of the study was physical growth parameters: weight-for-age (WFA), length-for-age (LFA), weight-for-length (WFL), head circumference for age (HFA), and respective Z-scores at 12 months of age. The secondary outcomes were to determine the morbidity profile, which was recorded in a questionnaire. Maternal details and other potentially confounding maternal and family covariates were noted. Socioeconomic status was classified as per the Modified Kuppuswami Classification [12].

Naked weight was measured by calibrated digital weighing machine (Dolphin India), with precision error of 5 gram. Length was measured with infantometer designed to measure lengths between 0 and 100 cm with precision of 1 mm. Head circumference (HC) was measured using a self-retracting, 0.7 cm wide, flat metal tape with black lead-in strip (range 0-200 cm, calibrated to 1 mm). Measurements were recorded by two invesigators throughout the duration of study. WFA, WFL, LFA and HFA were calculated using WHO multicenter growth reference study (MGRS) charts. Z score for these values was calculated using 'WHO Anthropometric Calculator' version 3.2.2 (www.who.int/child growth/ software/en/). Those with WFA, LFA and WFL scores below -2SD were labelled underweight, stunted and wasted, respectively [13].

At every follow-up, we examined the children and prescribed routine immunization as per hospital schedule. Parent(s) were asked about number of episodes of diarrhea, pneumonia, hospitalizations, and feeding difficulties. Feeding difficulties were classified as difficulties attributable to the infant (poor attachment/ latching, excessively sleepy infant) and those attributable to the mother (not enough milk, flat or inverted nipples). Difficulty in initiation of breast feeding, doctor visits seeking medical advice for feeding difficulties, duration of exclusive breast feeding, diluted feeding and bottle feeding were also recorded. Diarrhea, pneumonia and exclusive breast feeding were defined as per standard WHO definitions [14-16]. Fever was defined as oral temperature more than 99.5°F or axillary temperature over 99°F documented by a health care professional. Hospitalization was defined as admission for >24 hours for any medical illness.

At 12 months of age, hemoglobin (Hb) and serum ferritin was measured in these infants. Serum ferritin was measured using one step enzyme immunoassay sandwich method with a final florescent detection using ferritin kit (Biomeriux Company, Marcy l'Étoile, France).

Data were analyzed using STATA 12.0 software. Continuous data was analyzed using student unpaired t test for parametric data and Rank Sum test for non-parametric data. Categorical data was compared using Chi square or Fisher exact test as applicable. Odds ratio with 95% confidence interval was calculated for preterm and term group. Logistic regression was done using WFA, WFL, LFA and HFA as a dependent variable and sex of the baby, maternal weight, height, socioeconomic status, exclusive breast feeding and re-hospitalization as covariates. *P* value of <0.05 was considered significant.

RESULTS

***Fig.* 1** shows the flow of participants in the two groups. We enrolled 200 neonates in each group. ***Table* I** compares the baseline characteristics of the two groups.

TABLE I COMPARISON OF BASELINE CHARACTERISTICS OF THE TERM AND LATE PRETERM NEONATES

Characteristics	*Term (n=199)*	*Late preterm (n= 200)*
#Weight at birth (kg)	2.8 (0.3)	2.3 (0.3)
#Length at birth (cm)	49.2 (1.6)	46.2 (1.3)
#Head circumference (cm)	35 (0.9)	32 (0.9)
#Gestational age (wks)	38.4 (1)	35.2 (0.8)
Sex (male)*	103 (51.7)	107 (53.5)
Vaginal delivery*	118 (59.3)	117 (58.5)
Maternal age (y)	26.1 (3.6)	25.8 (3.7)
$Maternal weight (kg)	61.6 (7.3)	63.2 (4.2)
Maternal height (cm)	140.1 (0.5)	141.5 (0.5)
Maternal Hb (g/dL)	9.5 (1.3)	9.6 (0.9)
*Socioeconomic status**		
Lower	78 (39.2)	60 (30.3)

*Values indicate mean (SD) or *number (%); #P<0.001; $P=0.008; MOD: mode of delivery; Hb: hemoglobin.*
Oxytocin was used in all the mothers.

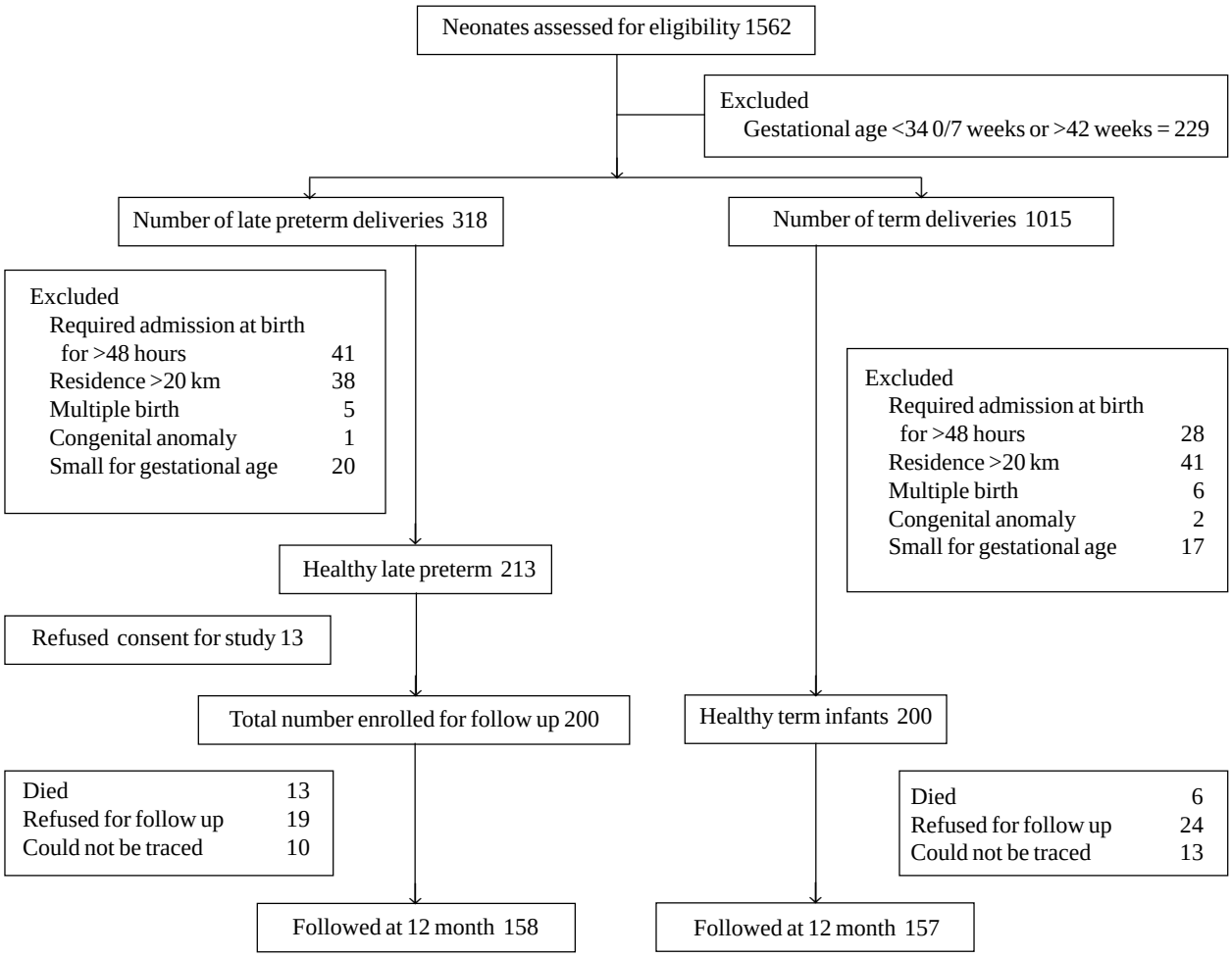


Fig. 1 *Flow of the participants in the study.*

At mean age of 12 months, mean (SD) weight, length and head circumference of late preterms were significantly lower than that in the full term group (***Table* II**). On univariate analysis, as compared to term birth, late preterm birth was associated with higher odds of being underweight, stunted and wasted. However, on multivariate analysis only adjusted odds of being underweight was significant (***Table* III**). Over first year, late preterm infants gained lesser weight as compared to full term infants. This 1 [0.7, 1.2] kg difference was statistically significant (P <0.001). Weekly weight-gain was significantly lesser in late preterms as compared to full term infants. Length gain was comparable in both the groups. The mean growth of HC was more by 1.8 [1.5, 2] cm in the late preterms as compared to full term infants. Despite this gain in HC, 34% Late preterm remained below -2 z scores as compared to only 14% in the term group (P < 0.0001). Their mean HC at one year also remained significantly lower than the full term infants (***Table* II**).

Jaundice requiring phototherapy, feeding problems and hospitalization rates were higher in late preterms as compared to full term group. Incidence of diarrhea and fever was also significantly higher in the late preterm group (***Table* IV**). Morbidity was inversely proportional to the gestational age (***Fig.* 2)**.

The mortality in the late preterm group was 7% as compared to 4% in full term group [OR (95% CI) of 2.1 (0.8, 6), P=0.1]. Mortality also had an inverse relationship with gestation age (***Fig.* 2**).

DISCUSSION

We observed that the healthy late preterm infants who do not suffer from morbidities in immediate neonatal period are at increased risk of being underweight during first year of life. Feeding difficulties and hospitalization due to diarrhea and fever were higher in late preterm group than full term infants while exclusive breastfeeding rates were

TABLE II GROWTH OUTCOMES OF LATE PRETERMS AND TERM INFANTS AT 12 MONTHS OF AGE

Parameter	*Term(n=157)*	*Late preterms(n=158)*	*P*	OR (*95% CI*)
Weight (kg)	8.7 (1.6)	7.3 (0.7)	<0.001	1.4 (1.1, 1.6)
Length (cm)	72.2 (3.1)	69.2 (2.5)	<0.001	3 (2.3, 3.6)
HC (cm)	44.2 (1.1)	43 (1.1)	<0.001	1.2 (0.9-1.4)
*Weight gain (kg/y)	5.9 (1.6)	4.9 (0.7)	<0.001	1(0.7-1.2)
*Weight gain(g/wk)	115 (26.2)	102.2 (35.6)	<0.001	12.8 (8, 17)
*Length gain (cm/y)	23.1 (3.4)	23.1 (2.7)	0.968	0 (-0.6, 0.6)
*HC gain (cm/y)	9.1 (1.3)	10.9 (1.2)	<0.001	-1.8 (-2.0,-1.5)

*Value in Mean (SD); *In first year.*

TABLE III GROWTH OUTCOMES OF THE LATE PRETERMS AT 12 MONTHS OF AGE

Growth Parameters	*Crude OR (95% C.I.)*	*Adjusted odds (95% C.I.)*
Underweight[b]	5.6 (3.4, 5.5)	4.1 (1.6, 10.4)[a]
Stunting[b]	3.5 (2.1, 5.8)	1.2 (0.5, 2.7)[a]
Wasting[b]	3.6 (1.9, 6.9)	1.4 (0.6, 3.7)[a]
Head circumference[b]	3.4 (1.9, 5.9)	1.3 (0.6, 2.9)[a]

a: Adjusted for sex, maternal weight, maternal height, re-hospitalization, exclusive breastfeeding and socioeconomic status; b: Odds ratio for late preterm infants with reference to term infants.

lower. Late preterm infants were also found to be having lower mean Hb and serum ferritin level at one year of age.

Our study differed from earlier studies on late preterms as only healthy late preterms were enrolled and compared to term counterparts. Limitation of the study was the small sample size and that the neurodevelopment outcomes were not studied. The late preterm infants who required admission to NICU soon after birth were not followed up as evidence is already available regarding out comes in this population. Another limitation of the study was the follow-up loss in about 20% of enrolled babies.

TABLE IV MORBIDITY PROFILE OF TERM AND LATE PRETERM INFANTS TILL 1 YEAR OF AGE

Variables	*Term(n=157)*	*Late preterm(n=158)*	*P*
Feeding related			
*Difficulty in initiation of breast feeding	25 (15.9)	44 (27.8)	0.014
*Feeding difficulties	29 (18.5)	51 (32)	
Trouble latching	7 (4.5)	25 (15.8)	0.004
Sleepy baby	0 (0.00)	6 (3.8)	
Not enough milk production	19 (12.1)	19 (12.0)	
Inverted nipples	3 (1.9)	1 (0.6)	
*Exclusive breast feeding for 6 months	109 (69.4)	92 (58.2)	0.046
*Medical consultations regarding feeding difficulties	11 (7.0)	23 (14.4)	0.045
*Bottle feeding	59 (37.6)	80 (50.6)	0.023
*Diluted feeding	61 (38.9)	58 (36.7)	0.728
Morbidity profile			
#Diarrhoea episodes	1.14 (0 -2)	1.84 (0-3)	0.0005
#Fever episodes	0.95 (0-2)	1.33 (0-2)	0.0143
#Prevalence of pneumonia	0.45 (0-1)	0.48 (0-1)	0.3510
*Jaundice requiring phototherapy	42 (26)	62 (39.2)	0.008
*Hospitalization	19 (12.1)	40 (25.3)	0.02
Hematological parameters			
**Hemoglobin (g/dL)	8.3 (1.1) (*n* = 136)	7.9 (1.1) (*n* = 133)	0.0113
#Serum ferritin (ng/mL)	90.1 (19.9-112) (*n* = 121)	69.9 (1.2-80.3) (*n* =129)	<0.001

*Values indicate *Number(%); **Mean (SD) or #Median (IQR).*

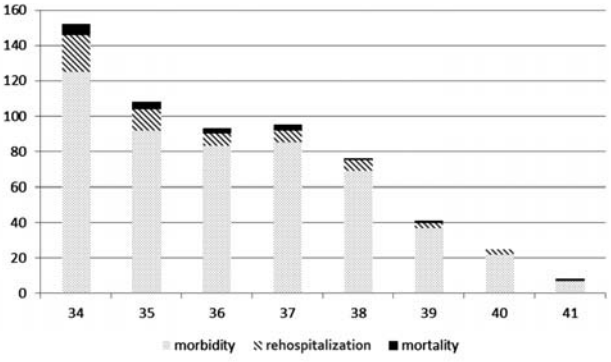
WHAT IS ALREADY KNOWN?

- Late preterms are at significant risk of higher mortality and morbidity in the immediate neonatal period.

WHAT THIS STUDY ADDS?

- Late preterm neonates, even if they do not require NICU admission at birth, are at significant risk of growth faltering, feeding difficulties, and morbidity during infancy.

Very few studies have evaluated the early childhood physical growth outcomes of healthy late preterms. Santos, *et al.* [17] reported an increased risk for being underweight and stunted in 371 late preterms as compared with full term children at 12- and 24-months of age. The odds of being wasted was higher at 12 months but not at 24 months of age. In our study, only the adjusted odds of being underweight only was significant. The difference could be because our study included only apparently healthy late preterms, while Santos, *et al.* included all late preterms, including those requiring admission to NICU. Goyal, *et al.* [18] in a retrospective study on 553 infants with gestational ages ranging from 34 to 36 weeks, also demonstrated a positive association between late preterms birth and being underweight at one year of age. Feeding difficulties in late preterms probably makes them more vulnerable to malnutrition, and therefore they may require special care and extra assistance than full term infants. It would be worth mentioning that we did not correct the late preterm babies for gestational age on follow-up. It was not corrected for gestation, as our unit protocol is to use corrected gestation only in babies less than 34 weeks of gestation. We agree that slightly shorter duration of growth in late preterms can be a confounding factor when comparing growth of full terms at 1 year of age. Other studies [17,18] comparing these two groups also did not mention about correction for gestation age in their papers.



Gestational age in weeks

*Morbidity includes episodes of diarrhea, pneumonia, fever and hyperbilirubinemia.

FIG. 2 *Gestation wise analysis of morbidity and mortality.*

Increased episodes of diarrhea and fever in late preterms may be attributed to malnutrition and feeding difficulties. Escobar, *et al.* [19] reported higher risk of re-admission among babies born between 33 to 36 weeks gestation as compared to babies born after 37 weeks. Re-admission rates of late preterm infants have been reported to be 1.5-3 times higher than that of term infants, and the main reasons for re-hospitalization are jaundice and feeding difficulties in the neonatal period [1,20,21]. Boyle, *et al.* [4] in a prospective population-based study of 1146 late preterms, also reported that they were less likely to be fed breast milk than term infants [4].

We conclude that late preterm neonates who do not even require admission at birth are at significantly higher risk of growth faltering in the first year of life. They tend to have lower weight, as compared to their term counterparts. They have higher morbidities like feeding difficulties, jaundice, diarrhea, pneumonia and fever as compared to full term infants in the first year of life. All babies born as late preterm should be followed up in high-risk clinics with special monitoring of growth and feeding difficulties.

Contributors: PG, MJ: collected and compiled the data for the study, and drafted the manuscript: AU: conceptualized and designed the study, finalized the manuscript. AY, BK, RM: provided intellectual inputs from protocol stage and helped in drafting the paper. The final version of manuscript was approved by all authors.
Funding: None. *Competing Interests*: None stated.

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