RESEARCH PAPER

Predictors of Significant Jaundice in Late Preterm Infants

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Objectives: To study (*i*) the incidence and course of jaundice, and (*ii*) the predictors of 'significant jaundice' in late preterm infants.

Design: Prospective analytical study.

Setting: Urban perinatal center.

Patients: Inborn late preterm infants (post menstrual age of 34 0/7 to 36 6/7 weeks).

Methods: Infants were followed till day 14 of life or till onset of significant jaundice. Relevant maternal, perinatal and neonatal variables were prospectively recorded. Transcutaneous bilirubin (TcB) was measured in each infant twice daily for the first 48 hours of life.

Outcomes: Significant jaundice defined as requirement of phototherapy/exchange transfusion as per hour specific total serum bilirubin (TSB) nomogram of AAP guidelines.

Results: 216 infants were enrolled, of which 123 (57%) had significant jaundice. 36% of the jaundiced infants had TSB greater than 15 mg/dL. The mean duration of onset of significant jaundice was 61 ± 32 hours. The mean duration of phototherapy was 49 ± 26 hours. Large for gestation, lower gestational age, birth trauma and previous sibling with jaundice predicted severe jaundice. TcB measured at 24-48 hrs was a better predictor of 'significant jaundice with onset after 48 hrs' than clinical risk factors.

Conclusion: There is a high incidence of significant jaundice in late preterm infants. TcB measured at 24-48 hrs of life better predicts 'significant jaundice after 48 hours of life', in comparison with clinical risk factors.

Key words: *Late-preterm, Outcome, Prediction, Significant jaundice, Transcutaneous bilirubin.*

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Jaundice in the newborn is a common cause for hospital readmission during the first week of postnatal life [1]. Late preterm gestation has been identified as one of important risk factor for the development of severe jaundice and kernicterus [2]. Jaundice in late preterm infants is more prevalent, more pronounced, and more protracted in nature than in their term counterparts [3]. With most infants getting discharged at or before 48 hours of life, outpatient follow-up is needed to identify the infants in whom total serum bilirubin levels will rise high enough to require treatment. The American Academy of Pediatrics (AAP) clinical practice guidelines on the management of neonatal hyperbilirubinemia recommend that all newborn infants be assessed before discharge for the risk of developing subsequent severe hyperbilirubinemia [4]. Several recent studies have looked at ways of predicting the risk of significant post discharge jaundice by taking measurements before hospital discharge [5-7]. All the previous studies have evaluated the predictors of jaundice in term and near term infants, but none exclusively in this high risk group.

METHODS

All consecutive inborn late preterm infants between 1st February to 31st July, 2009 with post-menstrual age of 34 0/7 to 36 6/7 weeks were eligible for inclusion. Infants with major malformations and Rh incompatibility were excluded. Gestational age was assessed from the first trimester ultrasound or mother's last menstrual period.

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The relevant perinatal and neonatal data were recorded prospectively in a predesigned case reporting form. A single trained nurse did the TcB measurement in each infant twice daily (7 AM – 9 AM and 6 PM – 8 PM) for the first 48 hours of life. All measurements were obtained from the forehead using transcutaneous bilirubinometer (Bilichek-HHU, Respironics). Whenever the neonate was clinically jaundiced, or when TcB was >12mg/dL, total serum bilirubin (TSB) estimation was done. Treatment of jaundice was based on the TSB and not on the TcB. TSB was estimated from the capillary sample using spectrophotometer (Unibeam). Significant jaundice was defined as requirement of phototherapy/exchange

transfusion as per hour specific total serum bilirubin (TSB) nomogram of AAP guidelines. Infants discharged from the hospital were followed in the outpatient clinic daily till day 14 of life or till onset of significant jaundice. Neonates with significant jaundice were started on phototherapy as per the AAP guidelines [4]. Infants with gestation 34 weeks and SGA infants were started on phototherapy at TSB levels 1mg/dL less than the treatment threshold on the AAP charts.

Continuous variables were summarized using mean ± SD and categorical variables as frequencies and percentages. Based on the hour of measurement, the TcB measurements were grouped into TcB 0-12 hrs, TcB 13-24 hrs, TcB 25-36 hrs and TcB 37-48 hrs. The clinical risk factors and the grouped TcB measurements were compared between infants with and without significant jaundice after 48 hours of life. Sensitivity, specificity, predictive values and ROC curves were plotted for all significant clinical variables and median TcB measurements for the prediction of significant jaundice. Discriminative ability of predictive variables for the outcome of interest was compared with ROC curves (area under the curve). *P* value <0.05 was considered significant.

The study was approved by the Institute's ethics committee and consent was obtained from the parents immediately after the birth of the child.

RESULTS

Of the 265 late preterm infants born in the hospital during the study period, 216 (58% males) were enrolled in the study (***Fig.* 1**). Two hundred and thirteen infants were followed till onset of significant jaundice or till day 14 of life. The mean gestation and the mean weight of study subjects were 35.42 ±0.75 weeks and 2375 ± 490 grams, respectively. Thirty four (16%), 56 (26.3%) and 123 (57.7%) infants were of gestation 34, 35 and 36 weeks, respectively, 23 (10.8%) neonates were small for gestation (SGA) and 15 (7%) were large for gestational age (LGA). Forty six (21.5 %) infants were born of twin or triplet gestation. One twenty three (57%) subjects developed significant jaundice. The incidence of jaundice was significantly higher at 34 (65%) and 35 weeks (68%) than at 36 weeks (51.2%) (*P* =0.02). The mean duration of onset of significant jaundice was 61 ± 32 hours. Three (1.4%) infants developed significant jaundice within first 24 hours of life, 61 (26.5%) infants between 25 to 48 hours of life and 59 (28.8%) after 48 hours of life. The mean duration of phototherapy was 49 ± 26 hours. The mean peak TSB was 14.3 mg/dL ±2.6; 36% of the jaundiced infants had TSB greater than 15 mg/dl. Among the infants who developed significant jaundice after 48 hours, the mean age of onset was 81±34 hours, the mean peak bilirubin was 14.7±2.8 mg/dL, and the mean duration of phototherapy was 41±18 hours.

Mother's blood group O and neonate's blood group A or B or AB, birth trauma, history of jaundice in previous sibling, large for gestation, and gestation 34 or 35 weeks was significantly higher in neonates who developed significant jaundice (***Table* I**). The median TcB values were 1.3 mg/dL, 4 mg/dL, 5.9 mg/dL, and 7.5 mg/dL at 0-12 hrs, 13-24 hrs, 25-36 hrs and 37-48 hrs of life, respectively. The mean TcB (13-24hrs) was significantly higher in infants who developed significant jaundice between 24 to 48 hours compared with those that developed jaundice after 48 hours of life (4.9 ±2.3 *vs* 4.1±1.6 mg/dL) (*P* =0.03) On comparing the clinical risk factors with TcBs, the ability to discriminate neonates with and without significant jaundice was better for grouped median TcBs from 24 to 48 hours i.e. TcB 25-36 hrs (AUC 0.75) and TcB 37-48 hrs (AUC 0.73) (***Web Table* I**).

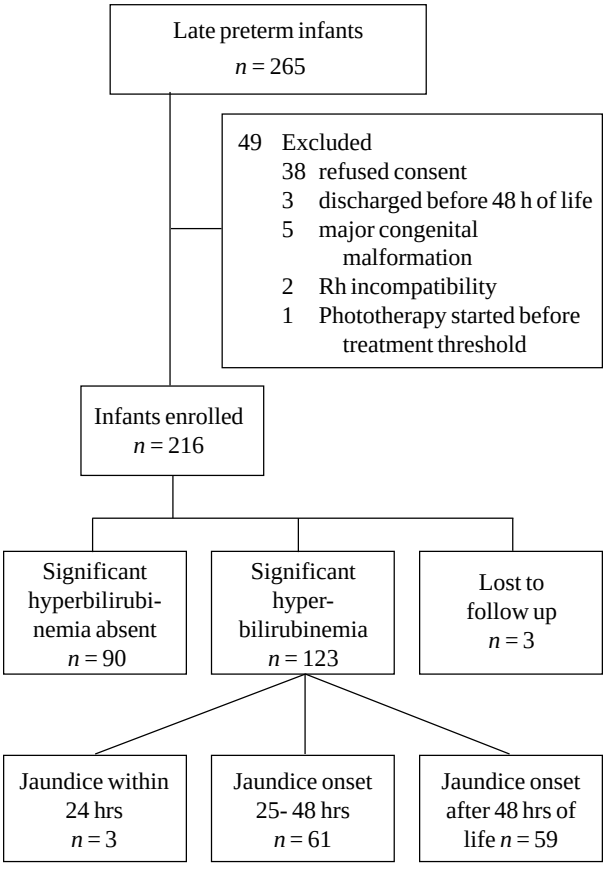

FIG. 1 *Enrollment and follow up of study subjects.*

TABLE I RISK FACTORS IN NEONATES WITH AND WITHOUT 'SIGNIFICANT JAUNDICE AFTER 48 HOURS OF LIFE

Variable	*Significant Hyperbilirubinemia*	
	Absent (n=90)	*Present (n=90)*
Birthweight (g)*	2420 ± 411	2404 ± 609
Gestation (wks)‡	35.42 ± 0.75	35.29 ± 0.72
Males	46 (51.1%)	35 (59.3%)
SGA (Small for gestation)#	6 (6.7%)	9 (15.3%)
LGA (Large for gestation)$	3 (3.3%)	11 (18.6%)
OA setting#	2 (2.22%)	6 (10.1%)
Maternal oxytocin	4 (4.4%)	6 (10.1%)
Sibling jaundice#	0	4 (6.8%)
Birth trauma	0	4 (6.8%)
Exclusive Breastfeeding	22 (24.4%)	10 (16.9%)
Stools/day**	2 (1-3)	2 (1-3%)
Meconium passage (in d)**	2 (1-5)	2 (1-6%)
Weight loss/d (g)	30 ± 27	33 ± 22
NICU admission	17 (18.8%)	18 (30.5%)

**Mean±SD, numbers in parenthesis are percentages; #P<0.05; $P=0.001; ‡P=0.05; significant jaundice defined as requirement of phototherapy/exchange transfusion as per hour specific total serum bilirubin (TSB) nomogram of IAP guidelines; **Values in median (range).*

DISCUSSION

This study is one of the few prospective studies to evaluate the incidence and course of jaundice in late-preterm infants. Fifty seven percent of late preterm infants developed significant jaundice. This highlights a need for the early recognition and screening of jaundice in this group.

In the only other prospective study comparing near term and term infants, the incidence of significant jaundice was 25.3% in near term infants [8]. In a retrospective study performed in a well infant population, infants of 35 to 36 weeks, 36 to 37 weeks and 37 to 38 weeks gestation were 13.2, 7.7 and 7.2 times more likely, respectively, to be readmitted to hospital and require phototherapy for significant jaundice than those of >39 weeks gestation [1]. Similarly in our study, infants of lower gestation were at higher risk of developing significant jaundice. The high incidence of significant jaundice in late preterm infants may be attributed to their inability to handle bilirubin load, decreased hepatic UDP glucuronyl transferase enzyme activity, and a slower post natal maturity of hepatic bilirubin uptake [9,10]. In contrast to the study by Sarici, *et al*. [9], a higher incidence and early onset of significant jaundice in our study may be explained by the inclusion of infants with 34 weeks gestation and by the difference in definition of significant jaundice.

As demonstrated in other studies evaluating pre-discharge risk assessment [11], large for gestation, gestational age, birth trauma and previous sibling with severe jaundice are the clinical variables significantly associated with significant jaundice in our study. Pre-discharge TcB as a predictor variable was similar or sometimes even better than clinical risk factors alone for prediction of significant jaundice. In the only other prospective cohort study on term and near term infants [6], combining predischarge TcB measurements with gestational age (compared with TcB measurement alone) improved the accuracy of the prediction of a subsequent TSB rising to within 1mg/dl of the hour specific phototherapy threshold recommended by the AAP. Considering that 25% to 50% of late preterm infants are at risk for subsequent jaundice, routine predischarge TcB measurement can help in predicting infants' needing delayed discharge and/or early follow up assessment for neonatal jaundice.

Treatment of late preterm infants with gestation 34 weeks as per APP guidelines and special treatment of SGA infants, are some the limitations of this study. There are no other published nomograms validated for our population and for uniformity of management we used the AAP guidelines.

There is a very high incidence of significant jaundice in late preterm infants. TcB measured at 24-48 hrs of life significantly predicts significant jaundice after 48 hours of life, which may help in identification of neonates requiring delayed discharge or early follow up assessment for jaundice after hospital discharge.

Contributors: SM designed the study and supervised the data collection. RL collected and analyzed the data. PG was involved in study design. All the authors were involved in preparation of the manuscript.
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WHAT IS ALREADY KNOWN?

- Late preterm infants are at increased risk of jaundice compared with term infants.

WHAT THIS STUDY ADDS?

- TcB values greater than 5.9 mg/dL between 24 to 36 hours of life, and >7.5mg/dL between 37 to 48 hours of life better predict subsequent onset of significant jaundice than any of the clinical risk factors.

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