Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

Evaluation of the Thyroid Hormone Status among Normal New Born Preterm Infants

Dr. Juwel Das[1*], Dr. Sayeed Haq[2], Dr Palash Sarker[3], Dr. Bijoy Pal[4]

[1]Assistant Professor, Department of Pediatrics, Brahmanbaria Medical College, Brahmanbaria, Bangladesh
[2]Assistant Professor, Department of Pediatrics, Brahmanbaria Medical College, Brahmanbaria, Bangladesh
[3]Registrar, Department of Pediatrics, Brahmanbaria Medical College, Brahmanbaria, Bangladesh
[4]Assistant Registrar, Department of Pediatrics, Brahmanbaria Medical College, Brahmanbaria, Bangladesh

DOI: 10.36347/sjams.2024.v12i02.016 | **Received:** 29.12.2023 | **Accepted:** 05.02.2024 | **Published:** 26.02.2024

***Corresponding author:** Dr. Juwel Das
Assistant Professor, Department of Pediatrics, Brahmanbaria Medical College, Brahmanbaria, Bangladesh

Abstract **Original Research Article**

Introduction: Thyroid dysfunction poses a greater risk in preterm newborns (PN) compared to term newborns (TN), often eluding detection in neonatal screening due to delayed thyrotropin (TSH) elevation in these cases. ***Objective:*** To assess thyroid function during the second week of life in PN born before 32 weeks gestation and identify factors associated with its alteration. ***Methods:*** A retrospective study examined thyroid function in < 32 weeks gestation neonates, analyzing thyroxine (T4L) and TSH levels in relation to perinatal and neonatal outcomes. The study included 358 patients with a mean gestational age of 29.3 weeks and a mean birth weight of 1127 grams. ***Results:*** Linear correlations were observed between T4L and birth weight (BW) (R=0.356; p<0.001) and gestational age (GA) (R=0.442; p<0.001). TSH values were associated with small for gestational age (SGA) (5.3 mU/L [1.5-37] for SGA vs. 2.89 mU/L [0.2-19.5] for non-SGA; p<0.001), inotropic support (3.98 mU/L [0.6-22.9] for Yes vs. 3.16 mU/L [0.2-37] for No; p=0.019), and BW (R=-0.249; p<0.001). Levothyroxine treatment was administered to 2.5% of patients, with six being SGA. ***Conclusions:*** Analyzing thyroid function in the second week aids in identifying asymptomatic newborns at risk of thyroid dysfunction, particularly in the case of SGA newborns who exhibit a higher susceptibility to thyroid function alterations.

Keywords: Thyroid function, Prematurity, Small for gestational age, Thyrotropin, Thyroxine.

INTRODUCTION

The thyroid hormone plays a crucial role in the growth and development of newborns, making the evaluation of its status among normal and preterm infants a topic of significant clinical interest. Thyroid hormones, particularly thyroxine (T4) and triiodothyronine (T3), are vital for the maturation of the central nervous system and overall metabolic regulation [1-5]. In full-term infants, the thyroid gland is expected to function adequately, ensuring the synthesis and release of sufficient thyroid hormones. However, preterm infants may face unique challenges due to the immaturity of their thyroid axis, potentially leading to alterations in thyroid hormone levels. Understanding the thyroid hormone status in both normal and preterm newborns is essential for early identification of any abnormalities and prompt intervention to support optimal neurodevelopment and growth [6-10].

The thyroid hormone evaluation in newborns involves assessing various parameters such as T4 and T3 levels, thyroid-stimulating hormone (TSH) levels, and the ratio of free T4 to free T3. The delicate balance of these hormones is crucial for neurodevelopmental outcomes, making it imperative to explore how preterm birth may impact the thyroid hormone profile. Preterm infants, born before completing 37 weeks of gestation, often experience challenges in adapting to extrauterine life, including the potential for immature thyroid function. 11-15 As such, a comprehensive evaluation of thyroid hormone status in both normal and preterm newborns is vital for gaining insights into potential variations, identifying risk factors, and guiding clinical management to ensure optimal outcomes for this vulnerable population.

OBJECTIVE

This study aims to contribute to our understanding of thyroid hormone dynamics in

newborns, shedding light on the nuances associated with preterm birth and offering valuable insights for clinical practice.

METHODS

The study conducted a retrospective, observational analysis on preterm (PT) infants born at or before 32 weeks of gestation admitted neonatal ward (SCANU) at Brahmanbaria Medical College over a 3-year period (January 1, 2021, to December 31, 2023). Patients who died before the first thyroid function screening, those transferred after 14 days post-birth, or those not screened within the established protocol were excluded. The hospital's thyroid function monitoring protocol involves measuring TSH and FT4 levels in the second week of life, with additional tests based on initial screening results. Treatment decisions, including levothyroxine administration, were made in collaboration with the pediatric endocrinology unit, and patients were followed up for treatment duration and potential discontinuation. Data analysis involved descriptive statistics and inferential analysis using various tests for different types of variables.

The study collected comprehensive data on antenatal, postpartum, and neonatal variables, including gestational age, birth measurements, respiratory support, sepsis, and thyroid hormone levels. Statistical analysis utilized SPSS Statistics, employing tests such as Kolmogorov-Smirnov, Shapiro-Wilk, Student t test, Mann-Whitney U test, $\chi 2$ test, and Fisher exact test to assess normality, compare quantitative variables, and analyze qualitative variables. The study received approval from the respective research committees of the hospital, ensuring ethical compliance in data retrieval and analysis.

RESULTS

The study included a total of 358 preterm newborns with a mean gestational age of 29.3 weeks and a mean birth weight of 1127 grams. Among the notable findings, 31.6% were from multiple gestations, 31.8% had a gestational age less than 28 weeks, and 35.5% had a birth weight less than 1000 grams. Additionally, 17% were classified as small for gestational age. A majority of the infants (76.8%) received antenatal steroids, and 91.6% required continuous positive airway pressure (CPAP). Other significant observations include 26.5% experiencing intraventricular hemorrhage (any grade), 20.4% having nosocomial sepsis, and 2.8% resulting in death.

Tavle-1: The prenatal characteristics and neonatal outcomes of the patients

Characteristics	**n (%)**
Multiple gestation	113 (31.6%)
Gestational age < 28+0 weeks	114 (31.8%)
Birth weight < 1000 grams	127 (35.5%)
Small for gestational age	61 (17.0%)
Antenatal steroids (2 or more doses)	275 (76.8%)
Intubation in delivery room	72 (20.1%)
Need of surfactant	162 (45.3%)
Need of mechanical ventilation	128 (35.8%)
Need of CPAP	328 (91.6%)
Haemodynamically significant patent ductus arteriosus	85 (23.7%)
Administration of dopamine	59 (16.5%)
Vertical sepsis	37 (10.3%)
Necrotising enterocolitis (any grade)	27 (7.5%)
Nosocomial sepsis	73 (20.4%)
Intraventricular haemorrhage (any grade)	95 (26.5%)
Severe intraventricular haemorrhage (grade III, intraparenchymal haemorrhage)	15 (4.2%)
Death	10 (2.8%)

The study evaluated thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels at 7 to 14 days post-birth in preterm infants categorized by gestational age and birth weight. TSH values exhibited a range across gestational age and birth weight categories, with higher medians observed in infants born before 26 weeks of gestation and those with birth weights less than 750 grams. FT4 levels also varied, showing an increase with higher gestational age and birth weight. The presented percentiles (P5-P95) provide a comprehensive overview of the distribution of TSH and FT4 values within each subgroup.

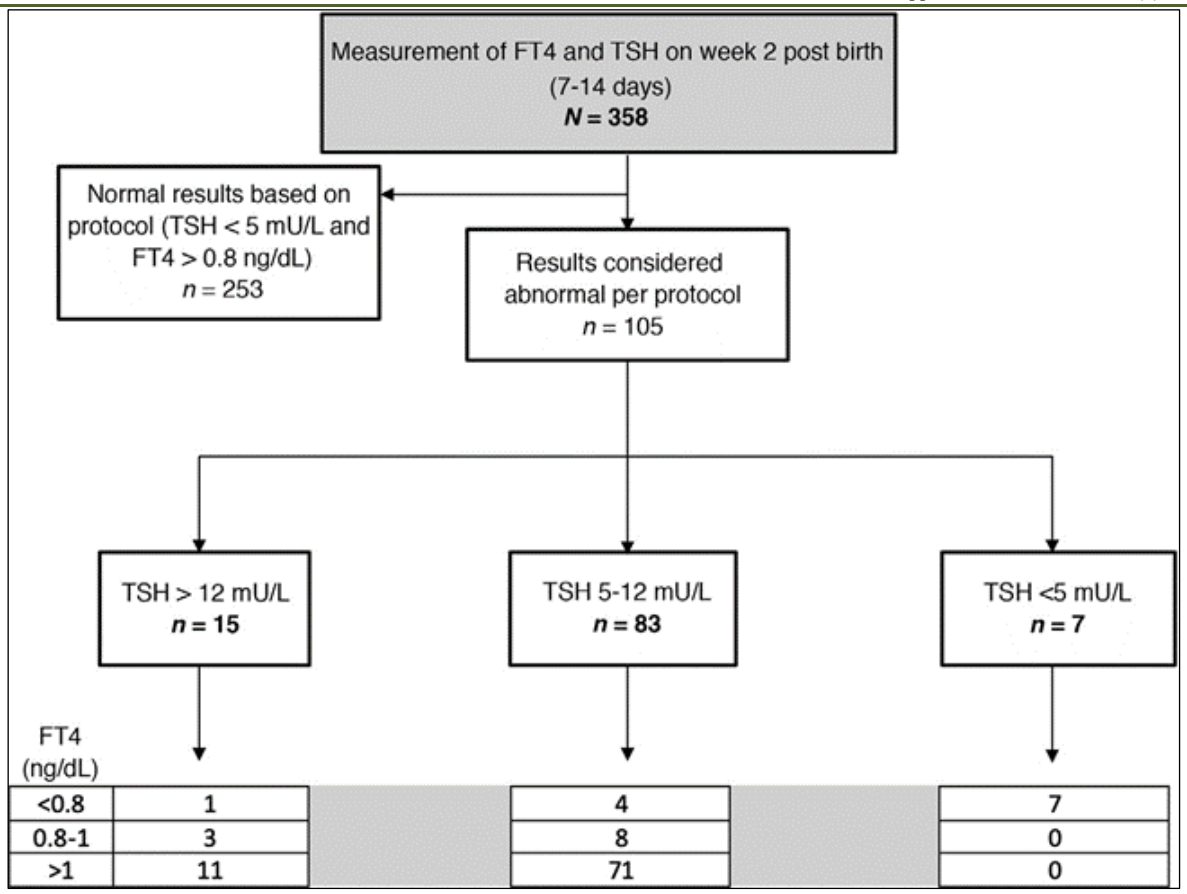

Figure-2: Distribution of thyroid hormone values in the sample, based on the thresholds established in the protocol

Table-2: Thyroid-stimulating hormone and free thyroxine values at 7 to 14 days post birth by gestational age and birth weight, expressed as median (minimum-maximum)

Gestational Age	**< 26 weeks**	**26+0 to 27+6 weeks**	**28+0 to 29+6 weeks**	**≥ 30 weeks**
n	41	73	92	152
TSH (mU/L)	3.5 (0.59 - 19.5)	3.4 (0.74 - 13.6)	3.6 (0.2 - 22.9)	2.9 (0.51 - 37)
P5-P95	0.65 - 16.1	1 - 10.5	1.15 - 13.3	1.18 - 11.5
FT4 (ng/dL)	1.01 (0.51 -1.66)	1.12 (0.72 - 1.9)	1.22 (0.82 - 1.9)	1.32 (0.73 -2.25)
P5-P95	0.68 - 1.48	0.81 - 1.56	0.84 - 1.61	0.94 - 1.72
Birth Weight	**< 750 g**	**750 - 999 g**	**1000 - 1249 g**	**≥1250 g**
n	49	78	88	143
TSH (mU/L)	4.3 (0.59 -22.9)	3.9 (0.65 - 37)	3.8 (0.74 - 12.8)	2.4 (0.2 -17.4)
P5-P95	0.72 - 18	0.88 - 12.5	1.2 - 9.7	1.1 - 8.8
FT4 (ng/dL)	0.99 (0.51 -1.66)	1.1 (0.68 - 2.03)	1.2 (0.75 - 1.9)	1.3 (0.73 -2.25)
P5-P95	0.69 - 1.57	0.74 - 1.6	0.83 - 1.6	0.94 - 1.73

In the presented cohort, thyroid function was assessed in preterm infants who underwent screening at 7-14 days post-birth. The study included 9 infants with varying gestational ages (GA) and birth weights (BW). Abnormal thyroid-stimulating hormone (TSH) levels were observed in 5 infants during the screening, prompting the initiation of levothyroxine treatment. The median time of treatment initiation was 24 days post-birth. Notably, the discontinuation of treatment occurred at different ages, ranging from 9 months to 30 days, with varied reasons such as small for gestational age (SGA), mosaicism trisomy 21, Williams syndrome, and nephrotic syndrome with dopamine administration.

Table-3: Anthropometric and laboratory characteristics of patients treated with levothyroxine

	Sex	**BW**	**GA**	**Newborn screening**			**TSH 7-14 days**	**FT4 7-14 days**	**TSH at treatment initiation**	**FT4 at treatment initiation**	**Time of treatment initiation (days post birth)**	**Discontinuation of treatment (months of life)**	**Other characteri**
				Days post birth	**Abnormal**	**TSH (mU/L**							
1	F	1000	32^{+0}	3	No		11.6	0.78	186.1	0.35	24	Yes (9)	SGA
2	F	735	29^{+2}	4	No	3.00	15.4	1.60	39.8	0.94	20	Yes (33)	SGA
3	F	645	30^{+5}	5	No		18.8	1.28	16.3	1.3	35	Yes (21)	SGA
4	M	1600	29^{+6}	5	No	4.20	17.4	1.48	20.8	1.2	18	No	Mosaicism trisomy 21
5	M	825	30^{+0}	4	No	5.30	37	0.94	39.2	0.94	12	No	SGA
6	M	880	29^{+2}	4	No	1.70	14.8	0.88	94.7	0.65	18	No	SGA, Williams syndrome
7	F	600	29^{+4}	13	Yes	13.00	22.9	1.29	23.4	1.29	14	Yes (12)	SGA, dopamine
8	M	1000	28^{+4}	3	No		5.3	1.20	15.1	1.05	60	Yes (14)	Nephrotic syndrome, dopamine
9	M	650	24^{+0}	3	No		19.5	0.68	18.6	0.67	15	30 days	Septic shock on week 2

DISCUSSION

Because PT newborns have a better chance of surviving, doctors have been able to diagnose more unusual conditions, such as thyroid dysfunction, than those previously reported seven, seventeen, twenty-two.

Reference values and analyses of thyroid function in pediatric patients have been the subject of several investigations, however data on levels discovered in PT newborns are few. Among the biggest case series to evaluate thyroid function in very preterm newborns, this one is relatively new numbers [12,13].

Reduced T4 levels without increase of TSH, known as hypothyroxinaemia of infancy, is rather common in neonates born before 32 weeks' gestation; in

newborns delivered before 28 weeks, the frequency can reach 50%.22,25 The Spanish Society of Paediatric Endocrinology has set an FT4 threshold of 0.8 ng/dL, which is lower than the 0.7 ng/dL cut-off number in international standards. On the other hand, our sample detected hypothyroxinaemia in 3.3% of patients, which is lower than the prior literature. FT4 levels have normalized in the second screening for all patients except for the three preterm infants who were treated for this condition. No cases of central hypothyroidism were found.

Consistent with previous research, we found that FT4 levels were lower in individuals whose body weight and GA were lower. We found no statistically significant link between TSH levels and GA, although we did detect a modest correlation between birth weight and TSH values and a history of SGA. It is probable that infants with lower GAs and similar BWs had a better developed hypothalamic-pituitary axis than infants with higher GAs and similar BWs, as patients with elevated TSH and low BWs were more likely to have a history of SGA.9,27 percent.

Additionally, we discovered that dopamine treatment was associated with elevated TSH levels. It is possible that neonates who have recovered from a severe illness in the first two weeks of life and who have received inotropes or steroids have recovered from an episode of transient central hypothyroidism, since previous research has discovered slightly elevated levels of TSH at fourteen days after birth in these babies [14, 15].

Although there were a few cases when levothyroxine could be stopped after 2 weeks in infants with septic shock and patients with genetic abnormalities, the majority of the individuals in our sample who took the medication were SGA (GA > 28 weeks and BW < 1000 g). Consistent with earlier research, we discovered that SGA newborns had a greater risk of thyroid dysfunction than GA infants.

We found that, similar to or somewhat higher than prior case series, 4.7% of patients with very low birth weight had thyroid malfunction that required therapy [16, 17].

The screening procedure used in the study was crucial in diagnosing thyroid dysfunction in these children since, with the exception of one patient, no one who received levothyroxine had aberrant findings in the initial newborn screening. Due to septic shock in the first days of life, which required multiple transfusions of blood products, testing was delayed in the one patient with abnormal results from the initial screening to 13 days after birth. This allowed the week 2 blood test included in the protocol to also help identify that anomaly early, and the patient was already receiving treatment when the results of the heel prick test were available, so it was a useful tool.

Because the newborn screening conducted 48 to 72 hours after birth cannot detect abnormal thyroid function owing to delayed elevation of TSH, these results support the importance of conducting a second screening in patients born prematurely or with risk factors for hypothyroidism [16, 17].

The ideal ranges for proper maturation, the necessity of hormone replacement in PT newborns, and the short- and long-term effects of a relative thyroid hormone shortage are also topics of heated debate [18, 2].

There is conflicting evidence regarding the effects of prematurity and hypothyroxinaemia on neurodevelopment. Some studies have shown worse outcomes for patients with this history, while others have shown no different results for psychomotor and cognitive outcomes in prematurity (PT) infants with normal thyroid function in the neonatal period. These studies have included those with long follow-ups to age 19 years, like the one published by other study [12, 10, 8].

Patients with persistent hypothyroxinaemia or hyperthyrotropinaemia should be treated after confirming test results. It is prudent to avoid starting treatment based on a single isolated value and to assess the possibility of discontinuation before age 3 years. This approach is supported by recent guidelines and some authors, and it is important to ensure adequate thyroid function during this critical period for the development of the central nervous system approximately [18].

CONCLUSION

In conclusion, the study emphasizes the significance of measuring thyroid hormone levels in preterm neonates during the second week post-birth for identifying potential abnormalities not captured in newborn screenings. Due to the absence of universally accepted cut-off values for treatment eligibility, individual hospitals should establish criteria based on patient outcomes. The study suggests initiating treatment for persistent abnormalities and evaluating the possibility of discontinuation in the early years of life, excluding patients with specific diseases linked to an increased risk of permanent congenital hypothyroidism. Additionally, the authors highlight the need for prospective, randomized, placebo-controlled trials to elucidate the short- and long-term benefits of levothyroxine replacement therapy in preterm infants with thyroid dysfunction, addressing the current lack of clear evidence in this regard.

REFERENCE

1. Calvo, R. M., Jauniaux, E., Gulbis, B., Asunción, M., Gervy, C., Contempré, B., & Morreale de Escobar, G. (2002). Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. *The Journal of Clinical Endocrinology & Metabolism*, *87*(4), 1768-1777.
2. Den Ouden, A. L., Kok, J. H., Verkerk, P. H., Brand, R., & Verloove-Vanhorick, S. P. (1996). The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. *Pediatric research*, *39*(1), 142-145.
3. Segura, S. A. (2014). Función tiroidea en la etapa fetal, neonatal y en el recién nacido prematuro. Necesidades de yodo. Thyroid function in the fetus, newborn and preterm infant. Iodine recommendations during the neonatal period. *Rev Esp Endocrinol Pediatr*, *5*(2), 13-22.
4. Cavarzere, P., Camilot, M., Popa, F. I., Lauriola, S., Teofoli, F., Gaudino, R., ... & Antoniazzi, F. (2016). Congenital hypothyroidism with delayed TSH elevation in low-birth-weight infants: incidence, diagnosis and management. *European Journal of Endocrinology*, *175*(5), 395-402.
5. Mandel, S. J., Hermos, R. J., Larson, C. A., Prigozhin, A. B., Rojas, D. A., & Mitchell, M. L. (2000). Atypical hypothyroidism and the very low birthweight infant. *Thyroid*, *10*(8), 693-695.
6. Williams, F. L., Visser, T. J., & Hume, R. (2006). Transient hypothyroxinaemia in preterm infants. *Early human development*, *82*(12), 797-802.
7. Vigone, M. C., Caiulo, S., Di Frenna, M., Ghirardello, S., Corbetta, C., Mosca, F., & Weber, G. (2014). Evolution of thyroid function in preterm infants detected by screening for congenital hypothyroidism. *The Journal of Pediatrics*, *164*(6), 1296-1302.
8. Fisher, D. A. (2008, December). Thyroid system immaturities in very low birth weight premature infants. In *Seminars in perinatology* (Vol. 32, No. 6, pp. 387-397). WB Saunders.
9. Williams, F. L., & Hume, R. (2008, December). Perinatal factors affecting thyroid hormone status in extreme preterm infants. In *Seminars in perinatology* (Vol. 32, No. 6, pp. 398-402). WB Saunders.
10. Srinivasan, R., Harigopal, S., Turner, S., & Cheetham, T. (2012). Permanent and transient congenital hypothyroidism in preterm infants. *Acta Paediatrica*, *101*(4), e179-e182.
11. Clemente, M., Ruiz-Cuevas, P., Almar, J., Potau, N., Carrascosa, A., & Salcedo Abizanda, S. (2004). Trastornos endocrinológicos del recién nacido pretérmino. In *Anales de Pediatría* (Vol. 60, No. Supl. 2, pp. 42-48).
12. Clemente, M., Ruiz-Cuevas, P., Carrascosa, A., Potau, N., Almar, J., Salcedo, S., & Yeste, D. (2007). Thyroid function in preterm infants 27-29 weeks of gestational age during the first four months of life: results from a prospective study comprising 80 preterm infants. *Journal of Pediatric Endocrinology and Metabolism*, *20*(12), 1269-1280.
13. Tfayli, H., Charafeddine, L., Tamim, H., Saade, J., Daher, R. T., & Yunis, K. (2018). Higher incidence rates of hypothyroidism and late TSH rise in preterm very-low-birth-weight infants at a tertiary care center. *Hormone Research in Paediatrics*, *89*(4), 224-232.
14. Hashemipour, M., Hovsepian, S., Ansari, A., Keikha, M., Khalighinejad, P., & Niknam, N. (2018). Screening of congenital hypothyroidism in preterm, low birth weight and very low birth weight neonates: A systematic review. *Pediatrics & Neonatology*, *59*(1), 3-14.
15. Woo, H. C., Lizarda, A., Tucker, R., Mitchell, M. L., Vohr, B., Oh, W., & Phornphutkul, C. (2011). Congenital hypothyroidism with a delayed thyroid-stimulating hormone elevation in very premature infants: incidence and growth and developmental outcomes. *The Journal of pediatrics*, *158*(4), 538-542.
16. Bijarnia, S., Wilcken, B., & Wiley, V. C. (2011). Newborn screening for congenital hypothyroidism in very-low-birth-weight babies: the need for a second test. *Journal of inherited metabolic disease*, *34*, 827-833.
17. LaFranchi, S. H. (2014). Screening preterm infants for congenital hypothyroidism: better the second time around. *The Journal of Pediatrics*, *164*(6), 1259-1261.
18. Ortí, R. S., Esteban, D. D. S., Jaume, M. C., Bennasar, A. B., Cortés, P. S., & Mulet, J. F. (2018). Valores de hormonas tiroideas en el prematuro y evolución con la edad Values of thyroid hormones in premature and evolution with age. *Rev Esp Endocrinol Pediatr*, *9*(1), 7-13.