Original Article

Congenital and Pregnancy Related Factors Governing the Risk of Pathological Jaundice in Neonates

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ABSTRACT

Objective: This study aims to determine the frequency and risk factors for pathological hyperbilirubinemia in our context to guide healthcare policy and practice.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Neonatal ICU, Ayub Teaching Hospital, Abbottabad from 1st January, 2024 to 31st June 2024.

Methods: One hundred and thirty-seven neonates with neonatal jaundice brought to the NICU were included in the study. Salient demographic characteristics, birth history suspected to be associated with neonatal jaundice and the day of appearance of jaundice were noted. Laboratory investigations were done to assess the causes of jaundice, to aid in diagnosis and evaluate prognosis of treatment.

Results: The study enrolled 137 neonates with neonatal hyperbilirubinemia. Males comprised 51.1% (n=70), while females made up 48.9% (n=67). Neonatal sepsis was the most frequent factor, occurring in 31.39% (n=43) of cases, followed by pre-term birth at 23.36% (n=32) and ABO incompatibility at 18.98% (n=26). Pathologic jaundice was found in 32 (23.4%) of the cases studied. When jaundice was analyzed by age, gender, birth weight, and pre-term birth, no statistically significant association was found ($p > 0.05$)

Conclusion: Pathologic jaundice was found in 32 (23.4%) of the cases studied. It is a more severe form of jaundice and leads to a considerable number of admissions to neonatal ICU. However, most factors responsible for neonatal hyperbilirubinemia are preventable and thus better management of pregnancy and during early neonatal period would address these preventable factors.

Key Words: ABO incompatibility, Bilirubin, Kernicterus, Sepsis.

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INTRODUCTION

Approximately 60%-80% of newborns globally experience neonatal hyperbilirubinemia, or jaundice. In some cases, this condition can lead to serious complications such as kernicterus or encephalopathy, significantly increasing the risk of death, hearing loss, and cerebral palsy.[1] Surviving infants may face long-term neurodevelopmental issues like cerebral palsy, sensorineural hearing loss, intellectual difficulties, paralysis of upward gaze, dental dysplasia, or gross developmental delays.[2]

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Clinical guidelines emphasize the importance of early detection of infants at risk for severe hyperbilirubinemia to prevent these outcomes. The causes and risk factors of neonatal jaundice in developing countries may differ from those in developed countries due to racial, cultural, environmental, and other factors.[3,4]

Various risk factors have been identified in the literature. For instance, a recent study from Bangladesh found that septicemia (28%), asphyxia (20%), prematurity (18%), Rh incompatibility (15%), and intrauterine growth restriction (IUGR) (11%) are common causes. Low birth weight and prematurity were also noted as significant risk factors for neonatal jaundice.[4-5]

A study from Iran identified premature labor (63%), breastfeeding jaundice (35%), ABO incompatibility (24.5%), and G6PD deficiency (12.8%) as major risk factors for severe neonatal hyperbilirubinemia requiring exchange transfusion. Meanwhile, a study from Taiwan found breastfeeding to be the most common cause (38.5%), followed by G6PD deficiency (24%), ABO incompatibility (21.8%), extravascular hemorrhage

(6.5%), bacterial infection (2.2%), hereditary spherocytosis (1.2%), dehydration (1.2%), diabetic mothers (1%), polycythemia (0.7%), and gastrointestinal obstruction (0.7%).[6]

Early identification of infants at risk for severe hyperbilirubinemia is crucial to reducing the burden of this condition in the first 14 days of life. However, the specific risk factors in our setting have not been systematically explored to inform necessary clinical and public health interventions. This study aims to determine the frequency and risk factors for pathological hyperbilirubinemia in our context to guide healthcare policy and practice.[7]

METHODS

A descriptive case series was conducted at the Department of Pediatrics, Ayub Teaching Hospital Abbottabad. After taking a duly signed ethical approval from the institutional review board of the aforementioned hospital, the study was conducted over a period of six months i-e from 1st January, 2024 to 31st June 2024. Sample size of 137 was calculated via WHO sample size calculator; using 15% frequency of Rh incompatibility in neonates with neonatal hyperbilirubinemia, 95% confidence interval and 6% absolute precision using WHO sample size calculations.[8] All the newborns (age up to 4 weeks) of either gender who got admitted with for jaundice or developed jaundice during hospital stay were included. Whereas, children diagnosed with congenital liver diseases, anatomic anomalies of hepatobiliary tract and viral hepatitis were excluded to omit the confounders. Consecutive non-probability sampling technique was used for the sample size completion.

Jaundice in neonatal can be physiologic or pathologic. In our study all the cases that demonstrated any of the following features were characterized as pathological jaundice: (1) Clinical jaundice appearing in the first 24 hours or greater than 14 days of life. (2) Increases in the level of total bilirubin by more than 8.5 µmol/l (0.5 mg/dL) per hour or (85 µmol/l) 5 mg/dL per 24 hours. (3) Total bilirubin more than 331.5 µmol/l (19.5 mg/dL). (4) Direct bilirubin more than 34 µmol/l (2.0 mg/dL). To analyze the risk factors that are associated with pathologic jaundice following factors were studied. (a) Preterm Labor (The birth of a baby at less than 37 weeks gestational age.) (b) Rh Incompatibility: (Rh incompatibility is a condition that occurs during pregnancy if a woman has Rh-negative blood and her baby has Rh-positive blood.) (c) ABO Incompatibility: (Condition that occurs if baby blood group doesn't match the maternal blood group. It is mostly seen in cases where maternal blood group is O and the baby blood group is A, B or AB.) (d) Glucose-6 Phosphate Dehydrogenase Deficiency: (An X-linked recessive inborn error of metabolism that predisposes to hemolysis and resultant jaundice in response to a number of triggers, such as certain foods, illness, or medication.) (e) Intrauterine Growth Restriction: (Intrauterine growth restriction (IUGR) is a fetal weight that is below the 10th percentile for gestational age.) (f) Neonatal Sepsis: (Any infection involving an infant during the first 28 days of life that is documented by positive C-reactive protein-CRP greater than 6 mg/ml.) (g) Neonatal Hypothyroidism: Decreased thyroid hormone production in a neonate, also known as congenital hypothyroidism. In hypothyroidism, the thyroid stimulating hormone (TSH) level is increased and the thyroxine (T_4) level is decreased. The normal value of TSH during first week in a full term neonate is 1-38.9 mU/l and in pre-term infants the value is 0.7-27 mU/l. During the first week of life, total thyroxine level in whole blood is 6.2-22 ug/dl (80-283 mmol/l). (h) Inborn Errors of Metabolism: (These are rare genetic (inherited) disorders in which body can not properly turn food into energy. The defects are usually caused by defects in specific enzymes that help to metabolize parts of food, e.g., galactosemia, maple syrup disease, fructose intolerance etc.) The data collected was recorded in a pre-designed pro forma.

Data analysis: All the data were inputted and processed using SPSS (version 23). For numerical variables such as age, birth weight, and total serum bilirubin levels, measures of central tendency were determined. For categorical variables like gender and different factors contributing to congenital hyperbilirubinemia as defined in operational definitions, frequencies and percentages were computed. The occurrence of jaundice was analyzed in relation to age, gender, pre-term birth, and birth weight to identify any effect modification. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The study enrolled 137 neonates with neonatal hyperbilirubinemia. Males comprised 51.1% (n=70), while females made up 48.9% (n=67). Quantitative variables are detailed in tables 1, and so are the frequencies of various factors studied in relation with neonatal hyperbilirubinemia. Neonatal sepsis was the most frequent factor, occurring in 31.39% (n=43) of cases, followed by pre-term birth at 23.36% (n=32) and ABO incompatibility at 18.98% (n=26). Pathologic jaundice was found in 32 (23.4%) of the cases studied. When jaundice was analyzed by age, gender, birth weight, and pre-term birth, no statistically significant association was found ($p > 0.05$) (Table 2 & 3).

Table No. 1: Descriptive statistics of the sample studied

Variable	Mean±SD	Frequency (percentage)
Age (yrs.)	13.91±7.05	
Birth weight (Kg.)	2.81±0.47	
Serum Bilirubin (mg/dL)	17.92±1.67	
Gender (Male:Female)		70(51.09%):67(48.91)
Preterm birth (Yes:No)		32(23.36):105(76.64)
IUGR (Yes:No)		9(6.57):128(93.43)
Rh Incompatibility (Yes:No)		14(10.22):123(89.78)
ABO Incompatibility (Yes:No)		26(18.98):111(81.02)
G6PD Deficiency (Yes:No)		10(7.3):127(92.7)
Neonatal Sepsis (Yes:No)		43(31.39):94(68.61)
Neonatal Hypothyroidism (Yes:No)		2(1.46):135(98.54)
Inborn errors of metabolism (Yes:No)		2(1.46):135(98.54)

Table No. 2: Inferential statistics summarizing association of studied categorical variable with neonatal jaundice.

Variable	Pathological Jaundice		Chi-square value	p-value
	Present	Absent		
Gender (Male:Female)	18:14	52:53	0.44	0.5
Preterm birth (Yes:No)	9:23	23:82	0.53	0.46
IUGR (Yes:No)	2:30	7:98	0.007	1.0*
Rh Incompatibility (Yes:No)	1:31	13:92	2.29	0.18
ABO Incompatibility (Yes:No)	8:24	18:87	0.98	0.32
G6PD Deficiency (Yes:No)	1:31	9:96	1.07	0.45*
Neonatal Sepsis (Yes:No)	12:20	31:74	0.72	0.39
Neonatal Hypothyroidism (Yes:No)	0:32	2:103	0.61	1.0*
Inborn errors of metabolism (Yes:No)	1:31	1:104	0.8	0.41*

Fischer's exact test used to calculate p-value

Table No. 3: Inferential statistics summarizing association of studied categorical variable with neonatal jaundice.

Variable	Pathological Jaundice		t-value	p-value
	Present	Absent		
Age in yrs. (Mean±SD)	14.88± 6.71	13.62±7.15	0.88	0.37
Birth weight in Kg (Mean±SD)	2.89± 0.42	2.78±0.47	1.12	0.26

DISCUSSION

This descriptive cross-sectional study enrolled all neonates who had developed neonatal jaundice as per operational definitions. While all study participants had neonatal hyperbilirubinemia, neonatal sepsis was the most common factor present in 43 (31.39%) neonates. It was followed by pre-term birth (n=32; 23.36%), ABO incompatibility (n=26; 18.98%), Rh incompatibility (n=14; 10.22%), G6PD deficiency (n=10; 7.3%), IUGR (n=9; 6.6%) neonatal hypothyroidism (n=2; 1.46%) and inborn errors of metabolism (n=2; 1.46%). Varying frequencies of factors for neonatal hyperbilirubinemia have been reported in the literature. For example, a study by Sciuto and colleagues reported that neonatal hyperbilirubinemia was present in 19% of their study cohort.[9] The common factors for neonatal hyperbilirubinemia in that study were Rh and ABO incompatibility, as well as glucose-6-phosphate dehydrogenase (G6PD) deficiency.[9] In a study from Nepal 18,985 newborn infants were evaluated for neonatal jaundice its incidence was reported to be 29.3 per 1000 live births.[10] The researchers reported that Male sex, high birth weight, breastfeeding patterns, warm air temperature, primiparity, skilled birth attendance, place of delivery, prolonged labor, oil massage, paternal education, and ethnicity were significant risk factors (p-values<0.01). After multi-variable adjustment, sex, birth weight, difficulty feeding, prolonged labor, primiparity, oil massage, ambient air temperature, and ethnicity remained important factors.[10] In contrast, this study focused on a limited number of variables and found that no statistically significant association existed between neonatal jaundice and age, sex, pre-term birth and birth-weight.

Interestingly, a study from Kerala, India reported a statistically significant relationship between hyperbilirubinemia and LBW, preterm delivery, PPROM, breast feeding, neonatal infection,

instrumental delivery and presence of GDM and IUGR.[11] The researchers in that study defined neonatal hyperbilirubinemia as a serum bilirubin level more than 10 mg/dl and their study cohort consisted of 140 singleton deliveries.[11] A study from Makkah, Saudi Arab reported that ABO incompatibility (31.6%) and G6PD deficiency (10.5%) frequently result in neonatal jaundice in Makkah.[12] In contrast, neonatal sepsis was the most common cause of neonatal hyperbilirubinemia in this study. A study from Iran reported that the most common major risk factors associated with neonatal hyperbilirubinemia were significant weight loss (27.5%), jaundice visible in the first 24 hours (16.3%), history of treatment with phototherapy and exchange transfusion in sibling (14.8%), Gestational age of 35 to 36 week (9.9%), ABO incompatibility (9.2%), RH incompatibility (3.3%) and G6PD deficiency (3.33%), and the most common minor risk factors were age over 25 years (51.4%), male (49.7%), history of hyperbilirubinemia in sibling (22.3%), diabetic mother's infants (1.5%).[13]

Interestingly, a recently published research from Hyderabad, Pakistan reported that most common risk factor was the sepsis 46.69%, following by birth asphyxia was in 11.40%, hypoglycemia 11.40%, hypothermia 07.89% and hypoalbuminemia was found in 0.87% cases and in 9.64% cases risk factors were unknown.[14] This indicates that neonatal sepsis is still a huge problem and a significant percentage of neonatal hyperbilirubinemia can be reduced by prevention of neonatal sepsis. A study from Kerala India also reported that sepsis contributed significantly to the causation of neonatal jaundice. The researchers in that study reported that common causes for neonatal jaundice were low birth weight 58.44%, blood group incompatibilities 58.86%, infections 33.33%, hypoxia 22.07%, refusal or difficulty in feeding 18.61%.[15]

Study limitations: The study was conducted on a limited number of uni-centric patients: this decreases the generalization of the inferences made. Thus, higher evidence generating multi-centric studies are invited to help postulate best practice guidelines regarding management of the disease.

CONCLUSION

Pathologic jaundice was found in 32 (23.4%) of the cases studied. It is a more severe form of jaundice and leads to a considerable number of admissions to neonatal ICU. However, most factors responsible for neonatal hyperbilirubinemia are preventable and thus better management of pregnancy and during early neonatal period would address these preventable factors associated with neonatal hyperbilirubinemia.

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