ORIGINAL ARTICLE

Maternal and Neonatal Factors Associated with Neonatal Hyperbilirubinemia at a Tertiary Care Neonatal Unit

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ABSTRACT

Objective: To identify maternal and neonatal factors associated with hyperbilirubinemia among neonates admitted to a tertiary care hospital in Lahore.

Study Design: Cross-sectional observational study

Place and Duration of Study: Neonatal Unit, Mayo Hospital, Lahore over six months (December 2022- June 2023)

Material and Methods: This study was conducted on 183 neonates aged uptil 28 days of life, with gestational age from 28 to 42 weeks, and birth weights from 800 g to 4200 g. Abandoned neonates were excluded. Neonates with hyperbilirubinemia were included using non-probability consecutive sampling. Data on maternal and neonatal factors were collected through medical records, clinical examinations, and interviewing mothers. For quantitative variables the mean and standard deviations, or median and interquartile range (IQR), were determined. For qualitative variables, the chi-square test was applied. P-value less than 0.05 was considered statistically significant. Cramer's V test was further applied to determine the strength of the association of the significant factors.

Results: Key neonatal factors contributing to hyperbilirubinemia included bruises (due to birth trauma) (12%), neonatal sepsis (70.5%), birth asphyxia (34.4%), UTI (4.4%), infant of diabetic mother (7.1%), polycythemia (1.1%), cephalhematoma (16.4%), and jaundice in siblings (24.6%). Significant associations were found between hyperbilirubinemia and age at admission (p=0.000), birthweight (p=0.034), age at onset of jaundice (p<0.000), resuscitation (p=0.002), mode of feeding (p=0.002), and constipation (p=0.006). No significant association was found with the studied maternal factors.

Conclusion: Neonatal hyperbilirubinemia was found to be associated with age at admission, birth weight, age at onset of jaundice, resuscitation need, mode of feeding, and constipation. No significant association was found with the studied maternal factors.

Key Words: *Neonatal hyperbilirubinemia, Neonatal jaundice, Maternal risk factors, Neonatal risk factors*.

INTRODUCTION

Neonatal jaundice is among the most common medical conditions in neonates. All babies may have a transient rise in serum bilirubin, with jaundice clinically evident when the serum

bilirubin levels are more than 5 mg/dl. Jaundice afflicts at least 60% of full-term and 80% of preterm neonates. Hyperbilirubinemia refers to total serum bilirubin (TSB) levels above the normal range for healthy babies. [1]

Among neonatal factors, various studies have underscored the influence of postnatal age, race, and gestational age on hyperbilirubinemia development.[1,2] Different other factors studied in this context include gender, history of birth asphyxia, birth trauma/cephalhematoma, and the mode of delivery.[2-5]

On the maternal front, maternal age, history of maternal diabetes, and pregnancy induced hypertension have garnered attention, with studies reporting variable findings regarding their association with incidence of neonatal hyperbilirubinemia.[6,7]

There is a literature gap from Pakistan regarding epidemiology and associated risk factors of neonatal hyperbilirubinemia. Siyal et al. found male gender, infection, and term babies to be particularly affected.[8] Korejo et al., however, documented prematurity to be an important predisposing factor.[9] Likewise, low birth weight was seen to be an important prognostic factor for hyperbilirubinemia in admitted neonates.[10] Blood group incompatibilities and G6PD deficiency have been studied across neonates admitted at various nurseries.[11,12] However, events around the birth and maternal factors contributing to the development of neonatal hyperbilirubinemia have not been locally studied.

Given Pakistan's unique social, cultural, and healthcare context, understanding these factors is crucial for improving neonatal care practices and outcomes. Therefore, comprehensive research focusing on the occurrence and determinants of neonatal jaundice in Pakistan is needed. Such studies could offer valuable insights into the condition's epidemiology and inform tailored interventions to reduce its burden and enhance neonatal health outcomes. Considering this, our study aims to identify maternal and neonatal factors associated with hyperbilirubinemia amongst neonates admitted to the Neonatal unit of a tertiary care hospital in Lahore.

MATERIAL AND METHODS

This cross-sectional observational study was performed in the Neonatal Unit, Department of Pediatrics Medicine, Mayo Hospital Lahore. Ethical approval was obtained from the Institutional Review Board (King Edward Medical University No 1052/RC/KEMU dated 17-12-2022). Taking a 5% margin of error and 95% confidence interval and considering the frequency of neonatal hyperbilirubinemia amongst admitted neonates to be 12.7% in Pakistan[13], 183 neonates were enrolled by non-probability consecutive sampling over six months. Serum bilirubin was measured from venous samples obtained from peripheral venous access, 1 cc in volume, and analyzed by Vandate liquid-type oxidation method using Beckman Coulter AU480 Chemistry Analyzer. Babies up to 28 days of age, admitted to the Neonatal unit, and with clinical evidence of jaundice or total serum bilirubin (TSB) >5mg/dl were included in the study.[6,9] Abandoned neonates were excluded from this study.

Informed consent was obtained from the parents. Neonatal hyperbilirubinemia was identified by clinical examination and total serum bilirubin (TSB level). Data was collected by post-graduate residents in the nursery on a pre-designed proforma by reviewing maternal and neonatal medical records, performing relevant clinical examinations, and interviewing the mothers. Possible neonatal factors recorded included prematurity, low birth weight, maternal and neonatal blood groups (ABO or Rh), presence of bruises, cephalhematoma, neonatal sepsis, birth asphyxia, constipation, polycythemia, infant of diabetic mother, presence of urinary tract infection (UTI), history of neonatal jaundice in sibling, and need for resuscitation at birth or during admission. Maternal factors recorded included mode of feeding (breastfeed/formula feed/both), maternal age, gestational diabetes mellitus, pregnancy-induced hypertension, premature rupture of membranes (PROM), abruptio placentae, placenta previa, prolonged labor, meconium-stained amniotic fluid, and mode of delivery (cesarean section/spontaneous vaginal delivery). All the information was recorded on a predesigned questionnaire.

Data obtained was analysed using SPSS version 28. The distribution of numerical variables was determined using the Shipro-Wilk test. For quantitative variables (neonate’s age at

admission, gestational age, birth weight, age at onset of jaundice, and maternal age), the mean and standard deviations, or median and interquartile range (IQR), were determined. For qualitative variables (neonate's blood group, sepsis, birth asphyxia, etc.), the chi-square test was applied to ascertain the presence of hyperbilirubinemia in neonates due to maternal and neonatal factors. A p-value less than 0.05 was considered statistically significant. Stratification was done for age at admission, gestational age, birth weight, age at onset of jaundice, and maternal age. Cramer's V test was further applied to determine the strength of the association of these significant factors in our population.

RESULTS

In our study of 183 neonates, the gestational ages ranged from 28 weeks to 42 weeks. Weight at admission of neonates ranged from 800 grams (g) to 4200 g. The onset of jaundice occurred at <24 hours of life in 10 (5.5%) neonates, at 24-72 hours in 67 (36.6%), at 72 hours-14 days in 90 (49.1%), and 14-28 days of life in 16 (8.7%) neonates. The occurrence of bruises [22, (12%)], neonatal sepsis [128, (70.5%)], birth asphyxia [63, (34.4%)], UTI [8, (4.4%)], infant of diabetic mother [13, (7.1%)], polycythemia [2, (1.1%)], cephalhematoma [30, (16.4%)] and jaundice in sibling [45, (24.6%)] were contributory to the development of hyperbilirubinemia. Regarding feeding practices, neonates were either formula fed [18, (9.8%)], breastfed [101, (55.2%)], both formula and breastfed [52, (28.4%)], or nil per oral due to any clinical indication [8,(6.6%)]. Constipation was documented among 23 (12.6%) of jaundiced neonates.

The maternal age of affected babies was <20 years in 4.4%, 21-30 years in 72.6%, and 30-40 years in 22.9% of cases. The presence of gestational diabetes (9.3%), gestational hypertension (16.4%), maternal infection (59.1%), PROM (16.4%), abruptio placentae (6%), placenta previa (3.8%), prolonged labor (12.6%), meconium-stained amniotic fluid (6.5%), SVD (55.2%), C-section (44.8%) and maternal blood groups (A+, B+, AB+, O+, A-, B- , AB-, O-) were also documented as maternal factors contributing to hyperbilirubinemia amongst the admitted neonates.

By applying the Chi-square test, we found significant associations of age at admission, birth weight, age at onset of jaundice, resuscitation at birth or during admission, mode of feeding, and constipation with different categories of TSB (p-values = 0.000, 0.034, 0.000, 0.002, 0.002, 0.006, respectively). All these factors were strongly associated with the measured TSB values, as indicated by Cramer's V=0.386, 0.295, 0.282, 0.219, 0.254, and 0.260, respectively.

There was no significant association between maternal age and hyperbilirubinemia. Likewise, the presence of gestational diabetes, gestational hypertension, maternal infection, PROM, abruptio placentae, placenta previa, prolonged labor, meconium-stained amniotic fluid, mode of delivery (SVD/C-section), and maternal blood groups were not significantly associated with the serum bilirubin levels in jaundiced neonates.

TABLE 1: Frequency distribution of neonatal factors

Characteristics	Total serum bilirubin (mg/dl)				p-value
	5-10 (%)	10.1-15 (%)	15.1-20 (%)	20.1-25 (%)	
Age at admission					
Less than 24 hours	55 (11.4)	12 (6.5)	21 (11.8)	5 (2.7)	
24-72 hours	15 (8.2)	2 (1.0)	28 (15.3)	4 (2.2)	
73hours-14 days	1 (0.5)	0 (0.0)	17 (9.3)	18 (9.8)	0.000
15 -28 days	0 (0.0)	0 (0.0)	4 (2.2)	1 (0.5)	
Gender					
Male	58 (31.7)	35 (19.1)	25 (13.7)	3 (1.6)	0.599
Female	35 (19.1)	13 (7.1)	11 (6.0)	2 (1.1)	
Weight at admission					
<1000	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	
1001-1500	3 (1.6)	6 (3.3)	1 (0.5)	0 (0.0)	
1501-2500	32 (17.5)	18 (9.8)	12 (6.5)	2 (1.1)	0.587
2501-3999	54 (29.5)	25 (13.7)	23 ((12.6)	3 (1.6)	
>4000	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	

Gestational age					
28-36 6/7 weeks	29 (15.8)	10 (5.5)	10 (5.6)	0 (0.0)	
37-38 6/7 weeks	35 (19.1)	26 (14.2)	12 (6.5)	1 (0.5)	0.245
39-41 6/7 weeks	28 (15.3)	13 (7.1)	14 (7.6)	4 (2.2)	
>42 weeks	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Birth weight (gms)					
<1000	6 (3.3)	7 (3.8)	0 (0.0)	0 (0.0)	
10001-1500	4 (2.2)	1 (0.5)	0 (0.0)	0 (0.0)	
1501-2500	28 (15.3)	7 (3.8)	5 (2.7)	1 (0.0)	0.034
2501-3999	37 (20.2)	18 (9.8)	14 (7.6)	1 (0.5)	
>4000	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	
Unknown	17 (9.3)	16 (8.7)	15 (8.2)	3 (1.6)	
Age at onset of jaundice					
Less than 24 hours	4 (2.2)	6 (3.3)	0 (0.0)	0 (0.0)	
24 – 72 hours	50 (27.3)	12 (6.5)	5 (2.7)	0 (0.0)	0.000
72 hours – 14 days	36 (19.7)	28 (15.3)	21 (11.5)	5 (2.7)	
14-28 days	3 (1.6)	3 (1.6)	10 (5.5)	0 (0.0)	
Baby's blood group					
A+	20 (10.9)	12 (6.5)	6 (3.3)	0 (0.0)	
B+	30 (16.4)	21 (11.5)	13 (7.1)	4 (2.2)	
AB+	7 (3.8)	2 (1.1)	2 (1.1)	0 (0.0)	
O+	33 (18.0)	12 (6.5)	12 (6.5)	1 (0.5)	0.760
A-	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	
B-	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.5)	
AB-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
O-	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	
Cephalhematoma	20 (10.9)	8 (4.4)	1 (0.5)	1 (0.5)	0.082
Bruises	13 (7.1)	7 (3.8)	2 (1.1)	0 (0.0)	0.444
Neonatal sepsis	69 (37.7)	35 (19.1)	22 (12.0)	2 (1.1)	0.297
Birth Asphyxia	36 (19.7)	16 (8.7)	9 (4.9)	2 (1.1)	0.511
Mode of feeding					
Exclusive formula feeding	5 (2.7)	8 (4.4)	5 (2.7)	0 (0.0)	
mixed feeding	15 (8.2)	17 (9.3)	18 (9.8)	2 (1.1)	
exclusive breastfeeding	61 (33.3)	24 (13.1)	13 (7.1)	3 (1.6)	0.002
NPO	8 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	
UTI	1 (0.5)	3 (1.6)	4 (2.2)	0 (0.0)	0.075
IDM	6 (3.3)	3 (1.6)	4 (2.2)	0 (0.0)	0.708
Polycythemia	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.581
Resuscitation at birth/during admission	38 (20.1)	8 (4.4)	5 (2.7)	1 (0.5)	0.002
Constipation	5 (2.7)	7 (3.8)	10 (5.5)	1 (0.5)	0.006
Jaundice in sibling	21 (11.5)	12 (6.5)	11 (6.0)	1 (0.5)	0.842

TABLE 2: Frequency distribution of maternal factors

Characteristics	**Total serum bilirubin** (mg/dl)				**p value**
	5-10 9 (%)	**10.1-15 (%)**	**15.1-20 (%)**	**20.1-25 (%)**	
Maternal age					
<20 years	4 (2.2)	2 (1.1)	1 (0.5)	1 (0.5)	
21-30 years	71 (38.8)	33 (18.0)	25 (13.7)	4 (2.2)	0.376
>31-40 years	18 (9.8)	14 (7.6)	10 (5.5)	0 (0.0)	
GDM	8 (4.4)	5 (2.7)	4 (2.2)	0 (0.0)	0.860
Gestational hypertension	17 (9.3)	11 (7.9)	1 (0.5)	1 (0.5)	0.091
Maternal infections	52 (28.4)	29 (15.8)	14 (7.6)	4 (2.2)	0.149
PROM	14 (7.6)	11 (6.0)	4 (2.2)	1 (0.5)	0.529
Abruptio placentae	6 (3.3)	2 (1.1)	3 (1.6)	0 (0.0)	0.797
Placenta previa	5 (2.7)	1 (0.5)	1 (0.5)	0 (0.0)	0.720

Prolonged labour	12 (6.5)	7 (3.8)	4 (2.2)	0 (0.0)	0.818
Meconium-stained amniotic fluid	8 (4.4)	1 (0.5)	3 (1.6)	0 (0.0)	0.423
Mode of delivery					
C-section	38 (20.7)	25 (13.7)	16 (8.7)	3 (1.6)	0.568
SVD	55 (30.1)	24 (13.1)	20 (10.9)	2 (1.1)	
Mother's blood group					
A+	15 (8.2)	9 (4.9)	6 (3.3)	0 (0.0)	
B+	26 (14.2)	16 (8.7)	10 (5.5)	0 (0.0)	
AB+	8 (4.4)	4 (2.2)	4 (2.2)	0 (0.0)	
O+	37 (20.2)	16 (8.7)	14 (7.6)	4 (2.2)	
A-	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.474
B-	2 (1.1)	1 (0.5)	2 (1.1)	0 (0.0)	
AB-	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	
O-	1 (0.5)	3 (1.6)	0 (0.0)	1 (0.5)	

TABLE 3: Cramer's V test for the strength of association

Variable	Cramer's V
Admission Age vs. TSB	0.386
Birthweight vs. TSB	0.219
Onset of Jaundice vs. TSB	0.295
Resuscitation vs. TSB	0.282
Mode of Feeding vs. TSB	0.254
Constipation vs. TSB	0.260

DISCUSSION

Neonatal hyperbilirubinemia has been associated with a wide array of neonatal and maternal factors, with literature reporting variations in the presence or absence of these factors.

Regarding neonatal factors, the mean age at onset for hyperbilirubinemia in this study was 4.5 days, which is later than the typical age of days 2-3 of life as reported in other studies.[14] This discrepancy may be attributed to variations in the timing of hospital visits and the demographic characteristics of the study population.

Our findings are consistent with previous research indicating a mean gestational age of 37.2 weeks and a mean birthweight of 2592.9 grams amongst the jaundiced neonates.[2,3,5] Onset of neonatal hyperbilirubinemia has been seen to occur with earlier onset and greater severity as birth weight decreases due to immature hepatocyte function, increased bilirubin load, and defective conjugation.[16] Our population showed birth weight to be significantly associated with TSB levels, as observed in previous studies as well.[4,17]

Resuscitation at birth or during admission was significantly associated with elevated TSB levels, highlighting the critical impact of perinatal complications on neonatal health. This finding has not been well established with neonatal hyperbilirubinemia in literature and hence underscores the importance of timely interventions for infants undergoing resuscitation to mitigate jaundice risks.

The significant association between constipation and TSB levels points to gastrointestinal factors as potential contributors to bilirubin metabolism and elimination.[18] This warrants management strategies to curtail constipation as an important contributory factor to neonatal hyperbilirubinemia in our population.

Contrary to some literature that associates the male gender with a higher risk of hyperbilirubinemia,[3,4] our study did not find a significant gender predilection. This may reflect geographic, genetic, and environmental factors contributing to this aspect.[15]

Most of our study participants were admitted within the first 24 hours or between 72 hours and 14 days of life, a pattern observed in other studies.[14,17] The significant association between age at admission and TSB values suggests that early and late presentations may have different etiologies and risk profiles. Establishing this relationship would help generate local guidelines and screening protocols and aid in determining when intervention would be necessary.

Consistent with existing literature, different modes of feeding (breastfeeding, formula feeding, mixed or no feeds due to any clinical indication) were

significantly associated with the development of hyperbilirubinemia. Most of our neonates were breastfed. Literature shows that breastfeeding portends a higher risk of hyperbilirubinemia due to factors such as reduced caloric intake and dehydration during the initial days of breastfeeding. [16,19]

Factors like neonatal sepsis, birth asphyxia, bruises, cephalhematoma, UTI, IDM, polycythemia, baby's blood group, and a history of jaundice in siblings were variably associated with TSB levels. These findings align with previous studies highlighting their roles in increasing bilirubin load and impairment of bilirubin clearance. [4, 20-22]

We evaluated numerous maternal factors that could contribute to neonatal hyperbilirubinemia in our population. Conditions such as gestational diabetes, gestational hypertension, maternal infections, PROM, abruptio placentae, placenta previa, prolonged labor, meconium-stained amniotic fluid, mother's blood group, and mode of delivery were not found to have a significant association with TSB levels in our study. These factors have been inconsistently found to be associated with neonatal hyperbilirubinemia amongst different populations.[4,16,23] This could be attributed to the complex interplay of these variables with the mechanics involved in the development of neonatal hyperbilirubinemia.

Similarly, our study population reflected most jaundiced babies born to mothers with ages between 21-30 years. Literature has demonstrated varied associations of mother's age, with few studies reporting mothers in specific age groups having a greater risk of having neonates with significant hyperbilirubinemia.[24] This wide variation could be due to different populations considered or other causal dynamics.[23]

Although the literature suggests that cesarean delivery is associated with lower risks of hyperbilirubinemia compared to vaginal delivery,[16] our study did not indicate a significant difference. This can be due to varying clinical practices and demographic differences.

In Pakistan, scant data assess all these aforementioned maternal risk factors in association with neonatal hyperbilirubinemia, thus leaving significant scope for exploring this avenue in the prevention and management of neonatal hyperbilirubinemia in our populace.

Our study's forte lies in its comprehensive analysis of a wide range of maternal and neonatal factors in a single population, providing insights into the epidemiology of neonatal hyperbilirubinemia in Pakistan.

Limitations: The limitations of our study are that we did not include neonates <28 weeks gestational age. The potential sampling bias is due to nonprobability consecutive sampling, restricting representativeness.

Considering these limitations, more extensive studies, with greater inclusivity and over a longer duration, are needed to determine the geographical variances in factors associated with neonatal hyperbilirubinemia.

CONCLUSION

Significant associations of neonatal jaundice were seen with resuscitation, feeding practices, and constipation, emphasizing the need for targeted interventions in these areas. Early breastfeeding promotion**,** lactation counselling and feeding support should be a routine practice. Babies requiring resuscitation should be monitored for jaundice as part of their post-resuscitation care plan. Neonates showing signs of constipation should receive early interventions, such as adequate hydration and optimal feeding practices to support bilirubin excretion. This approach would lead to better clinical outcomes, reduced hospital stays, and a reduction in the incidence of complications. The lack of significant associations with other commonly implicated factors underscores the need for further research in these domains to explore the underlying mechanisms and formulate effective preventive and management strategies tailored to the Pakistani context.

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