ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2023.2023-6-5

J Clin Res Pediatr Endocrinol 2024;16(1):60-68

Neurodevelopmental Outcome of Infants with Transient Hypothyroxinemia of Prematurity in a Newborn Intensive Care Unit

Erhan Aygün[1], Seda Yılmaz Semerci[1], Adviye Çakıl Sağlık[1], Emine Yurdakul Ertürk[2]

[1]Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Neonatology, İstanbul, Turkey
[2]Ordu University Training and Research Hospital, Department of Pediatrics, Ordu, Turkey

What is already known on this topic?

Transient hypothyroxinemia of prematurity (THOP) is defined as free thyroxine (fT4) level below the reference values despite normal thyroid stimulating hormone level in a preterm infant. THOP occurs in 35-50 % of preterm births and preterm births make up 12 % of all births. The lack of long-term outcome data about infants with THOP presents a challenge for the management of these babies.

What this study adds?

This study provides objective information on neurodevelopmental outcome of the infants with THOP. Levothyroxine replacement was associated with higher rates of steroid use for bronchopulmonary dysplasia, and anti-vascular epithelial growth factor therapy use for retinopathy of prematurity without any effect on long-term neurological outcomes in infants with THOP. Depending on the data provided by this study, clinicians may avoid prophylactic thyroid hormone use in preterm infants with THOP.

Abstract

Objective: The aim of this study was to evaluate neurological development of infants with transient premature hypothyroxinemia (THOP).

Methods: This prospective study included newborns who were born between 28-36 weeks of gestation (GW) and were admitted to the neonatal intensive care unit. Newborns exposed to maternal thyroid disease, or with severe intracranial problems, and congenital anomalies were excluded. Infants with THOP were the study group and those without THOP formed the control group. The study group was subdivided into those receiving levothyroxine replacement (5 µg/kg/day) and those who were untreated. Neonatal demographics, and morbidities, including respiratory distress syndrome, bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) were evaluated. The Ages and Stages Questionnaire (ASQ) and ASQ:Social-Emotional (ASQ:SE) developmental screening tests were administered to the entire study population at the corrected age of two years.

Results: Seventy infants were included in this study, 40 of whom had THOP. The mean GW was 34.4 ± 3.8 weeks in the study group and 37.2 ± 2.3 weeks in controls (p = 0.69). Mean overall birth weight was 1640 ± 428 g. Levothyroxine replacement was started in 12/40 infants (30 %). The groups were similar in terms of demographic characteristics. Rates of BPD and ROP were higher in the treated group (p = 0.01). ASQ and ASQ:SE results did not differ between groups (p = 0.75), nor did these scores differ between infants with THOP who did or did not receive levothyroxine (p = 0.14).

Conclusion: Although levothyroxine replacement therapy was associated with increased rates of BPD and ROP, this treatment did not appear to improve long-term neurological outcomes in this small group of infants with THOP. Prospective controlled studies with much larger sample sizes are needed to clarify the role of levothyroxine replacement in THOP.

Keywords: Ages and Stages Questionnaire, neurodevelopmental outcome, preterm, transient hypothyroxinemia of prematurity

Address for Correspondence: Seda Yılmaz Semerci MD, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Neonatology, İstanbul, Turkey
Phone: +90 533 718 06 83 **E-mail:** sedayilmazsemerci@gmail.com **ORCID:** orcid.org/0000-0002-0411-9610

Conflict of interest: None declared
Received: 09.06.2023
Accepted: 25.09.2023

Introduction

Transient hypothyroxinemia of prematurity (THOP) is defined as having a lower free thyroxine (fT4) level than age-appropriate reference values, in the context of a normal thyroid stimulating hormone (TSH) level in preterm infants (1). At present, the preterm birth rate is 12% and hypothyroxinemia occurs in 35-50% of all premature infants (2,3).

Hypothyroxinemia seen in preterm infants is usually temporary, and in these cases recovery may require 4-8 weeks. Although it is generally thought that this situation does not affect postnatal development, there are studies suggesting treatment is beneficial in very low birth weight (VLBW) premature infants. However, this issue is still controversial. Several studies examining whether preterm hypothyroxinemia affects development in infancy-early childhood have reported inconsistent results (4). Physiologically lower thyroid hormone levels in preterm newborns has been explained by thyroxine (T4) conversion into inadequate triiodothyronine (T3) and premature cessation of maternal T4 transport, increased thyroid hormone requirement (thermoregulation and muscle function), iodine metabolism dysregulation, lack of the maturity of the hypothalamic-pituitary-thyroid axis, and inadequate response of the thyroid gland to thyrotropin-releasing hormone (TRH) or a combination of these (5,6). In a large-scale study on long-term outcomes, when 398 infants born before the gestational age of 32 weeks and birth weight < 1500 grams were evaluated at the age of 19 years, no negative effect of THOP on intelligence quotient or motor functions was observed (7). In a randomized controlled study, no positive findings were found in the 36-month examinations of infants younger than 28 weeks of gestation who were treated (8). In contrast, another study reported better language skills, motor and cognitive functions in the thyroxine-replacement group (9). It should be kept in mind that thyroxine replacement to correct hypothyroxinemia may also have side effects in premature infants. Circulatory dysfunction was reported following thyroxine treatment in VLBW premature infants (10). Hence the recommendation about thyroid hormone therapy for premature infants with THOP is not clarified yet and it is open to discussion (2). There is no published study in which the neurological development of infants diagnosed with THOP is compared with a control group with a similar gestational week and at the same age. Therefore, the aim of this study was to evaluate the neurological development of infants with THOP compared to a matched control group and to investigate the effects of perinatal and neonatal risk factors on outcomes.

Methods

This prospective study included newborn infants who were born at 28-36 gestational weeks and were hospitalized in the neonatal intensive care unit between January 2020 and April 2021. Newborn infants with THOP constituted the study group while infants with similar demographic characteristics, but without THOP, formed the control group. Levothyroxine was started in a sub-group of the infants with THOP using the random number assignment method following informed consent being obtained from the parents. In cases when the parents did not give informed consent for randomization, the infants were assigned to the group without replacement, if the parents approved. Since this simple randomization method was used, group numbers were not the same. Levothyroxine was started for the replacement group at a dose of 5 µg/kg/day. Due to the unavailability of the liquid formulation at the study center, an oral suspension with a concentration of 25 mcg/mL is prepared using 100 mcg tablets by the pharmacy. Twenty-five 100 mcg LT4 tablets were crushed in a mortar to obtain a fine powder. A small amount of glycerol was added to the powder and thoroughly mixed to create a uniform suspension. This mixture was then transferred to a 100 mL calibrated amber bottle. The mortar was rinsed with 10 mL of glycerol, which was then poured into the bottle. This process was repeated until all 40 mL of glycerol was used. Finally, water was added to bring the total volume up to 100 mL. This suspension was well-shaken before use and refrigerated for a week. The necessary dose is adjusted weekly (at the same day of the week) according to the actual weight of the newborn. Besides, TFTs were checked weekly until the normal ranges were observed, then monthly measurements continued during replacement. Once started, levothyroxine replacement was planned to continue until two years of age.

Initial thyroid function tests (TFT) were taken on the 10-20th days of life. In addition to the national screening program at least two measurements performed at 10th, 17th days and more if necesseray. TFTs, including free thyroxine (fT4; ng/dL) and thyroid stimulating hormone (TSH; mIU/L) were performed by electrochemiluminescence immunoassay (ECLIA, Cobas e602, Roche Diagnostics, Basel, Switzerland).

Newborns with maternal thyroid disease, severe intracranial issues, chromosomal and congenital anomalies, or infants older than 36 gestational weeks were not included in the study. Normal ranges of TFTs were evaluated according to postnatal age and gestational week (2). THOP was defined as transient low fT4 levels without elevation in TSH levels (11). A TSH level > 10 mIU/L detected after the first week

was considered elevated/high; fT4 levels were considered low if < 1.3 ng/dL in 31-36 gestational week-old infants and < 0.5 ng/dL in 25-30 gestational week-old infants (12). In addition to THOP, demographic and clinical data including antenatal steroid therapy, inotropic support and the presence of respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA) and maternal disease characteristics were recorded in all infants.

Validated Turkish versions of the 'ASQ' and 'ASQ:SE' developmental screening tests were administered to the entire study population at the corrected age of two years.

The Use of the 'Ages And Stages Questionnaire' (ASQ) and 'ASQ:Social-Emotional' (ASQ:SE) Developmental Screening Tests in the Evaluation of Neurological Development

Neurological development is generally evaluated by screening tools and expert assessment, which may also include information from parents (13,14,15).

ASQ and ASQ:SE Inventories

The 'ASQ' is a screening tool for assessing the development of infants and preschoolers in the areas of communication, fine motor, gross motor, problem-solving and personal-social development, and 'ASQ:SE' is a screening tool for social-emotional development, based on information given by parents (16). Küçüker et al. (16) evaluated 608 children with the Turkish version of 'ASQ:SE'. When all months were analyzed, the sensitivity of ASQ was 83.7%, specificity was 89.9%, test-retest reliability was 87%, and inter-rater reliability was 83.6%.

Ethics

This study was approved by Ordu University Training and Research Hospital Local Ethics Committee (file number: 2021/249, date: 19.11.2021). Informed consent for participation was obtained from the parents. This study is registered in ClinicalTrials.gov with the number of NCT05901623.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Clinical data are presented as means ± standard deviation for parametric tests and categorical data displayed as mean rank for nonparametric tests. The Kolmogorov-Smirnov test was used to check the distribution of the variables. Comparisons were performed by the use of the t-test for normally distributed variables, or the Mann-Whitney U test in the case of non-parametric distribution. The chi-square test was used for qualitative data analysis. Statistical significance was accepted in case of a probability (p) value < 0.05. The sample size calculation using a one-sided McNemar's test has determined that a total of 42 participants, with at least 21 in each group, is sufficient to detect a clinically significant difference between the groups, with 80% power and a 5% level of significance.

Results

A total of 70 newborn infants were included, of whom 40 had THOP and the remainder were assigned to the control group. Of the infants with THOP, 55% (n = 22) were male. Sex mix in the control group was 63.3% (n = 19) male and 36.7% (n = 11) female. A comparison of demographic characteristics between the infants with and without THOP is shown in Table 1. There was no significant difference between the gestational weeks of the two groups ($p = 0.69$), nor was there a difference in birth weight ($p = 0.87$) or birth length. There was a significant difference in delivery mode, with infants in the THOP group being more likely to have been delivered by cesarean section ($p < 0.001$). The mean age at which children in the THOP and control groups were tested with the ASQ was 14.03 ± 1.67 and 13.73 ± 1.39 months ($p = 0.43$). The corrected age at the time of ASQ test was 20.7 ± 7.68 months in infants with THOP and 21.8 ± 7.95 months in control group ($p = 0.56$).

Neonatal morbidities, including RDS, BPD, IVH, hsPDA, ROP, sepsis, and duration of mechanical ventilation, steroid use for BPD or anti-vascular endothelial growth factor (anti-VEGF) use for ROP did not differ between the THOP and control groups (Table 2).

The day of first TFT was 14.03 ± 1.67 days in infants with THOP and 13.73 ± 1.39 days in control group ($p = 0.43$). The first value for fT4 was significantly lower in infants with THOP (5.02 ± 2.2 ng/dL) than the control group (14.99 ± 1.29 ng/dL), as expected ($p < 0.001$). Furthermore, the first value of TSH was significantly higher in infants with THOP (4.85 ± 2.2 mIU/L) than the control group (2.34 ± 0.66 mIU/L) ($p < 0.001$). When started, levothyroxine replacement was continued to two years of age. Only one infant stopped replacement before the age of two years because of TSH suppression.

No difference was found in the comparison of the 'ASQ and ASQ:SE' results of the THOP and control groups (Table 3).

Demographic characteristics were similar between the infants with THOP who did and did not receive levothyroxine replacement, except there was a significantly higher rate of antenatal steroid use in infants receiving levothyroxine compared to the infants who did not (Table 4). Testing time for initial fT4 and TSH level, and corrected age at ASQ evaluation time did not differ between the infants with and without L-T4 replacement.

There was no difference in rates of RDS, invasive mechanical ventilator support, hsPDA, IVH, sepsis, and blood transfusions between the infants with THOP who did or did not receive levothyroxine replacement (Table 5). However, the duration of non-invasive mechanical ventilation, and the rates of BPD, steroid use for BPD, ROP, and anti-VEGF use for ROP rates were significantly higher in infants with THOP who received levothyroxine. Furthermore, 'ASQ' and 'ASQ:SE' results did not differ between those infants

Table 1. Comparison of demographic characteristics between the infants with and without hypothyroxinemia

		Hypothyroxinemia (-) (n = 30)			Hypothyroxinemia (+) (n = 40)			p
		Mean ± SD/n-%		Mean rank	Mean ± SD/n-%		Mean rank	
Maternal age		29.4 ± 4.1			28.1 ± 4.2			0.74
Sex	Female	11	36.70%		18	45%		0.63
	Male	19	63.30%		22	55%		
Delivery mode	NSV	2	66.70%		1	33.30%		< 0.001
	C/S	28	41.80%		39	58.20%		
Birth weight		1394.5 ± 501.6			1359.5 ± 498.1			0.87
Gestational age		37.2 ± 2.3		36.6	34.4 ± 3.8		34.7	0.69
APGAR 1st min				36.93			34.42	0.6
APGAR 5th min				35.3			35.65	0.94
Antenatal steroid		6	20.00%		7	17.50%		0.79
SGA		3	10.00%		5	12.50%		0.94
PPROM		4	13.30%		7	17.50%		0.83
Chorioamnionitis		3	10.00%		4	10.00%		1
Urinary tract infection		4	13.33%		3	8.00%		0.54
GDM		1			0			N/A
Preeclampsia		3	10.00%		4	10.00%		1

Mann-Whitney U test, t-test, chi-square test.
SD: standard deviation, SGA: small for gestational age, PPROM: preterm premature rupture of membranes, N/A: not applicable, C/S: cesarean section, GDM: gestational diabetes mellitus

Table 2. Comparison of neonatal morbidities between infants with and without hypothyroxinemia

	Hypothyroxinemia (-) (n = 30)			Hypothyroxinemia (+) (n = 40)			p
	Mean ± SD/n-%		Mean rank	Mean ± SD/n-%		Mean rank	
RDS	24	80%		34	85%		0.89
IMV (hours)			36.7			34.6	0.67
NIMV (hours)	83.30 ± 51.03		36.85	76.3 ± 38.32		34.49	0.54
hsPDA	5	17%		8	20%		0.77
IVH (> grade 2)	9	30%		15	37.5%		0.8
Sepsis	10	33.3%		12	30%		0.64
ES tx	18	60%		25	62.5%		0.51
BPD	4	12%		7	28.00%		0.75
Steroid for BPD	4	12%		7	28%		0.75
ROP	10	33.30%		12	30%		0.64
Anti-VEGF for ROP	4	12%		7	28%		0.75

Mann-Whitney U test, t-test, chi-square test.
RDS: respiratory distress syndrome, SD: standard deviation, IVH: intraventricular hemorrhage, BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, hsPDA: hemodynamycally significant patent ductus arteriosus, ES: erytrocyte suspension, tx: transfusion, VEGF: vascular endothelial growth factor

with THOP who received and did not receive levothyroxine replacement (Table 6).

Discussion

This study illustrated that the replacement of levothyroxine did not lead to improved long-term neurological outcomes in the infants with THOP in comparision an age-matched control group.

Risk factors for THOP include infants with low gestational weeks, preeclampsia, intrauterine growth restriction, perinatal asphyxia, NEC, PDA, RDS, IVH, BPD, mechanical ventilation, and receiving medications such as dopamine or dexamethasone (17,18,19,20,21). Various studies have

Table 3. Comparison of ASQ testing results between the infants with and without hypothyroxinemia

		Hypothyroxinemia (-) (n = 30)		Hypothyroxinemia (+) (n = 40)		p
		n- %		n- %		
ASQ score	Normal	5	16.70 %	6	15 %	0.75
	Risk	17	56.70 %	22	55 %	
Follow-up required		8	26.7 %	12	30	
ASQ emotional	Normal	13	43.30 %	15	37.50 %	0.4
	Risk	17	56.70 %	25	62.50 %	
Communication	Normal	16	53.30 %	21	52.50 %	0.57
	Risk	14	46.60 %	19	47.50 %	
Gross motor	Normal	29	96.70 %	38	95 %	0.61
	Risk	1	3.30 %	2	55	
Fine motor	Normal	5	16.70 %	8	20 %	0.49
	Risk	25	83.30 %	32	80 %	
Problem-solving	Normal	16	53.30 %	17	42.50 %	0.26
	Risk	14	46.60 %	23	57.50 %	
Personal-social	Normal	16	53.30 %	18	45 %	0.33
Risk		14	46.60 %	22	55 %	

Chi-square test.
ASQ: Ages and Stages Questionnaire

Table 4. Comparison of characteristics between the infants diagnosed with THOP with and without levothyroxine replacement

		No levothyroxine (n = 28)			Levothyroxine (n = 12)			p
		Mean ± SD/n- %		Mean rank	Mean ± SD/n- %		Mean rank	
Maternal age		28.07 ± 4.6			28.25 ± 3.4			0.89
Sex	Female	15	53.57 %		5	41.67 %		0.53
	Male	13	46.43 %		7	58.33 %		
Delivery mode	NSV	6	21.43 %		2	16.67 %		0.8
	C/S	22	78.57 %		10	83.33 %		
Birth weight		1393.57 ± 468.74			1280 ± 574.77			0.52
Gestational age		30.18 ± 2.9			29.42 ± 3.99			0.32
APGAR 1st min				20.04			21.58	0.69
APGAR 5th min				20.96			19.42	0.67
Antenatal steroid		2	7.14 %		5	41.67 %		**0.02**
SGA		3	10.70 %		2	16.70 %		0.46
First TFT (postnatal day of life)		14.04 ± 1.7			14.75 ± 1.8			0.09
First value of fT4 (ng/dL)		5.02 ± 2.2			4.70 ± 1.7			0.66
First value of TSH (mIU/L)		4.74 ± 2.03			5.10 ± 2.63			0.64
Corrected age at ASQ testing (months)		20.36 ± 7.7			21.50 ± 7.88			0.68

Mann-Whitney U test, t-test, chi-square test.
SGA: small for gestational age, THOP: transient hypothyroxinemia of prematurity, ASQ: Ages and Stages Questionnaire, fT4: free thyroxine, TFT: thyroid function test, TSH: thyroid stimulating hormone, SD: standard deviation

shown that some medications, as well as non-thyroidal diseases such as RDS, sepsis, IVH, PDA, and NEC, are associated with THOP, and the degree of hypothyroxinemia correlates with the severity of such diseases (22,23,24). Furthermore, thyroid functions may be repressed due to commonly used medications including dopamine and dexamethasone, as well as by the presence of RDS, sepsis, NEC, PDA, malnutrition, and chorioamnionitis (5,22,25,26). Serum thyroid hormone levels are partially mediated by acute inflammatory cytokines in different pathologies such as RDS, PDA, sepsis, IVH, and NEC (27). In recent years, studies have shown that the suppression of thyroid functions decreases along with the decrease in the severity of RDS due to the improvement of antenatal care, particularly the rational use of antenatal steroids and the timely surfactant application (27).

In the present study and in contrast to previous studies, RDS, PDA, sepsis, need for inotropic medications, IVH, and blood transfusion were not identified as factors associated with THOP. The reason for these different results in our study may be that surfactants and antenatal steroids have become widespread in recent years, resulting in less need

Table 5. Comparison of neonatal morbidities between the infants with and without levothyroxine replacement

	No levothyroxine (n = 28)			Levothyroxine (n = 12)			p
	Mean ± SD/n-%		Mean rank	Mean ± SD/n-%		Mean rank	
RDS	24	85.70%		10	83.30%		0.6
IMV (hours)	87.64 ± 66.88		19.27	185.5 ± 44.78		23.38	0.06
NIMV (hours)	66.12 ± 30.01			100.5 ± 45.74			**0.03**
hsPDA	5	17.86%		3	25.00%		0.39
IVH (> grade 2)	21	75.00%		9	75.00%		0.51
Sepsis	13	46.43%		6	50.00%		0.89
ES tx	16	57.14%		9	75.00%		0.48
BPD	5	17.86%		7	58.33%		**0.01**
Steroid for BPD	2	7.14%		5	41.67%		**0.02**
ROP	5	17.86%		7	58.33%		**0.01**
Anti-VEGF for ROP	2	7.14%		5	41.67%		**0.02**

Mann-Whitney U test, t-test, chi-square test.
RDS: respiratory distress syndrome, SD: standard deviation, IVH: intraventricular hemorrhage, BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, hsPDA: hemodynamycally significant patent ductus arteriosus, ES: erytrocyte suspension, tx: transfusion, VEGF: vascular endothelial growth factor

Table 6. Comparison of ASQ testing results between the infants diagnsed with THOP who did or did not receive levothyroxine

		No levothyroxine (n = 28)		Levothyroxine (n = 12)		p
		n-%		n-%		
ASQ score	Normal	4	14.30%	2	16.70%	0.14
	Risk	13	46.40%	9	75.00%	
Follow-up required		11	39.30%	1	8.30%	
Emotional	Normal	12	43.00%	3	25.00%	0.48
	Risk	16	47.00%	9	75.00%	
Communication	Normal	16	57.10%	5	41.70%	0.49
	Risk	12	42.90%	7	58.30%	
Gross motor	Normal	27	96.40%	11	91.70%	0.52
	Risk	1	3.60%	1	8.30%	
Fine motor	Normal	6	21.40%	2	16.70%	0.55
	Risk	22	78.60%	10	83.30%	
Problem-solving	Normal	14	50.00%	3	25.00%	0.18
	Risk	14	50.00%	9	75.00%	
Personal-social	Normal	15	53.60%	3	25.00%	0.17
Risk		13	46.40%	9	75.00%	

Chi-square test.
ASQ: Ages and Stages Questionnaire, THOP: transient hypothyroxinemia of prematurity

for treatments and their temporary effects, and a decrease in disease severity in NICU. Tan et al. (28) found no relationship between PDA, IVH, antenatal steroid use, ROP, APGAR scores, sepsis, and THOP.

Premature and/or low birth weight infants may exhibit clinical features attributable to thyroid dysfunction, such as temperature imbalance, immature lung function, and inadequate surfactant reserves, as well as apnea, bradycardia, severe intestinal motility and slowed feeding, edema, and tardy growth and development. Several observational studies have demonstrated an association between low serum T4 levels and these clinical presentations (14,29).

In a study with preterm infants <1500 g, no significant differences were found between infants with and without hypothyroxinemia in terms of neurodevelopmental, visual, or hearing impairment at five years of age (28). In a double-blind, randomized, placebo-controlled study in preterm infants less than 28 GW from the UK, the thyroid hormone-treated group had significantly higher scores in language and cognitive domains and better motor skills as assessed by the Bayley III Mental and Psychomotor Developmental Indexes at 42 months (30). Randomized, placebo-controlled studies revealed complex results with some potential benefit of levothyroxine therapy in infants <28 weeks, but potential harm in infants older than 28 weeks (31). TFTs of premature infants can be affected by medications, free fatty acids, protein concentration, and use of furosemide and heparin (32). THOP is an important consideration because it occurs during a critical period for brain development, despite having a self-limiting course. Long-term studies found associations between THOP and mental development abnormalities in preterm infants, particularly reaching milestones later, lower scores on cognitive tests, increased school failure, and cerebral palsy risk (23,33). Yamamoto et al. (33) showed that the results of infants with THOP born under 30 GW to the TRH stimulation test was similar to that of infants with normal thyroid functions, suggesting that the hypothalamohypophyseal thyroid axis is functioning normally in infants with THOP. Depending on these results L-T4 replacement is thought to be non-essential in THOP. Furthermore, L-thyroxine replacement to preterm infants was thought to be safe, as in term infants. However, a case of circulatory disorder related to levothyroxine replacement was reported in a VLBW infant from Japan (34,35,36). Levothyroxine use is reported to increase the relative adrenal insufficiency of prematurity (37). Adrenal insufficiency is more evident if infants with panhypopituitarism receive levothyroxine replacement without glucocorticoids (37). Thus thyroid hormones enhance cortisol turn-over as well as the need for glucocorticoids. Also of concern is a probable increased risk of NEC due to the L-T4 administration (38). Besides, theoretical clinical risks may exist, such as unexplained tachycardia or arrhythmias, tremors, weight loss or hyperpyrexia, and neurobehavioral abnormalities due to excess or unnecessary use of thyroid hormone (39). Thyroid hormones are powerful biological triggers that can cause unexpected effects when given unnecessarily. Hence, the existing evidence suggest that L-T4 replacement brings no clinical benefit but can even harm infants with THOP (40).

One of the most important advantages of the development assessment tools the 'ASQ' with the 'ASQ:SE', which are filled directly by the parents, is that they benefit from the rich experience of the parents about their child and provide the opportunity to continuously evaluate the development of the child at certain time intervals. Research results support that parents can provide accurate information about their children's development regardless of socioeconomic level, region of residence, or mental health (14).

The high agreement between mothers' or fathers' evaluations of their children's developmental skills and expert evaluations and the low cost of evaluation triggered the development of evaluation tools filled by mothers or fathers (13). In 2006, the Council of Children with Disabilities outlined tools that can be safely used as a general developmental screening test (15).

In the present study, no association was found between the 'ASQ' with the 'ASQ:SE' subparameters of THOP in the first two years of life and adverse neurodevelopmental outcomes. For these studies that revealed associations between thyroid hormone abnormalities and adverse neurodevelopmental outcomes in preterm infants, we hypothesized that thyroid status may only be a confounder, that reflects the severity of disease or co-morbidities, such as IVH, which were actual risk factors associated with neurodevelopmental disorder. The study of Fisher (41) supported this hypothesis by showing low T4 levels and low T3 levels in preterm infants, were the result of non-thyroidal diseases and mirrored the disease severity in those infants. It has been suggested that decreased thyroid hormone synthesis, protein catabolism, and oxygen consumption in preterm infants may be a potentially beneficial adaptive response to the disease state. Furthermore, studies by Williams et al. (42) and Carrascosa et al. (43) examining the effect of RDS, IVH, NEC, and sepsis on thyroid function supported this phenomenon. Interestingly, the present study found that anti-VEGF use for ROP, and steroid use for BPD rates were higher in THOP group that received levothyroxine. Further much larger studies are required to elucidate the association with levothyroxine replacement and higher rates of steroid use

for BPD, and anti-VEGF use for ROP without affecting long-term neurological outcomes in infants with THOP. However, this association may be because those infants were 'sicker' or had more advanced stage of preterm morbidities than the others, then it would not be surprising for them to require further therapy for BPD and/or ROP too. Hence, these novel results can also be considered supportive findings. Ultimately, these data suggest that THOP may be an epiphenomenon of non-thyroidal disease but this does not appear to lead to long-term adverse outcomes in infants. Therefore, we believe that better clinical management of risky conditions in preterm infants may reduce the prevalence of THOP and the possible negative consequences that may develop thereafter, rather than routinely treating THOP with levothyroxine replacement (44).

Study Limitations

Although the statistical analysis indicated that the number of participants is sufficient to report, it is evident that the strait number of participants poses a limitation for this study. The other limitations of our study is that we did not question parental intelligence, home environment, breastfeeding or formula feeding, and post-discharge medication use histories.

Conclusion

This study demonstrated that levothyroxine replacement did not improve long-term neurological outcomes in this population of infants with THOP. However, given the limitations of this study, well-designed, much larger, prospective, controlled studies are needed to clarify the role of levothyroxine replacement in THOP.

Ethics

Ethics Committee Approval: This study was approved by Ordu University Training and Research Hospital Local Ethics Committee (file number: 2021/249, date: 19.11.2021).

Informed Consent: Informed consent for participation was obtained from the parents.

Authorship Contributions

Surgical and Medical Practices: Erhan Aygün, Seda Yılmaz Semerci, Adviye Çakıl Sağlık, Emine Yurdakul Ertürk, Concept: Erhan Aygün, Seda Yılmaz Semerci, Design: Erhan Aygün, Seda Yılmaz Semerci, Data Collection or Processing: Erhan Aygün, Seda Yılmaz Semerci, Adviye Çakıl Sağlık, Emine Yurdakul Ertürk, Analysis or Interpretation: Erhan Aygün, Seda Yılmaz Semerci, Literature Search: Erhan Aygün, Seda Yılmaz Semerci, Adviye Çakıl Sağlık, Emine Yurdakul Ertürk, Writing: Erhan Aygün, Seda Yılmaz Semerci.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Eerdekens A, Langouche L, Van den Berghe G, Verhaeghe J, Naulaers G, Vanhole C. Review shows that thyroid hormone substitution could benefit transient hypothyroxinaemia of prematurity but treatment strategies need to be clarified. Acta Paediatr 2019;108:792-805. Epub 2019 Jan 4
2. Özon A, Tekin N, Şıklar Z, Gülcan H, Kara C, Taştekin A, Demir K, Koç E, Evliyaoğlu O, Kurtoğlu S. Neonatal effects of thyroid diseases in pregnancy and approach to the infant with increased TSH: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report. Turk Pediatri Ars 2019;53(Suppl 1):209-223.
3. Kurtoğlu S, Özdemir A. Fetal neonatal hyperthyroidism: diagnostic and therapeutic approachment. Turk Pediatri Ars 2017;52:1-9.
4. Kadivar M, Parsaei R, Setoudeh A. The relationship between thyroxine level and short term clinical outcome among sick newborn infants. Acta Med Iran 2011;49:93-97.
5. Williams F, Hume R. The measurement, definition, aetiology and clinical consequences of neonatal transient hypothyroxinaemia. Ann Clin Biochem 2011;48:7-22.
6. La Gamma EF, Korzeniewski SJ, Ballabh P, Paneth N. Transient Hypothyroxinemia of Prematurity. Neoreviews 2016;17:394-402.
7. Hollanders JJ, Israëls J, van der Pal SM, Verkerk PH, Rotteveel J, Finken MJ; Dutch POPS-19 Collaborative Study Group. No Association Between Transient Hypothyroxinemia of Prematurity and Neurodevelopmental Outcome in Young Adulthood. J Clin Endocrinol Metab 2015;100:4648-4653. Epub 2015 Oct 19
8. van Wassenaer-Leemhuis A, Ares S, Golombek S, Kok J, Paneth N, Kase J, LaGamma EF. Thyroid hormone supplementation in preterm infants born before 28 weeks gestational age and neurodevelopmental outcome at age 36 months. Thyroid 2014;24:1162-1169. Epub 2014 May 21
9. van Wassenaer AG, Kok JH, de Vijlder JJ, Briët JM, Smit BJ, Tamminga P, van Baar A, Dekker FW, Vulsma T. Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. N Engl J Med 1997;336:21-26.
10. Yagasaki H, Kobayashi K, Nemoto A, Naito A, Sugita K, Ohyama K. Late-onset circulatory dysfunction after thyroid hormone treatment in an extremely low birth weight infant. J Pediatr Endocrinol Metab 2010;23:153-158.
11. Fisher DA. Thyroid system immaturities in very low birth weight premature infants. Semin Perinatol 2008;32:387-397.
12. Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC. Reference ranges for newer thyroid function tests in premature infants. J Pediatr 1995;126:122-127.
13. Küçüker S, Kapçı EG, Uslu R. Erken Gelişim Evreleri Envanteri, 2015.
14. Mercado M, Szymonowicz W, Yu VY, Gold H. Symptomatic hypothyroxinemia with normal TSH levels in preterm infants. Clin Pediatr (Phila) 1987;26:343-346.
15. Council on Children With Disabilities; Section on Developmental Behavioral Pediatrics; Bright Futures Steering Committee; Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental

disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006;118:405-420.

16. Küçüker S, Kapci EG, Uslu R. Evaluation of the Turkish version of the "Ages and Stages Questionnaires: Social-emotional" in identifying children with social-emotional problems. Infants Young Child 2011;24:207-220.
17. Kantor Herring MJ, Leef KH, Locke RG, Stefano JL, Bartoshesky L, Paul DA. Are perinatal risk factors helpful in predicting and optimizing treatment strategies for transient hypothyroxinemia in very-low-birth-weight infants? Am J Perinatol 2003;20:333-339.
18. Filippi L, Cecchi A, Tronchin M, Dani C, Pezzati M, Seminara S, Gasperini S, Zammarchi E, Rubaltelli FF. Dopamine infusion and hypothyroxinaemia in very low birth weight preterm infants. Eur J Pediatr 2004;163:7-13. Epub 2003 Nov 25
19. Tan LO, Tan MG, Poon WB. Correction: Lack of association between hypothyroxinemia of prematurity and transient thyroid abnormalities with adverse long term neurodevelopmental outcome in very low birth weight infants. PLoS One 2019;14:e0223867.
20. Williams FL, Mires GJ, Barnett C, Ogston SA, van Toor H, Visser TJ, Hume R; Scottish Preterm Thyroid Group. Transient hypothyroxinemia in preterm infants: the role of cord sera thyroid hormone levels adjusted for prenatal and intrapartum factors. J Clin Endocrinol Metab 2005;90:4599-4606. Epub 2005 May 10
21. Woo HC, Lizarda A, Tucker R, Mitchell ML, Vohr B, Oh W, Phornphutkul C. Congenital hypothyroidism with a delayed thyroid-stimulating hormone elevation in very premature infants: incidence and growth and developmental outcomes. J Pediatr 2011;158:538-542. Epub 2011 Jan 13
22. Williams FL, Ogston SA, van Toor H, Visser TJ, Hume R. Serum thyroid hormones in preterm infants: associations with postnatal illnesses and drug usage. J Clin Endocrinol Metab 2005;90:5954-5963. Epub 2005 Aug 16
23. Zdraveska N, Kocova M. Thyroid function and dysfunction in preterm infants-Challenges in evaluation, diagnosis and therapy. Clin Endocrinol (Oxf) 2021;95:556-570. Epub 2021 Apr 25
24. Simpson J, Williams FL, Delahunty C, van Toor H, Wu SY, Ogston SA, Visser TJ, Hume R; Scottish Preterm Thyroid Group. Serum thyroid hormones in preterm infants and relationships to indices of severity of intercurrent illness. J Clin Endocrinol Metab 2005;90:1271-1279. Epub 2004 Dec 21
25. van Wassenaer AG, Kok JH, Dekker FW, de Vijlder JJ. Thyroid function in very preterm infants: influences of gestational age and disease. Pediatr Res 1997;42:604-609.
26. Zung A, Bier Palmon R, Golan A, Troitzky M, Eventov-Friedman S, Marom R, Keidar R, Kats N, Almashanu S, Flidel-Rimon O. Risk Factors for the Development of Delayed TSH Elevation in Neonatal Intensive Care Unit Newborns. J Clin Endocrinol Metab 2017;102:3050-3055.
27. Williams FL, Mires GJ, Barnett C, Ogston SA, van Toor H, Visser TJ, Hume R; Scottish Preterm Thyroid Group. Transient hypothyroxinemia in preterm infants: the role of cord sera thyroid hormone levels adjusted for prenatal and intrapartum factors. J Clin Endocrinol Metab 2005;90:4599-4606.
28. Tan LO, Tan MG, Poon WB. Lack of association between hypothyroxinemia of prematurity and transient thyroid abnormalities with adverse long term neurodevelopmental outcome in very low birth weight infants. PLoS One 2019;14:e0222018.
29. Hadeed AJ, Asay LD, Klein AH, Fisher DA. Significance of transient postnatal hypothyroxinemia in premature infants with and without respiratory distress syndrome. Pediatrics 1981;68:494-498.
30. Ng SM, Turner MA, Weindling AM. Neurodevelopmental Outcomes at 42 Months After Thyroxine Supplementation in Infants Below 28 Weeks' Gestation: A Randomized Controlled Trial. Thyroid 2020;30:948-954. Epub 2020 Mar 17
31. LaFranchi SH. Thyroid Function in Preterm/Low Birth Weight Infants: Impact on Diagnosis and Management of Thyroid Dysfunction. Front Endocrinol (Lausanne) 2021;12:666207.
32. Delahunty C, Falconer S, Hume R, Jackson L, Midgley P, Mirfield M, Ogston S, Perra O, Simpson J, Watson J, Willatts P, Williams F; Scottish Preterm Thyroid Group. Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5 1/2 years: millennium cohort study. J Clin Endocrinol Metab 2010;95:4898-4908. Epub 2010 Aug 18
33. Yamamoto A, Kawai M, Iwanaga K, Matsukura T, Niwa F, Hasegawa T, Heike T. Response to thyrotropin-releasing hormone stimulation tests in preterm infants with transient hypothyroxinemia of prematurity. J Perinatol 2015;35:725-728. Epub 2015 Jun 25
34. Kawai M, Kusuda S, Cho K, Horikawa R, Takizawa F, Ono M, Hattori T, Oshiro M. Nationwide surveillance of circulatory collapse associated with levothyroxine administration in very-low-birthweight infants in Japan. Pediatr Int 2012;54:177-181. Epub 2012 Jan 13
35. Okada J, Iwata S, Hirose A, Kanda H, Yoshino M, Maeno Y, Matsuishi T, Iwata O. Levothyroxine replacement therapy and refractory hypotension out of transitional period in preterm infants. Clin Endocrinol (Oxf) 2011;74:354-364.
36. Yagasaki H, Kobayashi K, Nemoto A, Naito A, Sugita K, Ohyama K. Late-onset circulatory dysfunction after thyroid hormone treatment in an extremely low birth weight infant. J Pediatr Endocrinol Metab 2010;23:153-158.
37. Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. Br Med J (Clin Res Ed) 1986;292:1185-1186.
38. Phase 1 Trial of 4 Thyroid Hormone Regimens for Transient Hypothyroxinemia in Neonates of <28 Weeks' Gestation 2009;124:258-268. Epub 2009 Jul 5
39. La Gamma EF, Paneth N. Clinical importance of hypothyroxinemia in the preterm infant and a discussion of treatment concerns. Curr Opin Pediatr 2012;24:172-180.
40. Iijima S. Current knowledge of transient hypothyroxinemia of prematurity: to treat or not to treat? J Matern Fetal Neonatal Med 2019;32:2591-2597. Epub 2018 Feb 22
41. Fisher DA. Euthyroid low thyroxine (T4) and triiodothyronine (T3) states in prematures and sick neonates. Pediatr Clin North Am 1990;37:1297-1312.
42. Williams FLR, Ogston SA, van Toor H, Visser TJ, Hume R. Williams FL, Ogston SA, van Toor H, Visser TJ, Hume R. Serum thyroid hormones in preterm infants: associations with postnatal illnesses and drug usage. J Clin Endocrinol Metab 2005;90:5954-5963. Epub 2005 Aug 16
43. Carrascosa A, Ruiz-Cuevas P, Clemente M, Salcedo S, Almar J. Thyroid function in 76 sick preterm infants 30-36 weeks: results from a longitudinal study. J Pediatr Endocrinol Metab 2008;21:237-243.
44. Yoon SA, Chang YS, Yang M, Ahn SY, Sung SI, Cho HS, Park WS. Effect of levothyroxine supplementation in extremely low birth weight infants with transient hypothyroxinemia of prematurity. Sci Rep 2022;12:9717.