Health Dynamics
eISSN: 3006-5518
Publisher: Knowledge Dynamics
DOI: https://doi.org/10.33846/hd11006

Original Research

The Relationship Between TSH and Indirect Bilirubin Levels in Neonates Suspected of Having Jaundice

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Article history
Received: 20 September 2024
Revised: 26 October 2024
Accepted: 27 October 2024
Published Online: 31 October 2024

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How to cite this article: Alizah N, Handayati A, Museyaroh, Suhariyadi The Relationship Between TSH and Indirect Bilirubin Levels in Neonates Suspected of Having Jaundice. Health Dynamics, 2024, 1(10), 387-392. https://doi.org/10.33846/hd11006

ABSTRACT

Background: Congenital hypothyroidism (CH) is a condition of thyroid hormone deficiency that occurs at birth. The TSH (thyroid-stimulating hormone) test is crucial for diagnosing hypothyroidism. CH is known to cause prolonged unconjugated hyperbilirubinemia. Therefore, this study aimed to analyze the relationship between TSH and indirect bilirubin levels in neonates suspected of having jaundice. **Methods:** This is a non-experimental, retrospective study conducted at Lombok Dua Dua Lontar Mother and Child Hospital in Surabaya. The study involved data collection on neonates aged 2–7 days suspected of jaundice, whose TSH and indirect bilirubin levels were measured between November 2022 to April 2024. **Results:** Among 100 neonates, 62% were aged 2-4 days, while 38% were aged 5-7 days. The majority were male (56%), with female comprising 44%. Of the 100 neonates, only 1 (1%) had borderline TSH levels, while 99% had normal TSH levels. Hyperbilirubinemia was observed in 94% of the neonates, while 6% had normal indirect bilirubin levels. Statistical analysis using the Spearman correlation showed no significant link between TSH and indirect bilirubin levels ($p = 0.802$). **Conclusions:** While this study did not find a clear connection between TSH and indirect bilirubin levels in neonates suspected of having jaundice, one case of borderline TSH was identified. This neonate required referral to pediatric endocrinology, as untreated congenital hypothyroidism can lead to mental retardation. Despite limited research linking TSH and bilirubin levels in jaundiced neonates, routine screening for congenital hypothyroidism using TSH testing should be reconsidered. Future studies could benefit from focusing on specific causes of neonatal jaundice to help narrow down research questions in this area.

Keywords: TSH; indirect bilirubin; congenital hypothyroidism; neonatal jaundice

1. INTRODUCTION

The growth and formation of the myelin sheath during fetal, neonatal, and infant phases are heavily depends on thyroid hormones,[(1)] especially for brain development processes like synaptogenesis, dendrite and axon growth, myelination, and neuronal migration.[(2)] Hypothyroidism, a condition of thyroid hormone deficiency (thyroxine) impacting the peripheral tissues, is associated with developmental delays and, if untreated, can lead to preventable

intellectual disabilities.[3,4] Early detection of hypothyroidism through newborn screening and timely initiation of thyroxine treatment within the first two weeks of life can greatly reduce these risks.[5]

Thyroid hormone production in the thyroid gland is stimulated by thyroid-stimulating hormone (TSH), which is released by the anterior pituitary gland. The TSH test is a widely accepted diagnostic tool for identifying hypothyroidism.[6] In Indonesia, a TSH level higher than 20 μU/mL prompts a resampling or duplicate test, followed by confirmation through TSH and T4 serum tests if elevated levels persist.[3]

The global incidence rate of congenital hypothyroidism (CH) is approximately 1 in 3,000 to 4,000 births,[3,7] though this rate increases significantly in iodine-deficient regions, reaching as high as 1 in 300 to 900 births. The prevalence of CH is notably higher in Asian populations compared to other ethnic groups.[8] Regional data also show variability, with a prevalence of 1 in 7,400 births in Japan,[1] 1 in 3,000 to 3,500 in Singapore, and 1 in 3,026 in Malaysia. In Indonesia, an assessment conducted by the endocrinology units of various hospitals in 2010 identified 595 CH cases. Data from 2012-2013 at Dr. Cipto Mangunkusumo Hospital and Dr. Hasan Sadikin Hospitals 85 CH cases among 213,669 screened newborns, equating to a higher incidence rate of 1 in2,513 births than the global average.[3] Despite this, over 70% of CH cases are diagnosed after one year, with only 2.3% detected before three months of age.[3,8]

A common clinical manifestation of elevated serum bilirubin levels is jaundice, noticeable when bilirubin exceeds 5 mg/dL.[4,9] High bilirubin levels cause yellowing of the skin, sclera, and mucous membranes,[10] typically due to increased red blood cell breakdown, impaired conjugation of indirect bilirubin, or inadequate bilirubin excretion.[11] In newborns, elevated unconjugated bilirubin levels often indicate jaundice,[12] stemming from either conjugation problems, excessive bilirubin production, or reduced hepatic uptake.[13] Prolonged unconjugated hyperbilirubinemia can also result from various conditions, such as breastfeeding jaundice, hemolytic disorders (e.g., Rh or AB0 incompatibility, G6PD deficiency), congenital hypothyroidism, urinary tract infections, or genetic disorders like Crigler-Najjar or Gilbert syndromes.[14]

Thyroid hormones play a role in bilirubin metabolism by stimulating heme oxygenase enzymes, which contribute to bilirubin production. Reduced thyroid hormone activity in patients with unconjugated hyperbilirubinemia may lead to decreased liver UDP-glucuronosyltransferase (UDPG-T) levels, further affecting bilirubin processing.[15]

In accordance with the above information about causes of neonatal jaundice, this study investigates the potential link between TSH and indirect bilirubin levels in neonates suspected of having jaundice. Although congenital hypothyroidism is not the only cause of neonatal jaundice, identifying these links is critical since jaundice can hinder a child's growth and development and, in severe cases, lead to fatal outcomes. Despite limited current data, the high prevalence of congenital disorders supports the need for nationwide newborn screening. This study highlights the practice of congenital hypothyroidism screening at Lombok Dua Dua Lontar Mother and Child Hospital Surabaya. Expanding this screening program to more healthcare institutions across Indonesia could help in the early detection and treatment of CH, potentially reducing the prevalence of associated complications.

2. METHODS

2.1 Research Design

This study employs a non-experimental, descriptive research design with a retrospective data collection approach. Data were obtained from laboratory tests conducted at Lombok Dua Dua Lontar Mother and Child Hospital in Surabaya, Indonesia in May 2024. The study population consists of neonates aged 2–7 days suspected of having jaundice, with 100 samples meeting the inclusion criteria collected between November 2022 and April 2024. Key variables in the study include: (1) neonates aged 2–7 days suspected of jaundice and (2) TSH and indirect bilirubin levels.

2.2 Data Collection

The data used in this study are secondary data and were collected retrospectively. Documented laboratory test results from Lombok Dua Dua Lontar Mother and Child Hospital in Surabaya include gender, age, TSH levels, indirect bilirubin levels, additional information like blood type and rhesus factor.

2.3 Data Analysis

Data were analyzed using SPSS statistical software. Descriptive characteristics were examined through univariate analysis, while the relationship between TSH and indirect bilirubin levels was tested with bivariate analysis. Prior to analysis, the One Sample Kolmogorov Smirnov test assessed data normality, showing a non-normal distribution at a 0.05 significance level. As a result, Spearman's correlation test was used for further analysis.

2.4 Ethical Clearance

Ethical approval for this study was granted by the Health Polytechnic of the Ministry of Health's Ethics Commission with the approval no: EA/2952/KEPK-Poltekkes_Sby/V/2024.

3. RESULTS

3.1 Neonate Characteristics

Table 1 shows that out of the 100 samples, 62% of neonates were 2–4 days old, while 38% were 5–7 days old. There were slightly more male neonates (56%) than female (44%). Blood type distribution showed the highest percentage with blood type O (39%), followed by B (26%), A (23%), and AB (12%). All neonates were Rh-positive.

In terms of TSH levels, 99% of neonates displayed normal TSH levels, with only 1% showing borderline levels. None of the neonates were diagnosed with hypothyroidism. Regarding bilirubin levels, 94% of neonates had high indirect and total bilirubin levels, while 6% had normal levels. Direct bilirubin levels were high in 48% of neonates, with the remaining 52% within the normal range.

Table 1. Characteristics of neonates

Respondent characteristic	Frequency	Percentage
Age		
2-4 days	62	62%
5-7 days	38	38%
Gender		
Male	56	56%
Female	38	44%
Blood type		
A	23	23%
B	26	26%
O	39	39%
AB	12	12%
Rhesus factor		
Positive	100	100%
Negative	-	-
TSH levels		
Normal	99	99%
Borderline	1	1%
Hypothyroid	-	-
Bilirubin levels		
Indirect: Normal	6	6%
Indirect: High	94	94%
Direct: Normal	52	52%
Direct: High	48	48%
Total: Normal	6	6%
Total: High	94	94%

3.2 Analysis of TSH and Indirect Bilirubin Levels

The Kolmogorov-Smirnov test indicates that both TSH and indirect bilirubin levels are not normally distributed, with p-values below 0.05 (Table 2). Bivariate analysis using the Spearman correlation test found no statistically significant relationship between TSH and indirect bilirubin levels ($p = 0.802$), likely due to the non-

normal distribution of the data for these variables (Table 3)

Table 2. Data normality test for TSH and indirect bilirubin levels

Parameter	Kolmogorov Smirnov test	Conclusion
TSH	p = 0.000	Not normally distributed
Indirect Bilirubin	p = 0.000	Not normally distributed

Table 3. Correlation test between TSH and indirect bilirubin levels

Parameter	Spearman test
TSH and indirect bilirubin	p = 0.802

4. DISCUSSION

This study analyzed 100 neonates aged 2-7 days with suspected jaundice, aiming to assess the relationship between TSH and indirect bilirubin levels. Neonatal jaundice can stem from multiple factors, including congenital hypothyroidism, though this condition often lacks specific symptoms. Identifying any correlation between TSH and bilirubin levels in jaundiced neonates can be essential for timely intervention and preventing potential developmental impacts.

In this study, only one newborn (1%) displayed a borderline TSH level (10.96 μU/mL), while the remaining 99% of neonates had normal TSH levels (<9 μU/mL). This finding aligns with research by Jain et al. (2019), who observed only one case of congenital hypothyroidism among 100 neonates with jaundice, characterized by increased TSH levels.[15] Supporting findings from Agrawal et al (2015), serum TSH in neonates can rise as high as 39mU/L shortly after birth due to the typical TSH surge.[2,3,7] Confirmatory serum tests are typically performed within the first one to two weeks, by which time TSH levels stabilize closer to 10 mU/L.[7] A confirmatory thyroid serum test must be carried out as soon as feasible by inviting back the patient and drawing blood by venipuncture if the screening test reveals that the newborn has abnormal thyroid hormones. It is necessary to conduct thyroid-stimulating hormone and confirmation tests for free and total T4.[3]

The hypothalamic-pituitary-thyroid (HPT) axis regulates thyroid hormone synthesis through a feedback mechanism.[16] Reduced thyroid hormone levels cause the hypothalamus to produce more thyrotropin-releasing hormone (TRH) more often. Increases the thyroid-stimulating hormone (TSH) that the anterior pituitary gland secretes.[17] Most of the circulating T3 comes from peripheral tissue deiodination of T4.[6,17] Changes in thyroid hormone and TSH levels could therefore indicate potential thyroid function issues.[17]

In this study, suspected jaundice was more common among male (56%) than female neonates (44%), corroborating findings by Nurani et al. (2017), who reported that male newborns have a 56.9% greater likelihood of developing neonatal hyperbilirubinemia. Gender has been considered a potential risk factor for hyperbilirubinemia,[11] with jaundice affecting 60–70% of full-term newborns and 80% of preterm neonates.[18] About 60% of healthy newborns are diagnosed with neonatal hyperbilirubinemia and develop neonatal jaundice.[19] The main cause of increased indirect bilirubin in neonates include bilirubin conjugation disorders, impaired bilirubin absorption by the liver,[10] and an imbalance between bilirubin production and elimination.[20] According to research findings based on indirect bilirubin levels, infants aged two to four days (62%) are more likely than those aged five to seven days (38%) to have suspected jaundice. Indirect bilirubin levels in umbilical cord serum typically range from 1 to 3 mg/dL and increase at a rate of less than 5 mg/dL/24 hours. According to another study, indirect bilirubin typically increases over the first 2–4 days of life, peaking around5–6 mg/dL before gradually decreasing to normal levels.[19]

In neonates, elevated bilirubin production is mainly attributed to higher red blood cell mass and a shorter lifespan of red blood cells compared to adults. The process of red blood cell breakdown releases significant amounts of bilirubin, which, if not efficiently processed by the liver cells or bile ducts, resulting in the disruption of the transportation, secretion, and excretion processes of bilirubin.[13] For unexplained causes, jaundice typically starts on the face and develop Neonatal jaundice often appears initially on the face and spreads downward, with the severity of jaundice reflecting bilirubin levels s in a cephalocaudal progression (e,g., face: 4–8 mg/dL; upper trunk: 5–12 mg/dL; lower trunk: 8–16 mg/dL; soles: >15 mg/dL).[21]

Since 2014, Indonesia has implemented a nationwide congenital hypothyroidism screening program. However, program implementation remains limited, particularly in rural areas, due to several factors such as poor transportation facilities, limited healthcare infrastructure, and low public awareness of the importance of early screening for congenital hypothyroidism, which has an impact on the future neurocognitive development of Indonesia's younger generation. This initiative requires collaborative efforts from the government, healthcare facilities, and the public to fully realize its benefits for Indonesia's young population.

While this study observed no significant correlation between TSH and indirect bilirubin levels, identifying even one case with borderline TSH underlines the necessity for further assessment. Only one out of 100 neonates experience an increase in TSH in borderline conditions. Limited research exists on the link between excessive physiological jaundice and congenital hypothyroidism, demanding more in-depth studies to establish any potential relationship.

5. CONCLUSION

Although no correlation was observed between TSH and indirect bilirubin levels in neonates with suspected jaundice, a single borderline TSH case underscores the importance of further evaluation, as untreated congenital hypothyroidism could lead to significant developmental issues. Routine screening for congenital hypothyroidism through TSH testing should be re-evaluated to ensure timely intervention, especially given the complex causes of neonates jaundice. Further studies focusing on isolated variables are recommended to provide a clearer understanding of jaundice etiology in neonates.

Acknowledgement

Our gratitude extends to the director, the doctor in charge, the head of the laboratory, and the entire team at Lombok Dua Dua Lontar Mother and Child Hospital in Surabaya for their support during this research, as well as to all participants who contributed valuable data to this study.

Funding Information

No funds received for this study.

Conflict of Interest

The authors declare no conflict of interest.

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