SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 7.
Issue: 12
Page N. 157-164
Year: 2023

Research Article www.wjahr.com

RISK FACTORS OF SEVERE NEONATAL HYPERBILIRUBINEMIA IN MOSUL CITY

***Dr. Islam A. Al-Idrisi, M.B.Ch.B., F.A.B.H.S. / FM, Dr. Asmaa Sh. Aziz, M.B.Ch.B., F.A.B.H.S. / FM, Dr. Rakan Ahmed Hamid, M.B.Ch.B., F.I.C.M.S / FM**

Iraq.

Article Received date: 25 October 2023 **Article Revised date:** 14 November 2023 **Article Accepted date:** 04 December 2023

***Corresponding Author: Dr. Islam A. Al-Idrisi, M.B.Ch.B., F.A.B.H.S. / FM**

Iraq

INTRODUCTION

Neonatal hyperbilirubinaemia is the most common reason of readmission after early hospital discharge.[1] Jaundice is observed in approximately 60% of term infants and 80% of preterm neonate during the first week of life.[2]

Because of the potential toxicity of bilirubin, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus.[4,5]

Jaundice corresponds to the clinical expression of hyperbilirubinemia, defined as a serum unconjugated bilirubin concentration of greater than 1.3 to 1.5 mg/dL or conjugated bilirubin concentration of higher than 1.5 mg/dL, or as total serum bilirubin levels greater than 5 mg/dL.[9]

Hyperbilirubinemia defined as a total serum or plasma bilirubin >95 percentile on the hour-specific Bhutani nomogram[10] can be caused by certain pathologic conditions or by exaggeration of the mechanisms responsible for neonatal jaundice NNJ. Identification of the cause of neonatal hyperbilirubinemia is useful in determining whether therapeutic interventions can prevent severe hyperbilirubinemia.[11]

Epidemiology

Neonatal hyperbilirubinemia is extremely common because almost every newborn develops an unconjugated serum bilirubin level of more than 1.8 mg/dL during the first week of life. Studies seem to suggest that some of the ethnic variability in the incidence and severity of NNJ may be related to differences in distribution of the genetic variants in bilirubin metabolism.[14]

Kernicterus is a complication of NNJ. Its incidence in North America and Europe ranges from 0.4- 2.7 cases/ 100,000 births. Death from physiologic NNJ per se should not occur. Death from Kernicterus may occur, particularly in countries with less developed medical care systems.[15]

Classifications of Jaundice

It is essential to distinguish whether the jaundice is physiologic or pathologic. Jaundice noted within the first 24 hours is pathologic and a TSB should be drawn. Early jaundice is usually related to hemolysis, infection, drug effect, neonatal hepatitis or liver enzyme defects.[11] Physiologic jaundice is very common, usually harmless and becomes visible on the second or third day. While any TSB elevation exceeding 17 mg/dL is considered pathologic and warrants investigations for a cause and possible therapeutic intervention.[18,19] Jaundice that persists beyond 2 weeks should be evaluated beginning with a fractionated bilirubin.[4]

Another classification of neonatal hyperbilirubinemia done according to the type of bilirubin fraction into: unconjugated (indirect) hyperbilirubinemia and conjugated (direct) hyperbilirubinemia.[20]

Causes of Hyperbilirubinemia

1. Increase bilirubin production[23,24]
2. Decreased bilirubin clearance[28]
3. Increased bilirubin enterohepatic circulation[30]

Risk Factors for Development of Severe Hyperbilirubinemia

Table (1-1) lists those factors that are clinically significant and most frequently associated with an increase in the risk of severe hyperbilirubinemia in Infants of ≥ 35 Weeks' Gestation.[1,4]

Major risk factors
Predischarge TSB or TcB level in the high-risk zone (TSB ≥95th).[49]
Jaundice observed in the first 24 h.[50]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency).
Gestational age 35–36 wk.[45]
Previous sibling received phototherapy.[51]
Cephalohematoma or significant bruising.[45]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.[45]
East Asian race (Race as defined by mother's description.)[45]
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone (95th >TSB ≥75th)[49]
Gestational age 37–38 wk.[45]
Jaundice observed before discharge.[51]
Previous sibling with jaundice.[51]
Macrosomic infant of a diabetic mother.[47]
Maternal age 25y or more.[45]
Male gender.[45]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (TSB <40th).[49]
Gestational age 41 wk and more.[45]
Exclusive bottle feeding.[45]
Black race.[52]
Discharge from hospital after 72 h.[53]

AIM AND OBJECTS

Aim of the study: to identify risk factors of sever hyperbilirubinemia among neonate attending neonatal intensive care units in Mosul city.

Specific objectives: Early identification of risk factors for acute bilirubin encephalopathy may allow interventions to lower the risk, especially that the ability to measure TSB and treatment is widely available.

- To know the severity of neonatal hyperbilirubinemia due to ABO incompatibility or Rh sensitization.
- Recognize the effect of different types of feeding and the presence of pathological weight loss on the development of sever hyperbilirubinemia.
- To determine the effect of mother's age and the effect of her diabetes on neonatal jaundice.
- To know the effect of the presence of previous sibling with jaundice and received phototherapy or exchange transfusion.
- To determine the effect of birth weight, neonatal gender, gestational age, presence of neonatal infections on the severity of hyperbilirubinemia.

Patients and Methods Study setting

The present study was conducted at Al-Khansaa and Ibn Al-Atheer Teaching Hospitals/NICU in Mosul city.

During the period of the study (six month), both hospitals had admitted 1436 neonates with different indications, 563 of them was admitted due to neonatal hyperbilirubinemia or jaundice.

Study design

This study was a case-control study which is a type of observational study.

Study period

It has been planned to collect data during six months period from the beginning of Feb 2015 to the end of July 2015.

Study sample

One hundred neonates who admitted to NICU due to neonatal jaundice with age of ≤ 28 days old and TSB level ≥ 20.0 mg/dL (case), and another one hundred neonates (50 boys and 50 girls) who admitted to NICU

due to neonatal jaundice with age of ≤ 28 days old and TSB level < 20.0 mg/dL (control). Newborns above 28 days old, gestational age were < 35 weeks (preterm) and > 42 weeks (post term), Newborns who presented with twin, respiratory distress, G6PD deficiency, and congenital major malformations, or weighting below 2000 grams or diagnosed as small for gestational age and large for gestational age where excluded from this study.

Patient's data forms

The general information was taken from the relatives of all studied neonates to fill the patient data forms and depending on American Academy of Pediatrics Subcommittee on Hyperbilirubinemia / Clinical practice guideline 2004: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.[4]

RESULTS

Distribution of studied groups according to immune mediated hemolysis Table 3-1 shows that ABO incompatibility as a significant risk factor to develope sever hyperbilirubinemia (OR =1.9, p value = 0.03). while table 3-2 show that Rh sensitization had a relationship to the development of sever hyperbilirubinemia (OR = 1.949, p value = 0.06).

Table 3-1: according to the presence of ABO incompatibility.

ABO incompatibility	Case	Control	OR	(95% CI)	p*
present	30	18	1.952	1.009 – 3.775	0.034
absent	70	82			

* (chi- square test was used)

Table 3-2: according to the presence of Rh sensitization.

Rh sensitization	Case	Control	OR	(95% CI)	p*
present	21	12	1.949	0.911 – 4.165	0.063
absent	79	88			

* (chi- square test was used)

Gender

Table below shows that male gender was a significant risk factor to develop sever hyperbilirubinemia (OR= 1.7, P value =0.03).

Table 3.3 Distribution of studied groups according to the gender.

Gender	Case	Control	OR	(95% CI)	p*
Male	64	50	1.778	1.011 – 3.125	0.032
Female	36	50	0.563	0.320 – 0.989	0.984

* (chi- square test was used)

Infant of diabetic mother

Table 3-4 show that infant of diabetic mother had more risk to develop sever type of jaundice (OR= 2.5) and it is statistically significant with P value =0.03.

Table 3-4: The presence of diabetes among mothers of studied neonates.

Baby of diabetic mothers	Case	Control	OR	(95% CI)	p*
present	16	7	2.531	1.016 – 6.285	0.037
absent	84	93			

* (chi- square test was used)

Polycythemia

Table 3-5 showing that polycythemia had a relationship with the development of sever jaundice wiyh OR = 1.8 and P value more than 0.05.

Table 3-5: The presence of polycythemia among the studied neonates.

Polycythemia	Case	Control	OR	(95% CI)	p*
present	9	5	1.879	0.634 – 5.551	0.203
absent	91	95			

* (chi- square test was used)

Cephalhematoma

Table 3-6 showing that the presence of cephalhematoma had a relationship with the development of sever jaundice with (OR = 1.2 and P value = 0.4)

Table 3-6: The presence of cephalhematoma among the studied neonates.

cephal hematoma	Case	Control	OR	(95% CI)	p*
present	10	8	1.278	0.496 – 3.290	0.403
Absent	90	92			

* (chi- square test was used)

Gestational age

Table 3-7 showing that near term neonate was a statistically significant as a risk factor for sever hyperbilirubinemia (OR = 1.853 and P value = 0.04).

Table 3-7: Comparison of the neonatal gestational age in both groups.

Gestational age, wks	Case	Control	OR	(95% CI)	p*
Near term (35 – 37 wk)	33	21	1.853	0.985 – 3.485	0.04
Term (38 – 42 wk)	67	79	0.540	0.287 – 1.016	0.981

* (chi- square test was used)

Method of delivery

Table 3-8showing that vaginal delivery had a relationship with the development of sever jaundice rather than caesarian section (OR =1.5 and P value =0.1).

Table 3-8: Distribution of the groups according to the methods of delivery.

Methods of Delivery	Case	Control	OR	(95% CI)	p*
Vaginal Delivery	77	69	1.504	0.805 – 2.810	0.132
C/S	23	31	0.665	0.356 – 1.243	0.924

* (chi- square test was used)

Table below showing that assistant vaginal delivery had a relationship with the development of sever hyperbilirubinemia (OR=1.2)

Table 3-9: the use of vacuum during vaginal delivery in both groups.

Use of vacuum during vaginal delivery	Case	Control	OR	(95% CI)	p*
present	7	5	1.280	0.407 – 4.018	0.461
absent	70	64			

* (chi- square test was used)

Table below showing that induction of labour by using oxytocin had no significant association.

Table 3-10: the use of oxytocin during vaginal delivery in both groups

Use of oxytocin during vaginal delivery	Case	Control	OR	(95% CI)	p*
Present	39	42	0.660	0.343 – 1.270	0.920
absent	38	27			

* (chi- square test was used)

Type of feeding

The results show that the use of formula and supplementary feedings, both had a relation with the development of sever jaundice (OR= 1.5, 1.19 respectively) while breast feeding had no significant relation (OR=0.7).

Table 3-11: Type of feeding of the studied groups.

Type of feeding	Case	Control	OR	(95% CI)	p*
Breastfeeding	53	61	0.721	0.412 – 1.262	0.901
Formula	12	8	1.568	0.627 – 3.917	0.240
Supplementary	35	31	1.199	0.666 – 2.156	0.326

* (chi- square test was used)

Maternal age
Table below showing that maternal age above 25 yrs show a relation with development of sever hyperbilirubinemia.

Table 3-12: Maternal age for the studied neonates.

Age, yrs	Case	Control	OR	(95% CI)	p*
< 25	28	34	0.755	0.415 – 1.373	0.858
≥ 25	72	66	1.325	0.728 – 2.409	0.222

* (chi- square test was used)

Neonatal weight
This table showing that neonate birth weight > 2500g at birth, neonates with body weight on admission between 2000-2500g and the presence of pathological weight loss in neonate at time of admission, all had a relationship with the development of sever hyperbilirubinemia (OR= 1.39, 1.379 and 1.646 respectively).

Table 3-13: Comparison of the neonatal weight at birth, on admission and the presence of pathological weight loss in both group.

Birth weight, g	Case	Control	OR	(95% CI)	p*
2000 – 2500	21	27	0.719	0.376 – 1.374	0.877
> 2500	79	73	1.391	0.728 – 2.659	0.204

* (chi- square test was used)

Body weight on admission, g	Case	Control	OR	(95% CI)	p*
2000 – 2500	28	22	1.379	0.728 – 2.611	0.207
> 2500	72	78	0.725	0.383 – 1.374	0.874

* (chi- square test was used)

Pathological weight loss	Case	Control	OR	(95% CI)	p*
present	14	9	1.646	0.691 – 3.916	0.188
absent	86	91			

* (chi- square test was used)

Distribution of studied groups according to neonatal infections
The results below show that the presence of neonatal sepsis had arelationship with the development of sever hyperbilirubinemia (OR= 1.6). But the presence of urinary tract infection had no significant relation with jaundice (OR=0.6).

Table 3-14: according to the presence of sepsis that proven by clinical and laboratory evaluations.

Proven sepsis	Case	Control	OR	(95% CI)	p*
present	11	7	1.642	0.627 – 4.291	0.230
absent	89	93			

* (chi- square test was used)

Table 3-15: according to the presence of urinary tract infection that proven by urine culture.

Urinary tract infection	Case	Control	OR	(95% CI)	p*
present	15	22	0.626	0.306 – 1.281	0.928
absent	85	78			

* (chi- square test was used)

Previous sibling with jaundice received PT or ET
Table below showing that there is a relation between the history of previous sibling with jaundice and the occurrence of sever jaundice (OR=1.1).

Table 3-16: the presence of previous sibling with jaundice among groups.

Previous sibling received PT or ET	Case	Control	OR	(95% CI)	p*
present	9	8	1.137	0.433 – 2.986	0.500
absent	81	92			

* (chi- square test was used)

The order of child among the siblings
Table show that being the second child or after had a relation with sever jaundice (OR=1.2)

Table 3-17: The order of child among the siblings

Which child of family	Case	Control	OR	(95% CI)	p*
First child	27	32	0.786	0.429 – 1.441	0.824
Second child or after	73	68	1.272	0.694 – 2.332	0.268

* (chi- square test was used)

Postnatal age when jaundice noticed first
Table below show that first day jaundice was more in sever hyperbilirubinemia group than the other group, and it was statistically significant as a risk factor for sever hyperbilirubinemia (OR = 3.773 and P value = 0.00)

Table 3-18: Postnatal age when jaundice noticed first.

Time when jaundice notice first	Case	Control	OR	(95% CI)	p*
First 24 hr of life	57	26	3.773	2.082 – 6.835	0.00
24 – 48 hrs	19	42	0.324	0.172 – 0.611	1.00
> 48 hrs	24	32	0.671	0.362 – 1.245	0.922

* (chi- square test was used)

Table 3-19 show that jaundice notice among cases was earlier than controls (mean = 1.9 and 2,4 respectively) but there was delay in admission in cases than controls (mean = 7.4 and 5.6 respectively).

Table 3-19: Differences between the mean of postnatal age when jaundice notice first and the mean of age at admission.

Postnatal Age	Case	Control
Time jaundice noticed , days	1-8 (mean = 1.93)	1-9 (mean = 2.45)
Time of admission, days	2-20 (mean = 7.46)	1-21 (mean = 5.65)

frequency of risk factors
In this figure, the frequency of some risk factors of sever hyperbilirubinemia present in all neonates (n = 200). ABO incompatibility was in the top of list then followed by cases present with Urinary tract infection and Rh sensitization.

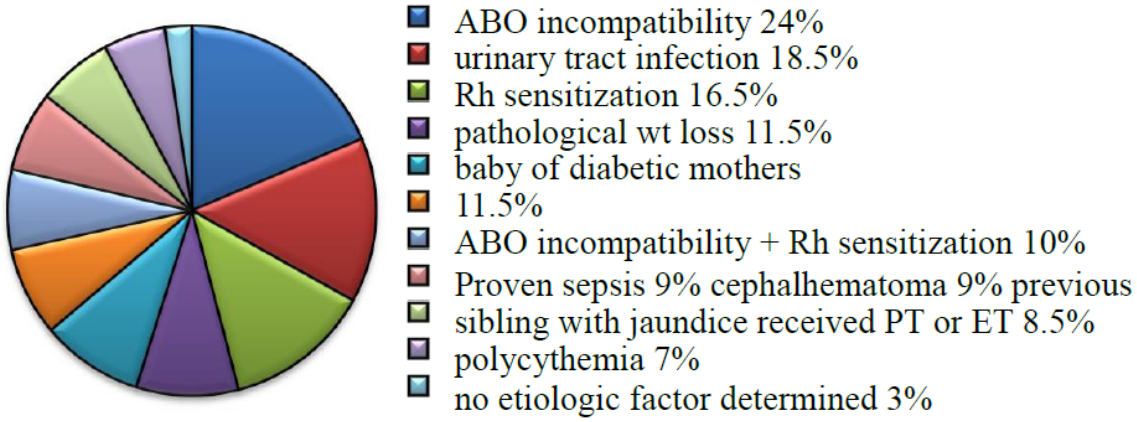
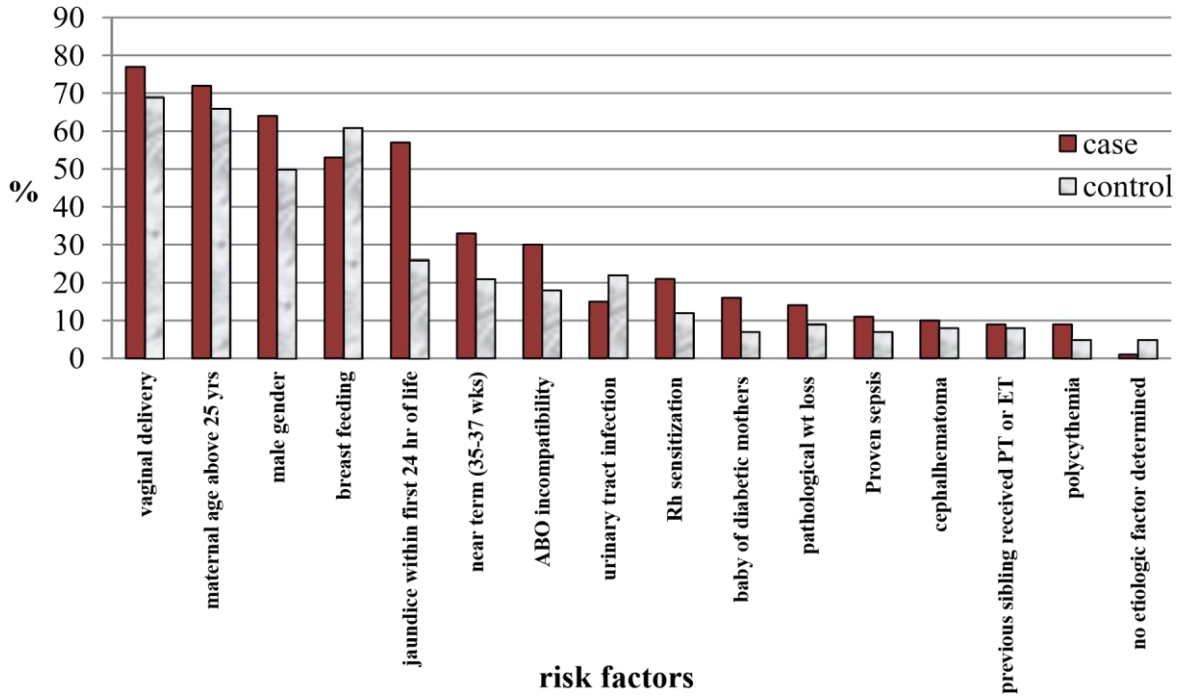


Fig (3-1): pie diagram showing the frequency of risk factors of hyperbilirubinemia in all studied neonates.

In this figure, the distribution of the studied groups according to the exposure to risk factors of severe hyperbilirubinemia



Fig(3-2) Bar-chart showing the distribution of studied groups according to the exposure to risk factors of severe hyperbilirubinemia.

DISCUSSION

Jaundice is the most common issue in the neonatal period. It is seen in 60 % of term newborns and 5–10% of these newborns with elevated bilirubin levels required admission to hospital and treatment.[7] Jaundice is usually benign. However, because of the potential toxicity of bilirubin, newborns must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus.[4, 5] Although kernicterus should almost always be preventable, cases continue to occur in Europe and North America.[4] The true incidence of kernicterus remains unknown. Recently, it has been estimated to range between 1 and 1.4 per 100,000 live births in North America and Europe.[6]

According to epidemiological studies, some risk factors are associated with severe hyperbilirubinemia in neonates. The risk factors are male gender, jaundice presenting in the first 24 hours after birth, jaundice noted at discharge from the hospital, previous sibling with jaundice, preterm labor, breast feeding, Rh and ABO incompatibility, G6PD deficiency and sepsis.[4,19]

CONCLUSIONS

1. ABO incompatibility is important cause of sever hyperbilirubinemia and then bilirubin encephalopathy (kernicterus). Failure to prevent Rh sensitization which is avoidable risk factor, still show an increase cases of sever hyperbilirubinemia.
2. The gender of neonate, gestational age, birth weight, pathological weight loss and age of the mother have a relation with the severity of the disease.
3. Poor information about neonatal jaundice, its management and complications with poor antenatal care can be the cause of the delay in seeking medical consultation, although a good percent of mothers whose previous babies had jaundice took their babies early to hospitals for treatment.
4. Baby of diabetic mothers is still a recognize risk factor while polycythemia, neonatal sepsis and cephal hematoma show a not significant association.
5. The phototherapy is effective in treating neonatal hyperbilirubinemia and in preventing the need for exchange transfusion.

Recommendations

1. All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies. Anti-D is found to be the most important and effective mean to prevent Rh isoimmunization and should be available at any time, lastly more education required about this problem.
2. All hospitals should provide written and verbal information for parents at the time of discharge, which should include an explanation of jaundice, the need to monitor infants for jaundice, and advice on how monitoring should be done.
3. Before discharge, every newborn should be assessed for the risk of developing severe hyperbilirubinemiaand parents counseling is required for bringing their babies early to prevent kernicterus.
4. Promote and support successful breastfeeding : at least 8 to 12 times per day for the first several days. Supplementation with water or dextrose water will not prevent hyperbilirubinemia or decrease TSB levels

5. Health care providers should continuously educate the expectant mothers during ANC, on NNJ with special focus on the causes and danger signs of complications of NNJ.
6. Infants of less than 37 weeks of gestation are at higher risk of developing hyperbilirubinemia and require closer monitoring and follow up.

REFRENCES

1. Jaundice and hyperbilirubinemia in the newborn. In Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of pediatrics. 19th ed. Philadelphia: Saunders, 2011; 603-612.
2. S. K. Gatea. "Cord bilirubin level as predictor for Newborns at Risk for post natal Hyperbiliruinemia". Kuf Med J, 2009; 2: 109-117.
3. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Maisels MJ, Baltz RD, Bhutani VK, Newman TB, Palmer H, Rosenfeld W, et al: Clinical practice guideline: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics, 2004; 114: 297–316. Available at: http:// www.aappolicy.aappublications.org/cgi/ content/full/pediatrics;114/1/297.
4. Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Revised Guidance to Help Prevent Kernicterus. Sentinel Event Alert: Issue No. 31. August 31, 2004, pp 1–4. Available at: http://www.jointcommission. org/SentinelEvents/SentinelEventAlert/ sea_31.htm.
5. Stoll B, Kliegman R. Jaundice and hyperbilirubinemia in the newborn. Behemen R, Kliegman R, Jenson H (editors). Nelson Textbook in Pediatrics. 18th ed. WB: Saunders, 2008; P. 756-65.
6. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics, 1999; 103: 6–14.
7. Jain SK. Index of suspicion. Case 3. Diagnosis: jaundice. Pediatr Rev, 2001; 22(8): 271-276.
8. Huang, MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatric research, 2004; 56(5): 682-9.
9. Maisels MJ, Newman TB. Prevention, screening, and postnatal management of neonatal hyperbilirubinemia. In: Stevenson DK, Maisels MJ, Watchko JF, editors. Care of the Jaundiced Neonate. New York, NY: McGraw Hill, 2012; 175–194.
10. B. P. Preethi, D. S. Maitreyee and M. Khemka. "Correlation of cord bilirubin levels with hyperbilirubinemia in ABP incompatibility. "Intern J Phar Bio Sci, 2011; 2: 258-262.
11. Dennery PA, Seidman DS, Stevenson DK. Neonatal Hyperbilirubinemia. N Engl J Med, 2001; 344(8): 581-590.
12. Hyperbilirubinemia. In Buonocore G, Bracci R, Weindling M, eds. A Practical Approach to Neonatal Diseases. Springer: Verlag Italia, 2012; 608- 639.
13. Riskin A, Gery N, Kugelman A, et al. Glucose-6-phosphate dehydrogenase deficiency and borderline deficiency: association with neonatal hyperbilirubinemia. J Pediatr, 2012; 161: 191.
14. Kaplan M, Wong RJ, Sibley E, Stevenson DK. Neonatal jaundice and liver disease. In: Neonatal - Perinatal Medicine: Diseases of the Fetus and Infant, 9th ed, Martin RJ, Fanaroff AA, Walsh MC (Eds), Elsevier Mosby, St. Louis, 2011; 2: 1443.
15. Skierka JM, Kotzer KE, Lagerstedt SA, et al. UGT1A1 genetic analysis as a diagnostic aid for individuals with unconjugated hyperbilirubinemia. J Pediatr, 2013; 162: 1146.
16. Preer GL, Philipp BL. Understanding and managing breast milk jaundice. Arch Dis Child Fetal Neonatal Ed, 2011; 96: F461.
17. Bhutani V, Gourley GR, Adler S, Kreamer B, Dalman C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. Pediatrics, 2000; 106(2). Available at: www.pediatrics.org/ cgi/content/full/106/2/e17
18. Newman TB, Liljestrand P, Escobar GJ. Jaundice noted in the first 24 hours after birth in a managed care organization. Arch Pediatr Adolesc Med, 2002; 156: 1244–1250.
19. Newman TB, Liljestrand P, Escobar GJ. Jaundice noted in the first 24 hours after birth in a managed care organization. Arch Pediatr Adolesc Med., 2002; 156: 1244–1250
20. Maisels MJ, Kring EA. Length of stay, jaundice, and hospital readmission. Pediatrics, 1998; 101: 995–998.
21. Nold JL, Georgieff MK (2004) Infants of diabetic mothers. Pediatr Clin N Am, 51: 619–637.
22. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics, 2001; 108: 31–39.
23. Soskolne El, Schumacher R, Fyock C, Young ML, Schork A. The effect of early discharge and other factors on readmission rates of newborns. Arch Pedia tr Adolesc Med, 1996; 150: 373–379.
24. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, et al. An evidencebased review of important issues concerning neonatal hyperbilirubinemia. Pediatrics, 2004; 114(1): e130-153.