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Original Article

Incidence and risk factors of transient hypothyroxinemia of prematurity: a prospective cohort study

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ABSTRACT

Background. Transient hypothyroxinemia of prematurity (THOP) is characterized by low thyroxine (T4) levels with normal thyroid-stimulating hormone (TSH) levels. This study aimed to determine the incidence and factors associated with THOP.

Methods. This prospective cohort study included neonates who were born before 37 weeks of gestation in the neonatal intensive care unit (NICU) between April 2017 and December 2020. Serum TSH and free thyroxine (FT4) levels were routinely screened at 3–5 days and 2, 4, and 6–8 weeks postnatally. The criteria for diagnosis of THOP were a TSH level <7 mU/L with a FT4 level <0.8 ng/dL at any screening timepoint.

Results. The incidence of THOP in infants born before 28, 34, and 37 weeks of gestation was 39.5 (17/43), 8.4% (29/343), and 4.8% (35/722), respectively. A multivariate analysis revealed that a gestational age of <28 weeks (adjusted odds ratio [aOR]: 5.35, 95% confidence interval [CI]: 1.89–15.13, p=0.002); 5-min Apgar score of ≤3 (aOR: 5.72, 95% CI: 2.2–14.89, p<0.001); and treatment with aminophylline (aOR: 2.95, 95% CI: 1.08–8.11, p=0.037), dobutamine (aOR: 4.12, 95% CI: 1.55–10.98, p=0.004), or morphine (aOR: 4.91, 95% CI: 1.29–18.74, p=0.011) were associated with an increased risk of THOP. The TSH and FT4 levels in infants with THOP returned to normal ranges by 2 weeks of age.

Conclusions. THOP is frequently found in preterm infants. An extremely low gestational age, a low Apgar score, and the use of certain medications in the NICU are risk factors for the development of THOP. Therefore, a thyroid screening program should be implemented for evaluating congenital hypothyroidism (CH) and THOP in preterm neonates in all settings.

Key words: neonatal screening, premature birth, risk factors, thyroxine, thyroid-stimulating hormone.

Thyroid hormone is essential for the maturation of many fetal tissues, including the brain, lungs, heart, and skeletal tissues.[1] In preterm infants, thyrotropin or thyroid-stimulating hormone (TSH) levels surge soon after birth, and serum thyroxine (T4) levels are frequently low at 1–2 weeks after birth.[2,3] Thyroid function is affected by several factors, such as immaturity of the hypothalamic-pituitary-thyroid axis, immaturity of thyroid hormone metabolism, loss of maternal T4 supply, iodine imbalance, and neonatal illness.[1,3,4] Thyroid dysfunction, especially low T4 levels, frequently occurs in premature infants and is a potential risk factor for impaired neurodevelopmental outcomes.[5,6] Transient hypothyroxinemia of prematurity (THOP), characterized by low circulating thyroid hormone levels with normal TSH levels, is a common form of thyroid dysfunction, especially in preterm infants born before 30 weeks of gestation. The etiology of THOP is multifactorial, with several contributing factors.[7-9]

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Currently, there is no consensus on the thyroid hormone levels consistent with THOP. The incidence of THOP varies across studies depending on the defined free thyroxine (FT4) and TSH levels. Previous studies have reported that 8–20% of infants with a birth weight <1500 g or a gestational age <34 weeks develop THOP.[10,11]

Neonatal thyroid screening for congenital hypothyroidism (CH) is essential for early detection and prompt treatment of CH. The 2020-2021 European guidelines recommend measuring TSH to detect primary CH and including the measurement of total T4 or FT4 to screen for central CH.[12] In our institute, approximately 3000-3300 births occur per year, of which 210–240 are preterm births that require intensive care. The thyroid screening program for preterm infants born before 37 weeks of gestation was implemented in 2010 to detect abnormal thyroid hormone levels in the neonatal intensive care unit (NICU). According to a previous study, the overall incidence of CH has increased over the past decade, along with an increase in the prevalence of CH in preterm infants owing to increased thyroid screening.[13] Here, we aimed to evaluate the incidence of THOP and identify factors associated with THOP in preterm infants born before 37 weeks of gestation.

Material and Methods

Study population

This prospective observational study was conducted from April 1, 2017, to December 31, 2020. We enrolled all preterm infants born before 37 weeks of gestation in the NICU. The exclusion criteria were a lack of thyroid screening data, major congenital anomalies, and death before thyroid function tests. Preterm infants with normal thyroid function test results were assigned to the control group and compared with infants diagnosed with THOP. Written informed consent was obtained from the parents of all the included infants.

Neonatal TSH screening program

In our NICU, thyroid screening for preterm neonates was implemented in 2010, and the protocol was revised in 2017. Serial thyroid function tests measuring both serum TSH and FT4 levels are performed routinely at 3–5 days and 2, 4, and 6–8 weeks postnatally in all preterm infants born before 37 weeks of gestation. In preterm infants with hypotension requiring inotropic drugs, thyroid screening is postponed until the drugs have been discontinued for 48 h.

The diagnostic criteria for THOP were a FT4 level <0.8 ng/dL and a TSH level <7 mU/mL at any screening timepoint, which resolved in a subsequent thyroid function test.[14] The diagnostic criteria for CH were either TSH ≥20 mU/L with any FT4 level or TSH >10 mU/L and FT4 <1.00 ng/dL at the time of the first or second screening. The third FT4 and TSH tests were performed in the next 2 weeks. If the FT4 remained <1.00 ng/dL or TSH ≥6 mU/L, the infant was treated with thyroxine 10–15 μg/kg/day.[15,16] The thyroid function tests were conducted 2–4 weeks after starting levothyroxine treatment. Neonatal hyperthyrotropinemia was defined as elevated TSH levels (10–20 mIU/L) with normal FT4 levels (>1.00 ng/dL), with TSH levels normalizing when measured at 28 days of life.

TSH and FT4 levels were measured by electrochemiluminescence immunoassay (ECLIA) using a Modular Analytics E170 machine (Roche Diagnostics, Mannheim, Germany) with an intra-assay coefficient of variation of 1.6–5.0% and inter-assay coefficient of variation of 1.7–5.8%.[13]

Data collection

Demographic data of preterm infants included gestational age, birth weight, Apgar score, ventilator days, and length of

hospital stay. Maternal and obstetric data included the presence of maternal thyroid disease, pregnancy-induced hypertension (PIH), or chorioamnionitis; and antenatal glucocorticoid administration. The gestational age of infants was calculated from menstrual history, ultrasound examination during the first trimester, and the Ballard score test. Neonatal morbidity data were also collected, including respiratory distress syndrome (RDS), transient tachypnoea of the newborn (TTN), patent ductus arteriosus (PDA), hypotension, necrotizing enterocolitis, intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD). We obtained information on the treatment during admission, including dopamine, dobutamine, morphine, aminophylline, and caffeine administration. In our hospital, aminophylline (intravenous form) is prescribed for preterm infants weighing <1500 g at birth and weaned from mechanical ventilation and for the treatment of apnea of prematurity. BPD was diagnosed based on the National Institute of Child Health and Human Development criteria.[17] Cranial ultrasonography was performed in preterm infants at the first and fourth weeks and at a postmenstrual age of 36 weeks by the pediatric radiologist, and the results were classified into four grades of severity.[18] Hearing screening test was performed using the otoacoustic emission technique or automated auditory brainstem response test (Sentiero, PATH medical GmbH, Germering, Germany) at the time of discharge.

Statistical analysis

The Epicalc package in R Software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. The Shapiro-Wilk normality test was used to determine whether the sample values were normally distributed. Nominal variables are expressed as the number of infants and percentage. Descriptive statistics for continuous variables are presented as mean ± standard deviation (SD) and median (interquartile range; IQR). For comparisons between the THOP and control group, statistical analysis was performed using Fisher's exact test and chi-square test for categorical variables and Student's t-test and Wilcoxon rank sum test for continuous variables. We performed univariate and multivariate analyses to assess the factors associated with THOP. Independent variables with $p < 0.2$ in the univariate analysis were entered into backward stepwise logistic regression models in the multivariate analysis. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were computed for significant variables independently associated with THOP. We applied propensity score methodology to matched subgroups of neonates with similar gestational age and birth weight for evaluating neonatal outcomes. For each infant with THOP, one control infant was randomly selected from the pool of neonates who met the matching criteria. Statistical significance was set at $p < 0.05$.

Results

During the study period, 1360 infants were hospitalized in the NICU and 781/1360 (58.8%) were inborn and premature. Fifty-nine neonates were excluded due to major congenital anomalies (n=2), death before thyroid function tests (n=11), and no thyroid screening data (n=46). In total, 722 preterm infants were enrolled, of whom 35 (4.8%), 21 (3.0%), and 72 (9.8%) were diagnosed with THOP, CH, and neonatal hyperthyrotropinemia, respectively.

594 infants had normal thyroid function test results (control group). The flow chart of the study population is presented in Fig. 1. The median gestational age in all patients was 33 (31–35) weeks and the overall mortality rate was 2.5% (16/629).

In the THOP group, gestational age in 48.6% (17/35), 20% (7/35), 14.3% (5/35), and 17.1% (6/35) of infants was 24–27, 28–30, 31–33, and

34–36 weeks, respectively. The incidence of THOP in preterm infants born before 28, 34, and 37 weeks of gestation was 39.5% (17/43), 8.4% (29/343), and 4.8% (35/722), respectively. The median age of infants with THOP was 3.8 (3.1–5.5) days. The mean TSH and FT4 levels at the time of diagnosis were 1.87±1.58 mU/L and 0.63±0.18 ng/dL, respectively. The mean FT4 level in infants with THOP gradually increased with time, as shown by the levels of 0.73±0.32, 1.16±0.58, 1.11±0.34, and 1.23±0.44 ng/dL at the first, second, third, and fourth screenings, respectively. The mean TSH levels were 1.99±2.09, 4.9±5.3, 4.4±3.6, and 4.5±2.0 mU/L at the first, second, third, and fourth screenings, respectively. TSH and FT4 levels in infants with THOP normalized within 2 weeks of life (Fig. 2). No infants with THOP received thyroid hormone supplementation.

Table I presents the clinical characteristics between the THOP and control groups. There were no significant differences in sex distribution, delivery mode, antenatal corticosteroid administration, maternal thyroid disease, and PIH between the groups. There

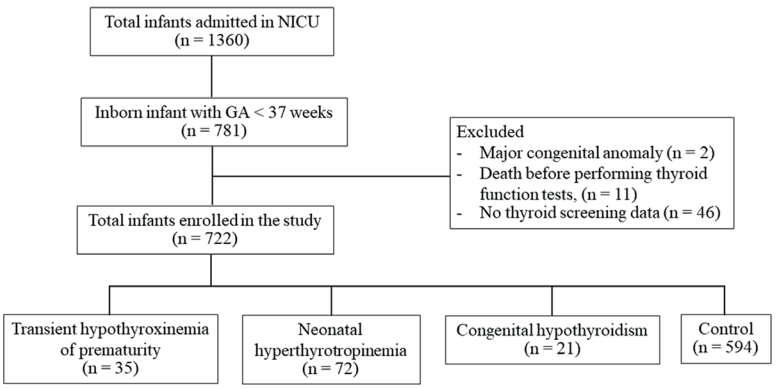

Fig. 1. Flow chart of the study population
Abbreviations: GA, gestational age; NICU, neonatal intensive care unit

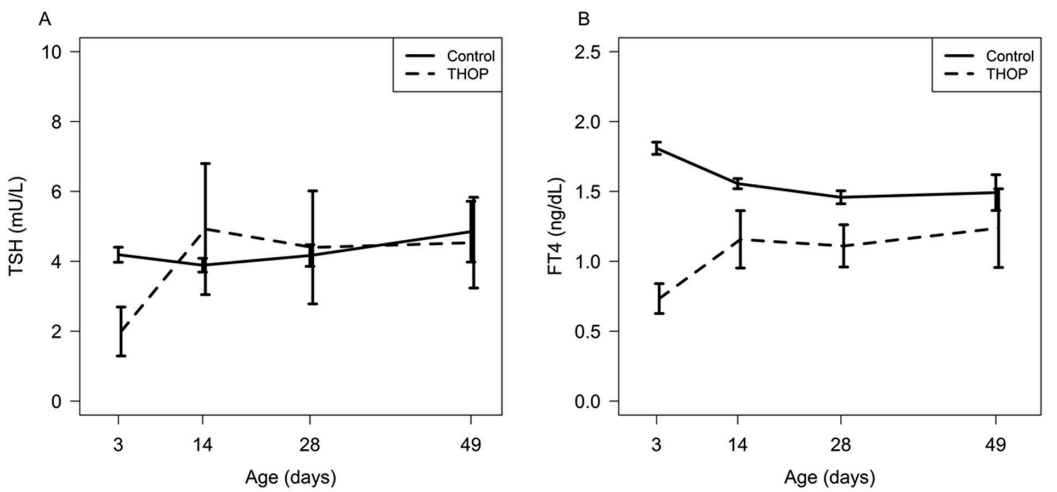

Fig. 2. Comparison of the TSH and FT4 levels between the THOP and control groups.
Abbreviations: FT4, free thyroxine; THOP, transient hypothyroxinemia of prematurity; TSH, thyroid-stimulating hormone

Table I. Clinical characteristics between the THOP and control groups.

Variable	THOP (n=35)	Control (n=594)	p
Gestational age, weeks	28 (25–31.5)	33 (31–35)	<0.001
24–27 weeks	17 (48.6)	26 (4.4)	<0.001
Birth weight, g	935 (687–1710)	1895 (1515–2319)	<0.001
<1000 g	20 (57.1)	34 (5.7)	<0.001
1-min Apgar score	3 (2–8)	8 (6–8)	<0.001
5-min Apgar score	5 (2–9)	9 (8–9)	<0.001
Cesarean section	28 (80)	466 (78.5)	0.763
Chorioamnionitis	3 (8.6)	9 (1.5)	0.051
RDS	28 (80)	274 (46)	<0.001
TTN	2 (5.7)	121 (20.4)	0.057
PDA	21 (60)	104 (17.5)	<0.001
Proven sepsis	8 (22.9)	37 (6.2)	0.002
Hypotension	26 (74.3)	148 (24.9)	<0.001
Aminophylline	25 (71.4)	134 (22.6)	<0.001
Morphine	32 (91.4)	214 (36)	<0.001
Dopamine	28 (80)	139 (23.4)	<0.001
Dobutamine	14 (40)	60 (10.1)	<0.001
Mechanical ventilation	33 (94.3)	255 (42.9)	<0.001

Data are expressed as n (%) or median (IQR).
PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, THOP: transient hypothyroxinemia of prematurity, TTN: transient tachypnea of the newborn.

were significant differences in the number of infants weighing <1000 g (57.1% vs. 5.7%, p <0.001) between the groups. The 1-min Apgar score of <4 was found in 18/35 (51.4%) and 55/594 (9.3%) of the infants in the THOP and control groups, respectively, which was a significant difference (p <0.001). Moreover, 15/35 (42.9%) and 21/594 (3.5%) infants had a 5-min Apgar score of <4 in the THOP and control groups, respectively, which was also a significant difference (p <0.001). We found significant differences in the RDS, PDA, hypotension, and proven sepsis rates between the groups. In addition, there were significant differences in the medications used, including aminophylline, caffeine, morphine, dopamine, and dobutamine, between the groups.

The results of univariate and multivariate logistic regression analyses of the risk factors between the groups are presented in Table II. Multivariate regression analysis confirmed that gestational age <28 weeks; 5-min Apgar score <3; and dobutamine, aminophylline, and morphine infusion were found to be independently associated with THOP.

The neonatal outcomes, are presented in Table III. The BPD rate, the rate of mechanical ventilator usage, ventilator days, length of hospital stay, and mortality in the THOP group were significantly higher than those in the control group. Cranial ultrasound was performed in 291/343 (84.8%) infants who were born before 34 weeks of gestation or weighed <1500 g. There were no significant differences in the IVH or PVL rates between the groups. However, when we used the propensity scores to match subgroups of neonates with similar gestational age and birth weight, we found that only the rate of mechanical ventilator usage in infants with THOP was significantly higher than that in the control group. Hearing screening was performed in 86.6% (545/629) of the total infants. In the THOP group, 15 infants did not have hearing screening data because they were referred back to a local hospital (n=8) or due to death (n=7).

Table II. Factors associated with THOP development based on univariate and multivariate analyses.

Factors	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	p	aOR (95% CI)	p
GA <28 weeks	20.63 (9.55–44.59)	<0.001	5.35 (1.89–15.13)	0.002
BW <1000 g	19.22 (5.37–68.74)	<0.001	-	
1-min Apgar score ≤3	10.38 (5.06–21.29)	<0.001	-	
5-min Apgar score ≤3	20.46 (9.21–45.48)	<0.001	5.72 (2.2–14.89)	<0.001
PDA	7.07 (3.48–14.35)	<0.001	-	
RDS	4.67 (2.01–10.86)	<0.001	-	
Mechanical ventilation	21.94 (5.22–92.22)	<0.001	-	
Proven sepsis	4.46 (1.89–10.5)	0.002	-	
Dopamine	13.09 (5.6–30.63)	<0.001	-	
Dobutamine	5.93 (2.87–12.28)	<0.001	4.12 (1.55–10.98)	0.004
Aminophylline	8.58 (4.02–18.32)	<0.001	2.95 (1.08–8.11)	0.037
Caffeine	5.22 (2.6–10.49)	<0.001	-	
Morphine	18.94 (5.73–62.58)	<0.001	4.91 (1.29–18.74)	0.011

aOR (95% CI), adjusted odds ratio (95% confidence interval); BW: birth weight, GA: gestational age, OR: odds ratio, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, THOP: transient hypothyroxinemia of prematurity.

Table III. Neonatal outcomes between the THOP and control groups.

Variable	Full cohort			Match cohort		
	THOP (n=35)	Control (n=594)	p	THOP (n=35)	Control (n=35)	p
BPD, n (%)	19 (54.3)	51 (8.6)	<0.001	19 (54.3)	16 (45.7)	0.633
Cranial U/S, n (%)	28 (80)	263 (44.3)	<0.001	28 (80)	24 (68.6)	0.412
Findings of cranial U/S, n (%)						
Normal	10 (35.7)	106 (40.3)	0.788	10 (35.7)	10 (41.7)	0.878
IVH	16 (57.1)	151 (57.4)	1	16 (57.1)	14 (58.3)	1
PVL	2 (7.1)	6 (2.3)	0.174	2 (7.1)	0 (0)	0.493
Hearing screening, n (%)	20 (57.1)	525 (88.4)	<0.001	20 (57.1)	25 (71.4)	0.266
Failed screening	3 (15)	22 (4.2)	0.058	3 (15)	1 (4)	0.309
Mechanical ventilation, n (%)	33 (94.3)	255 (42.9)	<0.001	33 (94.3)	25 (71.4)	0.026
Ventilator use, days	10 (4–17)	3 (2–6)	<0.001	10 (4–17)	7 (2–11)	0.387
LOS, days	43 (20.5–69.5)	14 (9–27)	<0.001	43 (20.5–69)	33 (15–52.5)	0.366
Death, n (%)	7 (20)	9 (1.5)	<0.001	7 (20)	3 (8.6)	0.306

Discussion

In our study, after the revision of the screening program guidelines in 2017 and the use of FT4 and TSH cut-off values of <0.8 ng/dL and <7 mU/mL, respectively, we found an overall incidence of THOP of 39.5%, 8.4%, and 4.8% in preterm infants born before 28, 34, and 37 weeks of gestation, respectively. The incidence of THOP varied across previous studies depending on the cut-off level of thyroxine. Sharma et al.[19] reported an incidence of 19% in infants born before 37 weeks of gestation by using an FT4 level of <0.65 ng/dL, while Kim et al.[20] reported an incidence of 28.9% in infants born before 32 weeks of gestation by using a cut-off FT4 level of <0.7 ng/dL. Further, Yoon et al.[21] reported that

the incidence of THOP was 38.3% in extremely low birth weight infants when using an FT4 level of <0.9 ng/dL. Rabin et al.[10] reported that a low FT4 level (<0.8 ng/dL) was found in 7.9% of infants with a birth weight <1500 g. A study from Scotland used a T4 level less than the 10th percentile for gestational age and reported that 20% of infants born before 34 weeks of gestation developed THOP,[11] while a recent study reported an incidence of 39.2% on performing thyroid function tests between days 10 and 20 postnatally and using FT4 levels less than the reference range.[22]

In our study, the factors associated with THOP were gestational age <28 weeks; 5-min Apgar score ≤3; and aminophylline, dobutamine, and morphine infusion. Similarly, Herring et al.[9] reported that gestational age, dopamine infusion, and mechanical ventilation were associated with THOP. Moreover, male sex, multiple pregnancies, birth weight, small for gestational age, congenital heart disease, and albumin levels were reported as factors associated with THOP in previous studies.[22-24]

Previous studies have revealed an association between low gestational age and low T4 levels.[25] Chung et al. found that infants born before 28 weeks of gestation had lower FT4 and TSH levels through 2 months postnatally than those born after 28 weeks of gestation.[26]

The Apgar scoring system is the standard method for assessing the postnatal clinical status of a newborn; perinatal asphyxia may result in low Apgar scores.[27] During perinatal asphyxia, blood flow to organs apart from the vital organs such as the brain and heart is decreased, resulting in functional abnormalities of the thyroid gland.[28] The effect of asphyxia on thyroid hormone levels has been previously reported. Infants who were delivered via emergency cesarean section with 1-min Apgar scores of <6 had significantly lower T4 and FT4 levels in the cord blood than healthy infants.[29] Similar to our findings, infants with asphyxia, defined as those with Apgar scores ≤3 and ≤5 at 1 and 5 min, respectively, had significantly lower T4, FT4, and triiodothyronine (T3) levels than healthy infants.[30]

Contrary to our findings, critical illnesses, including RDS, sepsis, and PDA, were found to affect thyroid hormone levels in preterm infants.[31-33] In our study, multivariate analysis did not reveal associations between THOP and neonatal illnesses, including RDS, TTN, PDA, and sepsis.

Dopamine and dobutamine are adrenergic neurotransmitters commonly used for inotropic support in preterm infants. Dopamine inhibits TSH secretion through adenylyl cyclase and suppresses T4 secretion and alters hepatic T4 to T3 conversion.[33-35] However, dopamine was not significantly associated with THOP in our study, similar to the findings in a previous study.[33] Dobutamine possibly has the same effect on thyroid function as dopamine, and our study revealed a significant association between THOP and dobutamine infusion.

Morphine and fentanyl exert effects similar to those of opiate drugs that can interfere with serum thyroid hormone transportation.[36] Morphine reduces the TSH, T4, FT4, and T3 levels[32], which is consistent with the association between morphine and THOP found through multivariate analysis in the present study. Aminophylline and caffeine, which are commonly used in preterm infants with recurrent apnea, can cause thyroid dysfunction by increasing the T4, T3, and TSH levels.[34] In our study, aminophylline increased the risk of hypothyroxinemia in preterm infants.

De Felice et al.[37] reported an association between THOP and histological chorioamnionitis. In our study, no significant association was found between THOP and chorioamnionitis (THOP vs. control: 8.6% vs. 1.5%, p=0.051). Maternal preeclampsia can cause a decrease in the placental passage of T4 from mother to infant. A previous study reported that the T4, FT4, free T3, and thyroid binding globulin levels in neonates

born to mothers with maternal preeclampsia were significantly lower than those in neonates born to healthy mothers.[38] However, THOP was not associated with maternal preeclampsia in our study (THOP vs. control: 28.6% vs. 19.9%, p=0.318).

Short-term outcomes in infants with THOP have been previously reported. We found that the rate of mechanical ventilation usage was significantly higher in the THOP group than in the control group, whereas previous studies reported that the rate of BPD and duration of invasive mechanical ventilation usage was significantly higher in the THOP group than in the control group.[22,24] Other neonatal outcomes, including impaired hearing, IVH, and PVL, were not significantly different between the groups, similar to Tan et al.'s findings.[39]

In preterm infants, THOP is characterized by a temporary postnatal reduction in T4 levels with normal TSH levels. T4 and T3 levels continue to increase up to 6–8 weeks postnatally.[4] A previous study reported that FT4 levels gradually increase, normalizing by 7 weeks in infants with hypothyroxinemia.[19] Whereas, we found that all infants with THOP exhibit normal FT4 and TSH levels by 2 weeks postnatally, without thyroxine therapy. These findings suggest that in preterm infants, thyroxine supplementation is not necessary for hypothyroxinemia and that THOP is a physiological phenomenon. Similarly, Uchiyama et al. reported that, in infants with THOP, thyroxine replacement had no beneficial effect on growth and neurodevelopmental outcomes assessed at 3 years.[40] A recent study revealed that THOP is not associated with adverse neurodevelopmental outcomes and does not require thyroxine supplementation.[39] However, monitoring and following up on T4 levels are crucial for confirming the presence of THOP in these infants.

Our study has some notable strengths and limitations. The main strength is that >90% of preterm infants who were delivered in our hospital were enrolled and underwent routine thyroid screening tests; our findings reveal the pattern of FT4 and TSH levels in preterm infants with THOP and healthy preterm infants. The second strength is that we were able to collect complete records of neonatal illnesses and medication use. The main limitation is that the study was performed in a single center with a small sample size. Therefore, large-scale studies are warranted to validate our findings. Moreover, there was a lack of long-term follow-up visits for evaluating growth and neurodevelopmental outcomes in infants with THOP.

In summary, THOP is a form of thyroid dysfunction associated with gestational age in preterm infants. Risk factors for THOP were gestational age <28 weeks; 5-min Apgar score ≤3; and dobutamine, aminophylline, and morphine use. These findings may help optimize care and follow-up of thyroid function in preterm infants. Furthermore, a thyroid screening program should be implemented for evaluating CH and THOP in preterm neonates in all settings.

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Ethical approval

The study protocol was approved by the Institutional Review Board and the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand. (REC 60−033−01−1).

Author contribution

The author confirms contribution to the paper as follows: study conception and design: GM, SJ; data collection: GM, MJ; analysis and interpretation of results: GM, MJ, AT; draft

manuscript preparation GM, WJ, SD, SJ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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