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Prolonged Jaundice in Term Newborns: Evaluation of Etiological and Clinical Characteristics

Sinem Özdemir[1], Zuhal Aydan Sağlam[1], Serdar Cömert[2], Nursu Kara[2], Yalçın Hacıoğlu[1], Didem Arman[2]

[1]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Family Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İstanbul, Türkiye

What is known on this subject?

Prolonged jaundice is common in term newborns and is most frequently associated with late-onset breast milk jaundice. Although usually benign, prolonged jaundice may be the first or only sign of underlying pathological and treatable conditions such as urinary tract infection, blood group incompatibility, or endocrine disorders. Current guidelines recommend systematic evaluation of infants with prolonged jaundice while continuing breastfeeding.

What this study adds?

In this cohort of term newborns with prolonged jaundice, urinary tract infection was identified as the second most common etiology, with a higher frequency than previously reported. Female sex was significantly more common among infants with breast milk–related prolonged jaundice compared with those with other etiologies, suggesting possible sex-related differences according to underlying cause. Exclusive breastfeeding rates were similar between infants with breast milk–related prolonged jaundice and those with pathological causes, reinforcing recommendations that breastfeeding should not be discontinued during evaluation and follow-up.

ABSTRACT

Objective: Prolonged jaundice is a common reason for neonatal outpatient visits and is usually benign; however, it may occasionally indicate underlying pathological, treatable conditions. This study aimed to evaluate the etiological and clinical characteristics of term newborns presenting with prolonged jaundice.

Material and Methods: In this single-center retrospective study, 150 term newborns diagnosed with prolonged jaundice were included between March 2022 and September 2022. Demographic and clinical data were recorded, and laboratory results were evaluated to determine potential underlying causes. All data were analyzed statistically.

Results: Among 150 newborns, 54.7% (n=82) were male. The mean gestational age and birth weight were 38.7±1.2 weeks and 3229±396 g, respectively. Late-onset breast milk jaundice was the most common etiology (57.3%), followed by urinary tract infection (22.7%), ABO/Rh incompatibility (14%), sepsis (3.3%), glucose-6-phosphate dehydrogenase deficiency (2%), and congenital hypothyroidism (0.7%). While 46% of the infants presented with jaundice, additional symptoms such as poor feeding (33%), vomiting (11%), and restlessness (5%) were observed in the remainder of the cohort. No significant differences were observed in demographic or laboratory parameters between infants with late-onset breast milk jaundice and those with pathological causes.

Conclusion: Late-onset breast milk jaundice is the leading cause of prolonged jaundice in term newborns.

Corresponding Author: Didem Arman, MD, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İstanbul, Türkiye

E-mail: dr_didemcaktir@yahoo.com **ORCID ID:** orcid.org/0000-0002-7218-9207

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ABSTRACT

Nevertheless, a systematic clinical and laboratory evaluation is warranted in all infants with prolonged jaundice to exclude underlying pathological conditions, even in the absence of additional symptoms. Breastfeeding should be continued during evaluation and follow-up, considering the unique and well-established benefits of breast milk.

Keywords: Prolonged jaundice, breastfeeding, urinary tract infection, newborn

Introduction

Prolonged jaundice is commonly observed in term infants, particularly those who are exclusively breastfed**.** Although the majority of cases follow a benign and self-limiting course, prolonged jaundice may occasionally be the initial or sole manifestation of underlying pathological conditions requiring timely diagnosis and treatment. In term infants, prolonged jaundice is defined as persistence of jaundice beyond the 14th postnatal day, whereas in preterm infants it is defined as persistence beyond the 21st day of life (1). It accounts for one of the most frequent reasons for outpatient referrals and is reported in approximately 2–15% of newborns (1).

While the management of indirect hyperbilirubinemia during the first postnatal week is well established, diagnostic and therapeutic approaches to prolonged jaundice remain less clearly defined (2). A wide spectrum of etiologies, including hematological, infectious, metabolic, genetic, hepatic, and biliary disorders, may underlie prolonged jaundice, warranting thorough clinical assessment and etiological investigation (3). Identifying underlying pathological and treatable conditions is a key component in the management of infants with prolonged jaundice.

Late-onset breast milk jaundice is considered the most common cause of prolonged unconjugated hyperbilirubinemia in healthy term infants (4,5). Despite its benign nature, late-onset breast milk jaundice remains a diagnosis of exclusion, and potentially serious conditions must be ruled out before attributing prolonged jaundice to breastfeeding alone. Failure to identify underlying pathological causes may result in delayed treatment and adverse outcomes.

Therefore, this study aimed to evaluate the etiological and clinical characteristics of term newborns presenting with prolonged jaundice at a tertiary care neonatal outpatient clinic.

Material and Methods

A single-center, retrospective cross-sectional study was conducted at the Neonatal Outpatient Clinic of an İstanbul Training and Research Hospital. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (decision number: 195, date: June 17, 2022). Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Study Population

Newborns born at ≥37 weeks of gestation who were diagnosed with prolonged jaundice were eligible for inclusion. Prolonged jaundice was defined as persistence of total serum bilirubin levels above 5 mg/dL beyond the 14th postnatal day. Direct bilirubin levels were evaluated in all infants. Infants with direct bilirubin levels >1 mg/dL were considered to have possible cholestatic jaundice and were excluded from the study. Late-onset breast milk jaundice was defined as prolonged unconjugated hyperbilirubinemia in otherwise healthy breastfed infants after exclusion of other identifiable causes, such as hemolytic disease, urinary tract infection (UTI), sepsis, endocrine disorders, and metabolic diseases. Sepsis was defined as culture-confirmed sepsis based on a positive blood culture accompanied by compatible clinical and laboratory findings. Newborns with major congenital anomalies, chromosomal abnormalities, or incomplete medical records were excluded from the study.

Data Collection

Demographic and clinical data were obtained retrospectively from İstanbul Training and Research Hospital medical records. Recorded variables included sex, gestational age, birth weight, length, head circumference, mode of delivery, parity, family history of neonatal jaundice, age at first outpatient admission, age at diagnosis of prolonged jaundice, presenting symptoms, feeding type, and weight changes. Newborns meeting the inclusion criteria were identified retrospectively from İstanbul Training and Research Hospital medical records and included consecutively during the six-month study period.

Laboratory Evaluation

Laboratory data collected for etiological evaluation included serum total and direct bilirubin levels, complete blood count, liver function tests (alanine aminotransferase

and aspartate aminotransferase), thyroid function tests (thyroid-stimulating hormone and free thyroxine), C-reactive protein levels, glucose-6-phosphate dehydrogenase (G6PD) activity, and serum electrolytes. Urinalysis and urine culture were performed when clinically indicated to evaluate for UTI. Blood group incompatibility was assessed by maternal and neonatal blood group analyses. Urine samples for culture were obtained by sterile urethral catheterization.

Statistical Analysis

Sample size estimation was performed prior to the study using the equation $n = t^2pq/d^2$. Calculations were based on a 5% type I error rate (α=0.05) and 80% statistical power. G*Power (version 3.1.9.2) was used to verify the adequacy of the estimated sample size. The analysis indicated that a minimum of 118 participants would be sufficient. To enhance statistical reliability and compensate for potential data limitations, 150 infants were included in the final dataset.

Data analysis was carried out with IBM SPSS Statistics (version 23.0). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were summarized as mean ± standard deviation or median with range according to distributional characteristics. Group comparisons were conducted using parametric or non-parametric tests depending on whether distributional assumptions were met (independent t-test or Mann–Whitney U test, respectively). Associations between categorical variables were evaluated using the chi-square test. All hypothesis tests were two-sided, and results were considered statistically significant at $p<0.05$.

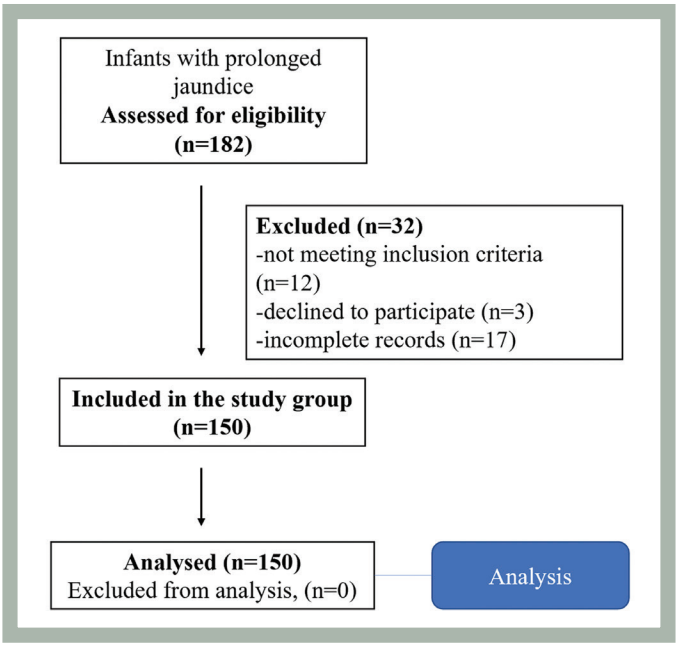

Figure 1. Flow diagram of the study population

Results

A total of 150 term newborns diagnosed with prolonged jaundice were included in the study. The flow diagram of the study is shown in Figure 1. Of the infants, 82 (54.7%) were male and 68 (45.3%) were female. Seventy-six infants (50.7%) were delivered via normal spontaneous vaginal delivery. The mean gestational age was 38.7±1.2 weeks (37-41 weeks). The mean birth weight, length and head circumference were 3229±396 g, 49.39±1.04 cm, and 35.6±0.54 cm, respectively (Table 1). Seventy-three infants (48.7%) were born to primigravid mothers. A positive history of neonatal jaundice in a sibling was reported in 32 infants (21.3%). The mean age at the initial admission to outpatient clinic and the diagnosis of prolonged jaundice was 9.84±6.29 and 15.1±2.28 postnatal days, respectively. Among the infants, 46% presented to the hospital with jaundice as the primary complaint, while the remainder presented with symptoms including poor feeding (33%), vomiting (11%), and restlessness (5%). Caregivers' presenting complaints at admission are shown in Figure 2. Laboratory findings of the study population are summarized in Table 2.

Table 1. Demographic and clinical characteristics of the study population

Variable		(n)/(%)
Gender	Female	68 (45.3%)
	Male	82 (54.7%)
	Mean ± SD	**Minimum-maximum**
Gestational week (w)	38.7±1.2	(37-41)
Birth weight (g)	3229±396	(2510-4000)
Length (cm)	49.39±1.04	(47-52)
Head circumference (cm)	35.6±0.54	(34-38)

SD: Standard deviation

The most common causes were in 86 infants (57.3%), followed by UTI in 34 infants (22.7%), ABO incompatibility in 13 infants (8.7%), Rh incompatibility in 8 infants (5.3%), sepsis in 5 infants (3.3%), G6PD deficiency in 3 infants (2%), and congenital hypothyroidism in 1 infant (0.7%) (Figure 3).

When infants with late-onset breast milk jaundice were compared with those with pathological causes of prolonged jaundice, no significant differences were observed in demographic, clinical, or laboratory parameters, except for sex. Male sex was more frequent in infants with late-onset breast-milk jaundice (p=0.046). The formula-feeding rate was 49% in newborns with late-onset breast milk jaundice, while this rate was 53% in newborns diagnosed with prolonged jaundice for other reasons (p=0.205). Type of feeding, serum bilirubin levels, liver enzyme levels, thyroid function tests, and inflammatory markers were similar between the two groups (Table 3).

Table 2. Laboratory values of the study group

	Mean ± SD
T. bilirubin (mg/dL)	13.05±5.03
D. bilirubin (mg/dL)	0.96±0.60
ALT (U/L)	18.1±8.9
AST (U/L)	35.15±11.67
Sodium (mEq/L)	138.7±3.24
Hemoglobin (g/dL)	15.12±3.2
Hematocrit (%)	43.10±9.7
Free T4 (ng/dL)	1.09±0.32
TSH (mIU/L)	2.75±2.67
CRP (mg/L)	10.97±3.32

T. bilirubin: Total bilirubin, D. bilirubin: Direct bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Free T4: Free thyroxine, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein, SD: Standard deviation.

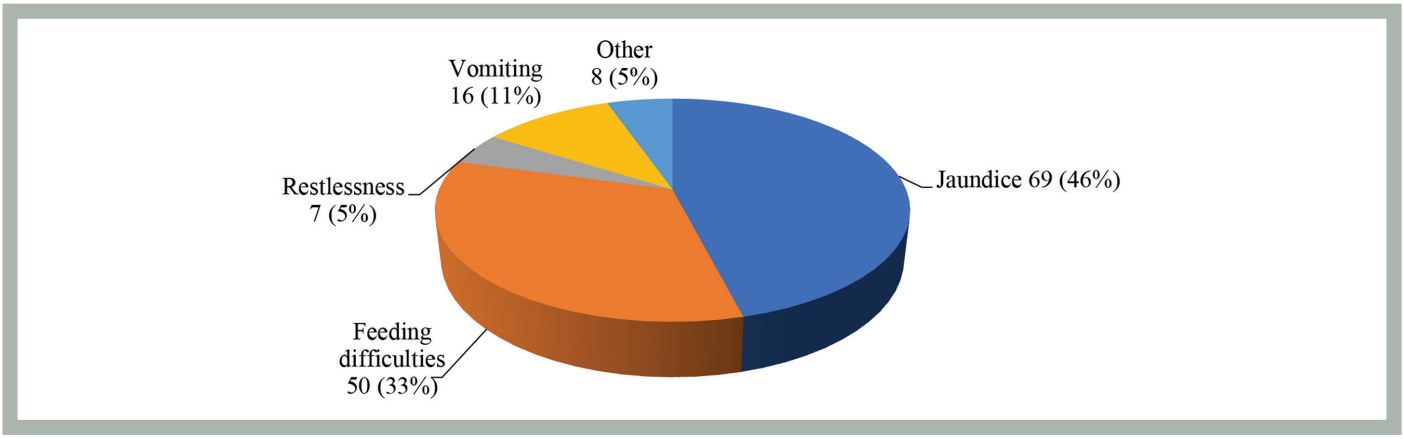

Figure 2. Presenting complaints reported by caregivers at the time of hospital admission

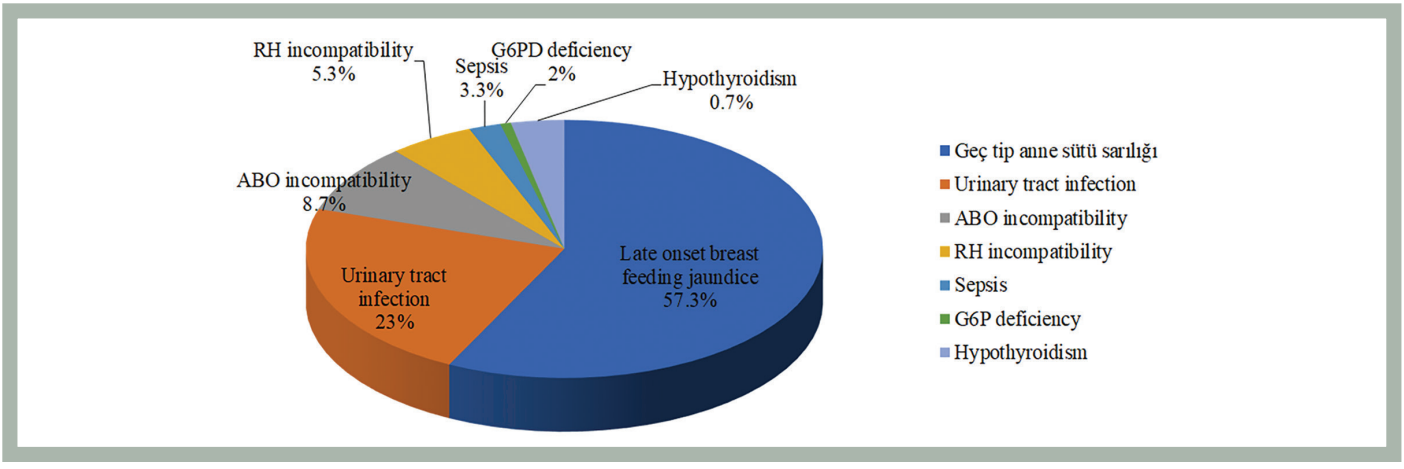

Figure 3. Late-onset breast milk jaundice
G6PD: Glucose-6-phosphate dehydrogenase

Table 3. **Comparison of neonates with prolonged jaundice due to late-onset breast milk jaundice and due to other etiologies**

	Late-onset breast milk jaundice (n=86)	Other etiologies (n=64)	p
Demographic and clinical characteristics			
First pregnancy (n, %)	37 (48.1)	36 (49.3)	0.877
Gender, female, (n, %)	40 (51.9)	28 (38.4)	**0.046**
Route of delivery (NSD)	43 (50.0)	33 (51.5)	0.258
Consanguinity	9 (11.7)	15 (20.5)	0.140
Mixed feeding	49 (63.6)	53 (72.6)	0.241
Laboratory values			
Sodium (mEq/L)	138.19±3.24	138.71±3.17	0.055
Hgb (g/dL)	15.29±3.07	14.94±3.36	0.42
Hct (%)	43.85±8.97	42.28±10.42	0.15
ALT (U/L)	17.89±8.63	18.3±9.2	0.775
AST (U/L)	35.2±10.82	35.05±13.1	0.92
Free T4 (ng/dL)	1.05±0.36	1.14±0.29	0.197
TSH (mIU/L)	2.80±3.05	2.69±2.1	0.544
CRP (mg/L)	2.56±2.46	3.0±2.74	0.310
Bilirubin value at admission (mg/dL)	13.16±3.07	14.26±2.57	0.723

NSD: Normal spontaneous delivery, Hgb: Hemoglobin, Hct: Hematocrit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Free T4: Free thyroxine, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein. A p value <0.05 was considered statistically significant

Discussion

In this study, late-onset breast milk jaundice was identified as the most common cause of prolonged jaundice in term newborns, accounting for more than half of the cases. UTI was the second most frequent etiology, followed by blood group incompatibilities, sepsis, G6PD deficiency, and congenital hypothyroidism. These findings highlight the heterogeneous nature of prolonged jaundice and the importance of systematic evaluation.

Consistent with previous reports, male sex was more common among infants with prolonged jaundice. Male predominance has been described as a risk factor for neonatal hyperbilirubinemia (2,6), potentially reflecting sex-related differences in bilirubin metabolism. However, in our cohort, female sex was significantly more common in infants with late-onset breast milk jaundice than in infants with other etiologies. This finding suggests that sex-related differences may vary according to the underlying etiology of prolonged jaundice. However, the clinical significance of this observation remains uncertain, and the finding may reflect sample characteristics rather than a true biological association. Primiparity has also been reported as a risk factor for prolonged neonatal jaundice (7,8). Consistent with previous reports, a high proportion of infants in our cohort were born to primiparous mothers; nevertheless, primiparity rates did not differ between infants with late-onset breast milk jaundice and those with other etiologies. A family history of neonatal jaundice in a sibling has been reported as a risk factor for prolonged jaundice. Brown (9) showed that a history of neonatal jaundice in a sibling increases the likelihood of jaundice in subsequent offspring, while Hansen (10), identified a positive family history as an independent risk factor for severe hyperbilirubinemia. In our study, approximately one in five infants (21.3%) had a sibling with neonatal jaundice requiring phototherapy, underscoring the importance of obtaining a detailed family history when evaluating infants with prolonged jaundice.

Although several studies have evaluated the clinical presentation of infants with neonatal jaundice, data specifically focusing on infants with prolonged jaundice remain limited. In our cohort, jaundice was the most common presenting symptom (46%), followed by poor feeding (33%), vomiting (11%), restlessness (5%), and weight loss or lethargy (5%). Notably, more than half of the infants presented with symptoms beyond isolated jaundice, underscoring the importance of a comprehensive systemic examination when evaluating infants with prolonged jaundice.

A wide range of etiological factors has been implicated in prolonged jaundice. Late-onset breast milk jaundice remains the most common and benign cause of prolonged unconjugated hyperbilirubinemia in healthy term infants (1). Previous studies have consistently reported late-onset breast milk jaundice as the most common cause, accounting for approximately 50–70% of cases (11,12,13). Despite its benign course, late-onset breast milk jaundice should remain a diagnosis of exclusion. Consistent with the literature, late-onset breast milk jaundice was the leading cause in our cohort, accounting for 57.3%. Clinical guidelines and observational studies indicate that prolonged jaundice occurs more frequently in breastfed infants, with longer durations of hyperbilirubinemia reported in breastfed infants than in formula-fed infants. Although a higher rate of exclusive breastfeeding would be expected among infants diagnosed with late-onset breast milk jaundice, the frequency of exclusive breastfeeding was similar between the two groups in our cohort (14). These findings reinforce current recommendations that breastfeeding should be continued in infants with prolonged jaundice, as breast milk provides unique benefits for newborns.

UTI are an important pathological cause of prolonged jaundice in neonates. Previous studies have reported UTI rates ranging between 7% and 15% among infants with prolonged jaundice (11,12,15,16,17,18). In our cohort, UTIs were identified in 34 infants (22.7%), representing the second most common etiology of prolonged jaundice. This rate is higher than rates reported in previous studies and may be related to regional variations, differences in screening practices, or characteristics of the study population. Nevertheless, a UTI may present solely as prolonged jaundice in early infancy; therefore, routine urinalysis and urine culture should be considered in the diagnostic evaluation of infants presenting with prolonged jaundice.

G6PD deficiency is a well-recognized cause of neonatal hyperbilirubinemia and is relatively common in our country. Although G6PD deficiency has been primarily associated with early and severe neonatal jaundice, it may also contribute to prolonged jaundice in some infants (19). In our cohort, G6PD deficiency was identified in a small proportion of cases, which may be related to the limited sample size or to the characteristics of the study population.

Congenital hypothyroidism is a rare but important and treatable cause of prolonged jaundice. Hyperbilirubinemia has been reported in up to 10% of affected newborns (20). The low frequency observed in our study may reflect the effectiveness of national newborn screening programs. Evaluation of infants with prolonged jaundice for congenital hypothyroidism is strongly recommended (21).

Study Limitations

This single-institution study relied on retrospectively collected data, which should be considered when interpreting the findings, particularly regarding their generalizability. Because this study was conducted in a tertiary care referral center, the study population may include a higher proportion of referred or clinically complex cases, which may limit the generalizability of the findings and may have influenced the observed distribution of etiological factors. However, the relatively large sample size and comprehensive etiological evaluation strengthen the validity of our findings.

Conclusion

In conclusion, late-onset breast milk jaundice is the most common cause of prolonged jaundice in term newborns. However, a substantial proportion of infants may have underlying pathological conditions, particularly UTIs. Therefore, infants presenting with prolonged jaundice should undergo systematic clinical and laboratory evaluation. Importantly, breastfeeding should be continued during follow-up, given the well-established benefits of breast milk for the newborn.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (decision number: 195, date: June 17, 2022).

Informed Consent: Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions

Concept: S.Ö., D.A., Design: S.Ö., Z.A.S., D.A., Data Collection or Processing: S.Ö., N.K., Analysis or Interpretation: S.Ö., Y.H., D.A., Literature Search: S.Ö., Z.A.S., S.C., D.A., Writing: S.Ö., Z.A.S., S.C., D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. Acta Paediatr. 2000;89:694-697.
2. Preer GL, Philipp BL. Understanding and managing breast milk jaundice. Arch Dis Child Fetal Neonatal Ed. 2011;96:F461-F466.
3. Bhutani VK. Kernicterus as a 'Never-Event': a newborn safety standard? Indian J Pediatr. 2005;72:53-56.
4. Gartner LM, Arias IM. Studies of prolonged neonatal jaundice in the breast-fed infant. J Pediatr. 1966;68:54-66.
5. Newman AJ, Gross S. Hyperbilirubinemia in breast-fed infants. Pediatrics. 1963;32:995-1001.
6. Agrawal V, Goyal AK, Sharma JN, Yadav MD. Different causes of prolonged unconjugated jaundice in the newborns. Int J Contemp Pediatr. 2017;4:984-988.
7. Tavakolizadeh R, Izadi A, Seirafi G, Khedmat L, Mojtahedi SY. Maternal risk factors for neonatal jaundice: a hospital-based cross-sectional study in Tehran. Eur J Transl Myol. 2018;28:7618.
8. Gundur NM, Kumar P, Sundaram V, Thapa BR, Narang A. Natural history and predictive risk factors of prolonged unconjugated jaundice in the newborn. Pediatr Int. 2010;52:769-772.
9. Brown LP. Breastfeeding and jaundice: cause for concern? NAACOGS Clin Issu Perinat Womens Health Nurs. 1992;3:613-961.
10. Hansen T. Narrative review of the epidemiology of neonatal jaundice. Pediatr Med. 2021;4.
11. Çetinkaya M, Özkan H, Köksal N, Akacı O. Etiological distribution of prolonged jaundice in infants. Guncel Pediatri. 2009;7:99-103.
12. Sabzehei M, Basiri B, Gohari A, Bazmamoun H. Etiologies of prolonged unconjugated hyperbilirubinemia in neonates admitted to neonatal wards. Iran J Neonatol. 2015;6:37-42.
13. Bhutani VK, Johnson LH, Jeffrey Maisels M, et al. Kernicterus: epidemiological strategies for its prevention through systems-based approaches. J Perinatol. 2004;24:650-662.
14. National Institute for Health and Care Excellence (NICE). Jaundice in newborn babies under 28 days. NICE guideline NG98. London: NICE; 2023.
15. Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. Pediatrics. 2002;109:846-851.
16. Yılmaz H, Öz E, Kibar AE, et al. Evaluating babies with prolonged jaundice for urinary tract infection. Turkiye Klinikleri J Pediatr. 2007;16:25-32.
17. Najati N, Gharebaghi MM, Mortazavi F. Underlying etiologies of prolonged icterus in neonates. Pak J Biol Sci. 2010;13:711-714.
18. Baz AMK, El-Agamy OAE, Ibrahim AM. Incidence of urinary tract infection in neonates with significant indirect hyperbilirubinemia of unknown etiology: case-control study. Ital J Pediatr. 2021;47:35.
19. Lee HY, Ithnin A, Azma RZ, Othman A, Salvador A, Cheah FC. Glucose-6-phosphate dehydrogenase deficiency and neonatal hyperbilirubinemia: insights on pathophysiology, diagnosis, and gene variants in disease heterogeneity. Front Pediatr. 2022;10:875877.
20. Yordam N, Calikoğlu AS, Hatun S, et al. Screening for congenital hypothyroidism in Turkey. Eur J Pediatr. 1995;154:614-616.
21. van Trotsenburg P, Stoupa A, Léger J, et al. Congenital hypothyroidism: a 2020-2021 Consensus Guidelines update-an ENDO-European Reference Network Initiative Endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. Thyroid. 2021;31:387-419.