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Original Article

Hoffmann's Indirect Method-Based Establishment of Reference Interval of Thyroid Stimulating Hormone In Neonates: An Initiative Towards Less Biased Thyroid Status Screening in Neonates of Chamarajanagar

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ABSTRACT

Background: Congenital hypothyroidism (CH) is among the leading preventable cause of intellectual disability in neonates. Measurement of thyroid stimulating hormone (TSH), remains as a most reliable biochemical test to diagnose CH. The Clinical Laboratory Standards Institute recommends using local population and age-specific TSH reference range for assessing the thyroid status. Hoffmann's indirect computerized method is adopted by laboratories for estimation of RI, as it closely approximates the true RI. The study aimed to establish the RI of TSH in neonates using Hoffmann's indirect method.

Materials &Methods: The TSH data of new-born aged 0-30 days tested between 2022 to 2024 at the Maternal and Child Health Hospital of CIMS, Chamarajanagar were retrospectively retrieved from archives of Clinical Biochemistry laboratory. First report of TSH was obtained. Data were analyzed using Hoffmann's indirect method to derive age-specific RIs for the local population, based on Chemiluminescence Immunoassay technique.

Results: The TSH RI determined by Hoffmann's indirect method was 0.23–5.52 µIU/mL for neonates aged 0–7 days and 0.38–8.92 µIU/mL for those aged 8–30 days. These intervals differed notably from the manufacturer's reference range (0.3–4.2 µIU/mL), underscoring the need for population-specific calibration.

Conclusion: Laboratory-specific reference intervals are crucial for accurate interpretation of biochemical test results. Hoffmann's indirect method provides a simple and effective approach for deriving such customized RIs. The newly established TSH RIs are specific to the local population, assay method, and neonatal age group, and will henceforth be employed for evaluating thyroid status in neonates at this institute.

Keywords: *Thyroid-stimulating hormone, Reference interval, Hoffmann's indirect method, Neonates, Chemiluminescence immunoassay.*

INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common and preventable causes of intellectual disability in children worldwide. The condition often results due to insufficient production of the thyroid hormones, which are critical for normal growth and neurodevelopment during the early stages of life. Neonates with untreated CH are at higher risk of developing irreversible cognitive impairment, retardation of growth and a wide range of metabolic disturbances. When detected through early neonatal screening and treated promptly with thyroxine replacement, infants detected with the condition can still achieve normal physical and intellectual outcomes(1,2).

The global prevalence of CH ranges from 1 in 2,000 to 1 in 4,000 live births, though regional variations are common due to genetic, environmental, and methodological differences in screening and diagnosis (3). In India, recent reports have

shown a relatively higher prevalence, estimated between 1 in 1,000 and 1 in 1,200 live births, underscoring the need for accurate and context-specific diagnostic approaches (4). Neonatal screening for CH, therefore, forms a cornerstone of preventive public health programs, and its accuracy largely depends on the reliability of the laboratory parameters used amongst which notably is the thyroid-stimulating hormone (TSH) concentration.

TSH is a glycoprotein hormone which is secreted by the anterior pituitary gland which is under the control of thyrotropin-releasing hormone (TRH) from the hypothalamus. It plays a vital role in regulating thyroid hormone synthesis and secretion from the thyroid gland. In the neonatal period, serum TSH levels exhibit significant physiological variation, influenced by factors such as gestational age, mode of delivery, timing of sample collection, and even regional iodine status (5,6). Post delivery there is a physiological surge in the concentration of TSH which peaks within 30 minutes of delivery and then it gradually declines over subsequent days. Therefore, using uniform or adult reference intervals (RIs) for newborns can lead to misclassification and unnecessary anxiety or, conversely, missed diagnoses (7).

Acquainted with these challenges, the Clinical and Laboratory Standards Institute (CLSI) emphasized the importance of establishing an age, population and method specific reference intervals for biochemical analytes, including TSH (8). The reference interval represents the range of values expected in a healthy population and serves as the foundation for interpreting laboratory test results. However, defining accurate RIs for neonates poses unique difficulties due to ethical constraints in collecting blood samples from healthy newborns, limited sample sizes, and the dynamic nature of neonatal physiology. As a result, many laboratories rely on reference ranges provided by reagent manufacturers, which may not account for local population variations or methodological differences (9).

To overcome these challenges, statistical and computational methods like Hoffman's indirect method which was proposed in 1963, has emerged as a valuable alternative to the traditional direct sampling methods (10). This method especially utilizes accumulated data in the laboratory to estimate reference intervals indirectly, under the assumption that the majority of test results originate from healthy individuals. It offers several advantages of being ethical in nature, cost effective and can be implemented using large datasets without additional sample collection. Furthermore, recent advancements in computerized algorithms have made it feasible to apply Hoffmann's method with greater precision, even for analytes with skewed distributions like TSH (11).

Several studies have demonstrated that reference intervals derived using Hoffmann's indirect method closely approximate those obtained from direct sampling in healthy populations (12). This makes the approach particularly useful in resource-limited settings, where large-scale screening or healthy subject recruitment may not be feasible. In India, neonatal screening programs are expanding, but standardization of laboratory parameters remains a challenge. The reliance on imported assay kits and manufacturer-provided reference ranges may not accurately reflect Indian neonatal populations, which can differ in genetic background, nutrition, and iodine intake(13).

In this context, the present study was undertaken with **the primary objective** to collect and compile data on Thyroid Stimulating Hormone (TSH) values of newborns from January 2022 to November 2024 and to establish a reference interval for neonatal TSH levels using Hoffmann's indirect method, based on the compiled dataset.

at the Maternal and Child Health Hospital, Chamarajanagar Institute of Medical Sciences (CIMS), Karnataka. By retrospectively analyzing TSH data obtained through Chemiluminescence Immunoassay (CLIA), the study aims to establish both age- and population-specific RIs suitable for local interpretation.

METHODOLOGY

This cross-sectional study was conducted in the Clinical Biochemistry Laboratory of the Maternal and Child Health (MCH) Hospital, Chamarajanagar, over a period of three months. The study utilized retrospective data retrieved from the laboratory archives of the same hospital. The dataset comprised TSH reports of newborns aged 0 to 30 days who were delivered at the MCH Hospital of Chamarajanagar Institute of Medical Sciences (CIMS) between January 2022 and November 2024.

A universal sampling method was adopted, wherein all eligible TSH reports available during the study period were included. As the study involved retrospective data collection without predetermined limits, the sample size consisted of the total number of neonatal TSH reports retrievable within the defined time frame, in accordance with the inclusion and exclusion criteria. This approach was adapted from the study by Ashish Agravatt *et al.*(14).

The inclusion criterion was the first recorded TSH report of each newborn aged 0–30 days. Exclusion criteria included repeated measurements of the same infant to avoid duplication of data. All TSH data meeting the inclusion criteria were compiled, cleaned, and analyzed. The reference interval for neonatal TSH—specific to the local population and to the Chemiluminescence Immunoassay (CLIA) method employed in the laboratory was determined using Hoffmann's indirect

statistical method. This approach utilizes the distribution of observed test results in a large dataset to derive population-based reference limits, ensuring accuracy and applicability to the local demographic and analytical conditions.

RESULTS

A total of 423 neonatal TSH reports were analyzed, comprising 221 males and 202 females. The overall mean TSH value for the study population (0–30 days) was 2.58 ± 1.92 µIU/mL, with a median of 2.04 µIU/mL and a coefficient of variation (CV) of 75%, indicating moderate variability within the population. The TSH values ranged between the 2.5th and 97.5th percentiles (0.31–7.16 µIU/mL) (Table 1).

When stratified by age, neonates aged 0–7 days (n = 298) demonstrated a mean TSH of 2.17 ± 1.61 µIU/mL with a percentile range of 0.25–5.82 µIU/mL, while those aged 8–30 days (n = 125) had a higher mean TSH of 3.65 ± 2.48 µIU/mL and a broader percentile range of 0.40–9.40 µIU/mL (Table 1). These findings indicate a slight rise in TSH levels during the second to fourth week of life, suggesting physiological adjustment following birth.

Gender-based analysis revealed that male neonates (n = 221) exhibited a mean TSH of 2.75 ± 2.17 µIU/mL, higher than that of females (2.45 ± 1.70 µIU/mL). Males also showed greater dispersion (CV = 79%) compared to females (CV = 70%), implying marginally greater biological variability in TSH among male infants (Table 1).

Table 1: Comparison of TSH values among the neonates

TSH COMPARISON								
TSH	**n**	**Mean**	**Median**	**Mode**	**Standard Deviation**	**Coefficient of Variation (%)**	**Percentile 2.5th**	**Percentile 97.5th**
1 to 30	423	2.58	2.04	1.09	1.92	75%	0.31	7.16
0 to 7	298	2.17	1.62	1.08	1.61	74%	0.25	5.82
8 to 30	125	3.65	3.30	3.26	2.48	68%	0.40	9.40
Male	221	2.75	2.13	0.49	2.17	79%	0.40	7.94
Female	202	2.45	2.03	1.71	1.70	70%	0.17	5.84

Box plot analyses were performed after removal of outliers to visualize TSH distribution across age and gender subgroups. Among 0 to 30 days, the TSH levels for this time frame had a median value near the mid-range (approximately 2–4 µIU/mL). The interquartile range (IQR) was relatively narrow, suggesting moderate variability within this group. Whiskers extended upto approximately 10 µIU/mL, indicating that it had some high values but had no extreme outliers. Among 0 to 7 days, the distribution of TSH levels was slightly lower compared to the "0 to 30 days" group, suggesting a potential downward trend in TSH levels within the first week. However, the overall variability is similar. Among 8 to 30 days, TSH levels appeared to rise slightly compared to the "0 to 7 days" group, with a similar IQR and whisker length as the "0 to 30 days" group (Figure 1). This indicated that TSH levels might stabilize or increase marginally after the first week.

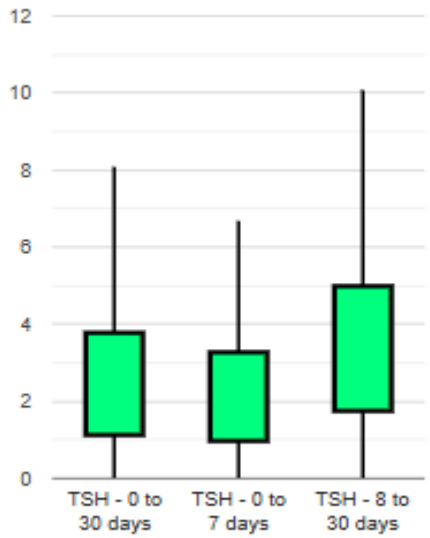

Figure 1: Box plot analysis of TSH distribution across age groups

Gender-based box plots demonstrated comparable medians for both sexes (approximately 2–4 µIU/mL), though male neonates displayed a wider interquartile range and longer whiskers, consistent with the higher standard deviation and coefficient of variation noted in descriptive analysis. In contrast, female neonates exhibited a tighter clustering of TSH values, reflecting less variability in thyroid response (Figure 2). Overall, no extreme outliers were observed in the dataset, suggesting a homogenous neonatal population with minimal data distortion.

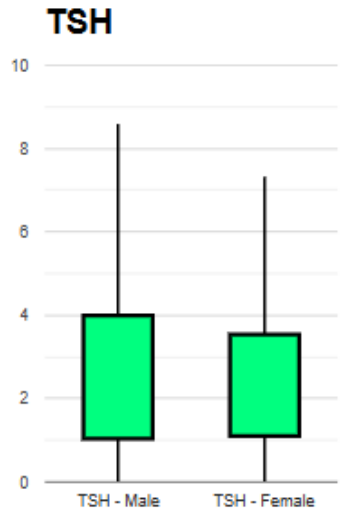

Figure 2: Box plot analysis of TSH distribution across gender

Reference Interval Establishment by Hoffmann's Method

Reference intervals (RIs) for TSH were calculated using **Hoffmann's indirect method**, which utilizes cumulative frequency distributions to estimate population-based limits.

0–30 Days (Overall Neonatal Population)

The cumulative distribution curve revealed a rapid rise at lower TSH levels (0–2 µIU/mL), followed by a plateau beyond 5 µIU/mL. Using Hoffmann's method, the reference interval for neonates aged 0–30 days was determined as 0.109–6.988 µIU/mL, with adjusted percentiles of 0.292 (2.5th) and 6.805 µIU/mL (97.5th) (Figure 3).

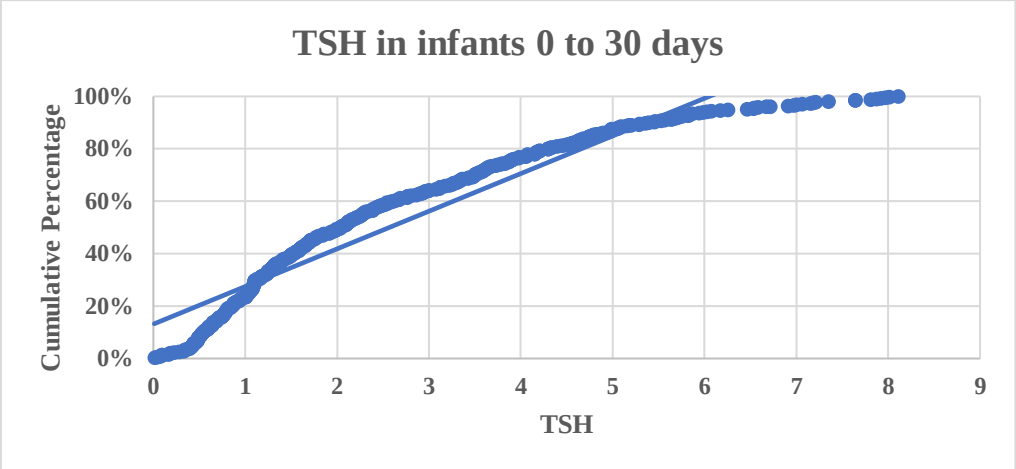

Figure 3: Reference Interval Establishment for TSH in infants 0-30 days

0–7 Days:

Among neonates within the first week of life, the reference interval was slightly narrower at 0.05–5.71 µIU/mL, with the adjusted 2.5th and 97.5th percentiles at 0.233 µIU/mL and 5.529 µIU/mL, respectively. This reflects lower and more stable TSH values immediately after birth, corresponding to transient neonatal hormonal adaptation (Figure 4).

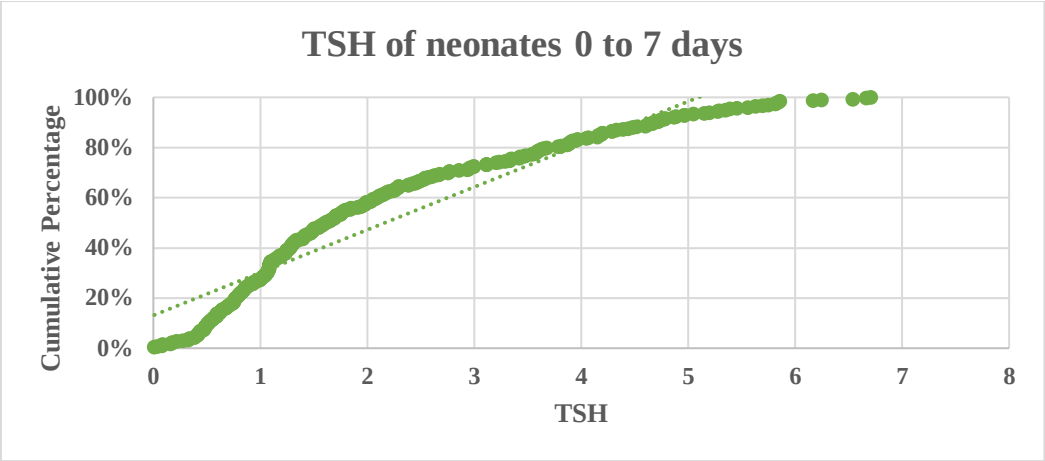

Figure 4: Reference Interval Establishment for TSH in infants 0-7 days

8–30 Days

For neonates aged 8–30 days, the reference interval widened to −0.05–9.36 µIU/mL, indicating greater variability and slightly elevated upper limits compared to the first week. The adjusted percentiles were 0.382 µIU/mL (2.5th) and 8.929 µIU/mL (97.5th). The upward shift in TSH levels during this period suggests a secondary physiological stabilization of thyroid function as the hypothalamic–pituitary–thyroid axis matures (Figure 5).

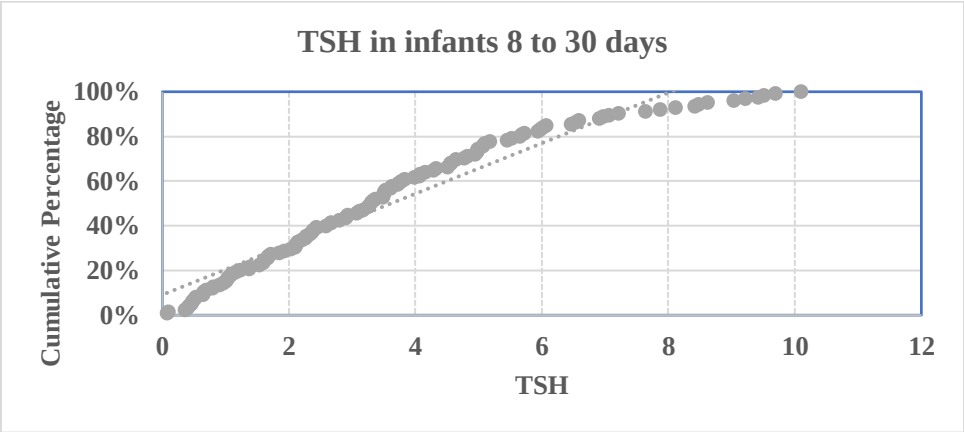

Figure 5: Reference Interval Establishment for TSH in infants 0-7 days

Gender-specific Reference Intervals

For male neonates, the reference interval was 0.097–7.828 µIU/mL (adjusted 2.5th percentile = 0.38 µIU/mL; 97.5th = 7.544 µIU/mL) (Figure 6), while female neonates showed a slightly lower and narrower range of −0.074–5.783 µIU/mL (adjusted 2.5th = 0.162 µIU/mL; 97.5th = 5.548 µIU/mL) (Figure 7). These findings reaffirm that male infants tend to exhibit higher and more variable TSH values, whereas female infants demonstrate more tightly regulated thyroid function during the neonatal period (Table 2).

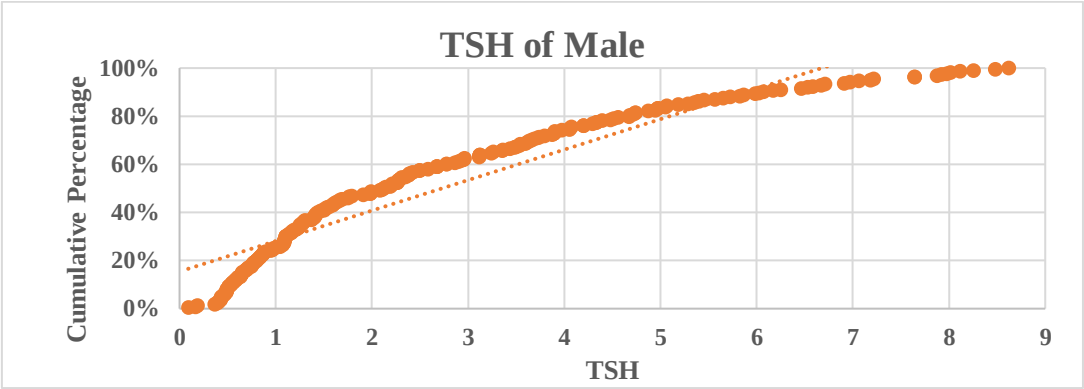

Figure 6: Reference Interval Establishment for TSH in males

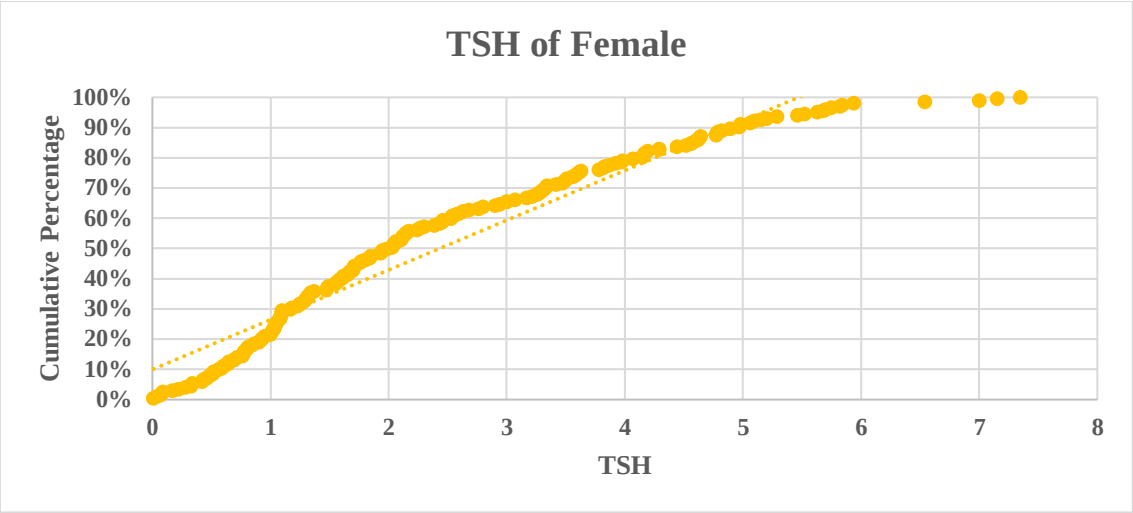

Figure 7: Reference Interval Establishment for TSH in females

Table 2: Summary of the reference interval establishment for TSH in infants

Thyroid Parameter TSH	Adjusted 2.5th Percentile	Adjusted 97.5th Percentile	Critical Value	Standard Error	Critical Difference	Reference Interval (RI)
TSH (0 to 30 days)	0.2921	6.8053	1.96	0.0934	0.1831	0.109-6.9884
TSH (0 to 7 days)	0.2332	5.529	1.96	0.0933	0.1832	0.05-5.7122
TSH (8 to 30 days)	0.3819	8.929	1.96	0.222	0.4353	-0.0534-9.3643
TSH (Male)	0.38	7.5441	1.96	0.1446	0.2834	0.0966 - 7.8275
TSH (Female)	0.1615	5.548	1.96	0.12	0.2352	-0.0737-5.7832

DISCUSSION

The aim of the present study was to establish age and gender specific reference intervals for serum thyroid-stimulating hormone (TSH) concentrations in neonates aged 0–30 days using Hoffmann's indirect method. Accurate interpretation of neonatal TSH levels is crucial in early identification of thyroid dysfunctions such as congenital hypothyroidism (CH), which is one of the most common preventable causes of intellectual disability. Even in the presence of large scale neonatal screening programs, various factors like variations in the reference ranges among population, laboratory methodologies necessitate intervals which are locally validated. The findings of this study provide important insights into the physiological fluctuations of TSH during early neonatal life and reinforce the importance of stratified interpretation by age and gender.

In the current study, the overall mean TSH value among neonates aged 0–30 days was 2.58 ± 1.92 µIU/mL, with a median of 2.04 µIU/mL and a coefficient of variation (CV) of 75%, indicating moderate variability within the cohort. The reference interval (RI) determined by Hoffmann's method was 0.109–6.988 µIU/mL. These findings are consistent with published neonatal TSH ranges, typically spanning from 0.7–11.0 µIU/mL during the first month of life (15,16). Such variability can be attributed to differences in geographic region, ethnicity, timing of sample collection post-delivery, and assay sensitivity.Immediately after birth, the neonate undergoes a physiological surge in TSH due to abrupt exposure to extrauterine cold stress, triggering a rise that peaks within 30 minutes and gradually declines over the first few days (5). The moderate variability observed in the present study supports this transitional endocrine adaptation.

In the present study a clear age-related pattern was observed. Neonates aged 0–7 days exhibited a mean TSH of 2.17 ± 1.61 µIU/mL, whereas those aged 8–30 days had a significantly higher mean value of 3.65 ± 2.48 µIU/mL, along with a broader percentile range. The reference interval widened from 0.05–5.71 µIU/mL in the first week to −0.05–9.36 µIU/mL thereafter, suggesting that TSH variability increases as the neonate transitions from early postnatal adaptation to homeostatic regulation of the hypothalamic–pituitary–thyroid (HPT) axis. This increase in TSH during the later neonatal period contrasts with the rapid postnatal decline reported by Kapelari K et al (2008), who noted that TSH and thyroxine (T4) levels peak within hours after birth and gradually normalize within the first two weeks (17). However, a study by Omuse G et al. (2023), has reported a secondary mild rise in TSH beyond the first week (18). The higher mean TSH in the 8–30-day group in our study could also reflect assay timing variations and feeding practices, as breast milk iodine content and feeding frequency influence neonatal thyroid hormone levels (Zimmermann et al., 2012) (19).

Our findings also demonstrated gender-specific differences, with male neonates showing higher mean TSH levels (2.75 ± 2.17 µIU/mL) compared to females (2.45 ± 1.70 µIU/mL), along with greater variability (CV 79% vs. 70%). The

Hoffmann-derived reference interval for males (0.097–7.828 μIU/mL) was broader than for females (−0.074–5.783 μIU/mL). This gender disparity has been observed in previous studies, such as those by Dalmazi GDi et al. (2020), Priyanto H et al (2025). and Omuse G et al. (2023), where males consistently exhibited higher neonatal TSH levels (18,20,21). The physiological basis for this difference may involve the interplay between sex steroids and thyroid regulation. Male neonates are known to experience transiently higher testosterone levels after birth, which can influence hypothalamic-pituitary feedback and thyroid hormone metabolism (22). Clinically, these findings suggest that a single universal cut-off for gender may be inadequate for accuracy of optimal screening. Gender specific RIs may assist in preventing false positive diagnosis of congenital hypothyroidism in infants, especially males wherein the TSH elevations physiologically are more common.

Hoffmann's cumulative frequency approach was employed to establish population-based RIs. The method yielded biologically plausible and clinically meaningful intervals across all subgroups. The derived percentiles closely mirrored observed values, confirming the reliability of this indirect statistical approach. Katayev et al. (2010) in this regard higjlighted that Hoffmann's method remains robust for estimating RIs in retrospective datasets where direct sampling of healthy individuals is impractical (11).

Our study reduces the confounding effects of physiological variability and offers refined RIs that can direct clinical interpretation of newborn screening results by stratifying results by age and gender. There are important clinical ramifications to developing precise, population-specific RIs for neonatal TSH. Overtreatment, anxiety, or missed cases of congenital hypothyroidism can result from misinterpreting newborn thyroid function tests. Applying adult or generalized pediatric cut-offs to neonates can lead to up to 10–15% false-positive rates, according to Kempers et al. (2010) (23). The findings of this study contribute valuable normative data for the regional neonatal population and support the adoption of stratified TSH cut-offs to enhance diagnostic accuracy and screening efficiency.

Despite information on the distribution of TSH in neonates, the current study has few limitations. Maternal and perinatal factors that may affect neonatal thyroid function, such as gestational age, delivery mode, and iodine status, were not available due to the retrospective design. A more comprehensive understanding of neonatal thyroid physiology may be possible with future prospective studies that include both TSH and free T4 levels and have larger sample sizes. Longitudinal follow-up would also help clarify whether the short-term variations seen are indicative of long-term thyroid outcomes.

CONCLUSION

In summary, this study established age and gender specific reference intervals for neonatal TSH using Hoffmann's indirect method. TSH levels showed an increasing trend after the first week of life and were higher in male neonates compared to females. These findings underscore the necessity of adopting age- and gender specific RIs for accurate interpretation of neonatal thyroid screening results. Population tailored intervals can minimize false-positive results and enhance the precision of early detection strategies for congenital hypothyroidism.

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