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Frequency of Thyroid Function Disorders among a Population of Very-Low-Birth-Weight Premature Infants

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ABSTRACT

***Background*:** Thyroid function disorders, particularly congenital hypothyroidism (CHT), are important endocrine dysfunctions associated with permanent morbidities. CHT is more prevalent among preterm low-birth-weight neonates compared to term infants with normal weight.

***Methods*:** This prospective cohort study was conducted on 126 very-low-birth-weight (VLBW) neonates referred to the neonatal intensive care units (NICUs) of two tertiary referral hospitals affiliated to Isfahan University of Medical Sciences in Isfahan, Iran during 2012-2014. On day five of birth and two, four, and six weeks after birth, blood samples were collected from the infants to determine thyroid function disorders, including transient hypothyroxinemia, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia.

***Results*:** In total, 126 infants with mean gestational age of 30.5±2.29 weeks and mean birth weight of 1246.90±193.58 g were enrolled in this study. Thyroid-stimulating hormone (TSH) level of <5 μU/mL was detected in 97 neonates. Transient hypothyroxinemia (low free T4 level, normal TSH) was the most frequent thyroid disorder detected in 42 infants (33.33%). Moreover, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were observed in 8 (6.34%), 15 (11.90%), and 9 neonates (7.14%), respectively. Clinical events were similar between infants with and without thyroid dysfunction. In addition, incidence of clinical events had no difference between infants with any type of thyroid function disorders.

Conclusion: According to the results of this study, thyroid function disorders are relatively common in preterm VLBW neonates, and serum T4 level is correlated with gestational age in these infants. Therefore, thyroid function tests with a consistent protocol are required for premature infants. It is recommended that further research be performed on larger sample sizes to investigate the prevalence of thyroid function disorders in preterm infants.

Keywords: Congenital hypothyroidism, Hypothyroxinemia, Low birth weight, Premature, Thyroid disorders, Transient hypothyroidism

Introduction

Thyroid function disorders, particularly congenital hypothyroidism (CHT), are among the most important endocrine and metabolic problems, which might progress to neurodevelopmental disorders in case of delayed diagnosis or treatment of neonates (1). CHT occurs in approximately one infant per a 3,500-4,000 population (2). In two studies conducted in Zanjan city (Iran) and Pakistan, incidence of CHT was reported to be 2% (3).

CHT is one of the most common and preventable causes of mental retardation in newborns. However, the majority of neonates with CHT might manifest few symptoms or even remain asymptomatic. In such cases, CHT is likely to become progressively symptomatic within months (4). Normal function of the thyroid gland is essential to the normal brain development of infants; as such, delayed diagnosis of thyroid disorders could lead to several mental complications (5). Since 1970, newborn screening has been implemented by collecting blood samples from the heels of preterm infants for the timely detection and treatment of metabolic and endocrine

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disorders (6).

The neonatal screening program initiated in 1974 in Canada and 1997 in Iran (7, 8). According to some studies conducted in Tehran and Isfahan (Iran), prevalence of CHT is higher than the reported rates in Western countries (8-10). In these studies, level of thyroid-stimulating hormone (TSH) was measured in heel prick or cord samples, and neonates with TSH levels of ≥5 mIU/L were reexamined in terms of TSH and T4 levels in order to confirm CHT diagnosis (8-10).

During the fetal period, thyroid multilobar is produced in week seven of gestation, and colloid-containing follicles are observed at week 10 of gestation. Moreover, thyroglobulin synthesis occurs in week four of gestation, and iodine trapping initiates during weeks 8-10. Pituitary portal vascular system of the fetus evolves during weeks 8-10 of gestation and thyrotropin-releasing hormone is released from the hypothalamus during weeks 6-8 and secreted at week 12 of gestation. Maturation of human hypothalamic-pituitary-thyroid axis occurs within the second half of pregnancy; however, the normal feedback may not appear until 1-2 months (11, 12).

Within 30-60 minutes after delivery, serum TSH levels immediately increase to 60-80 mU/L, which mainly depends on the low temperature of the environment and umbilical cord clamping. Afterwards, this level gradually reaches 20 mU/L within 24 h after birth and reduces to 6-8 mU/L during the first week of life. The initial increase in TSH level stimulates the secretion of T4, as well as the peripheral conversion of T4 to T3.

Levels of free T4, T4 and T3 reach a peak (10-22 mcg/dL) at 24-36 h after birth (129-283 nmol/L), decreasing to 2-5 ng/dL (25-64 pmol/L) afterwards (13). Furthermore, T3 level increases to a peak of 250 ng/dL (3.8 nmol/L), which stimulates the secretion of T4 and peripheral conversion of T4 to T3. During the first four weeks of life, levels of T4, T3 and free T4 decrease gradually, becoming slightly higher than the concentrations in adults. At this point, normal range of total T4 reaches 7-16 mcg/dL, while free T4 concentration reaches 0.2-0.8 ng/dL. After four weeks, TSH normal range increases to 0.9-7.7 mU/L, which is comparatively higher than adults (13).

In premature infants, levels of T4 and free T4 are correlated with birth weight and gestational age (14, 15), as observed in the blood samples of the heels in routine screening for CHT. According to the literature, within 2-5 days after birth, mean T4 serum level in extremely-low-birth-weight infants is 5.6 mcg/dL (72 nmol/L), while it is 6.7 mcg/dL (86 nmol/L) in infants aged less than 30 weeks (16, 17). In addition, free T4 level in infants with gestational age of less than 30 weeks has been estimated at 1.2 ng/dL (15 pmol/L) (15, 16).

In the postnatal period, T4, T3 and TSH levels of preterm neonates become similar to those of term infants (17). At gestational age of 25-30 weeks, initial level of free T4 is 0.0-3.3 ng/dL during the first week of life, while it is higher in weeks 31-36 (1.3-4.7 ng/dL) (17). In a study conducted on 72 infants with gestational age of 24-34 weeks, TSH level during the first 24 h after birth was reported to be lower in the majority of preterm infants (8, 20 and 23 mU/L in weeks 24-27, 28-30 and 31-34, respectively) (18). Therefore, it could be concluded that premature neonates (especially in weeks 24-27) experience a minor increase in the levels of TSH and free T4 compared to term infants, which could be attributed to the prematurity of the hypothalamic-pituitary-thyroid axis in preterm neonates.

Similar to term infants, T4 level reduces in the first week of life in low-birth-weight (LBW) neonates (14), while this reduction is more significant in very-low-birth-weight (VLBW) infants. Daily recom-mended dose of iodine for infants is 90 mg (19). In infants with endemic iodine deficiency, iodine deficiency leads to the reduction of T4 level (20). During the first week of life, T4 and T3 levels increase gradually in most preterm infants. In weeks 3-6, these levels in premature infants (especially those aged less than 28 weeks) overlap with the normal range in term infants; however, mean level of this hormone remains slightly lower in premature infants with gestational age of 30-35 weeks. At seven days after birth, T4 level reaches its peak, followed by a reduction. In premature infants, measured concentrations of thyroid hormones overlap with the normal ranges observed in term infants within one week after birth (21).

Considering the abnormal levels of some thyroid hormones in premature infants, they are predisposed to various thyroid disorders, such as transient hypothyroxinemia, neonatal hypothy-roidism, transient neonatal hypothyroidism, and transient hyperthyrotropinemia (22-24).

Thyroid dysfunction in preterm neonates could be attributed to the immaturity of the hypothalamic-pituitary-thyroid axis and thyroid hormone synthesis and metabolism, as well as systemic disorders associated with iodine intake (25). In neonates aged less than 28 weeks, the recommended treatment for hypothyroxinemia involves the prescription of levothyroxine (until the

age of three years). On the other hand, in neonates with gestational age of 28 weeks and normal TSH, levothyroxine treatment might increase morbidities (24). A recent Cochrane review has strongly recommended further investigations in this regard (26).

This study aimed to evaluate the frequency of thyroid function disorders in neonates with birth weight of less than 1500 g referred to the neonatal intensive care units (NICUs) of two tertiary referral hospitals in Isfahan, Iran.

Methods

Study design and participants

In this prospective cohort study, we evaluated the thyroid function of the VLBW neonates referred to the NICUs of Al-Zahra and Shahid Beheshti hospitals in Isfahan, Iran during 2012-2014.

Inclusion criteria were prematurity and birth weight of <1500 g. Exclusion criteria of the study were the presence of major congenital anomalies, blood exchange transfusion, and death in the first month of birth. Determinants included neonatal hypothyroidism, hypothyroxinemia (particularly in neonates with gestational age of <28 weeks), and transient CHT.

Selected neonates received thyroid function tests, including the measurement of TSH, free T4 and T4 levels on day five of birth and two, four and six weeks after birth via radioimmunoassay. Moreover, blood samples (1-1.5 cc) were obtained from the forearm of infants by trained nurses and sent to a single laboratory.

Data of blood sample analysis were collected and evaluated, and presence of neonatal hypothyroidism, neonatal hypothyroxinemia, and transient neonatal hypothyroidism was determined. Thyroid function disorders were diagnosed based on the normal ranges of thyroid function tests (Figure 1) and definitions of thyroid dysfunction.

Gestation (weeks)	Age of specimen	Free T4 (ng/dL)	T4 (microgram/dL)	T3 (ng/dL)	TSH (mU/L)
23-27 weeks	Cord	1.28 ± 0.4	5.4 ± 2.0	20 ± 15	6.8 ± 2.9
	7 d	1.47 ± 0.6	4.0 ± 1.8	33 ± 20	3.5 ± 2.6
	14 d	1.45 ± 0.5	4.7 ± 2.6	41 ± 25	3.9 ± 2.7
	28 d	1.50 ± 0.4	6.1 ± 2.3	63 ± 27	3.8 ± 4.7
28-30 weeks	Cord	1.45 ± 0.4	6.3 ± 2.0	29 ± 21	7.0 ± 3.7
	7 d	1.82 ± 0.7	6.3 ± 2.1	56 ± 24	3.6 ± 2.5
	14 d	1.65 ± 0.4	6.6 ± 2.3	72 ± 28	4.9 ± 11.2
	28 d	1.71 ± 0.4	7.5 ± 2.3	87 ± 31	3.6 ± 2.5
31-34 weeks	Cord	1.49 ± 0.3	7.6 ± 2.3	35 ± 23	7.9 ± 5.2
	7 d	2.14 ± 0.6	9.4 ± 3.4	92 ± 36	3.6 ± 4.8
	14 d	1.98 ± 0.4	9.1 ± 3.6	110 ± 41	3.8 ± 9.3
	28 d	1.88 ± 0.5	8.9 ± 3.0	120 ± 40	3.5 ± 3.4
≥37 weeks	Cord	1.41 ± 0.3	9.2 ± 1.9	60 ± 35	6.7 ± 4.8
	7 d	2.70 ± 0.6	12.7 ± 2.9	148 ± 50	2.6 ± 1.8
	14 d	2.03 ± 0.3	10.7 ± 1.4	167 ± 31	2.5 ± 2.0
	28 d	1.65 ± 0.3	9.7 ± 2.2	176 ± 32	1.8 ± 0.9

Figure 1. Normal ranges of thyroid function tests in premature infants (26)

Definition and diagnosis of thyroid function disorders

In this study, thyroid function disorders were diagnosed based on predetermined definitions and normal ranges of thyroid function tests in premature infants (Figure 2).

Transient hypothyroxinemia was confirmed in case of low T4 and free T4 levels and normal TSH level (2, 23). In addition, neonatal hypothyroidism was diagnosed in infants with elevated TSH levels and low free T4 and T4 levels during the neonatal period (low levels of free T4 and T4, TSH level of ≥10 mU/L or ≥20 mU/L with any level of free T4 (2, 23, 27).

Transient primary neonatal hypothyroidism was diagnosed in case of low or steadily reducing level of free T4, with the moderate elevation of TSH level (>5 mU/L in serial testing within the first month of birth) (2, 23). Additionally, transient hyperthyrotropinemia was confirmed in infants with elevated TSH level during the neonatal period despite normal T4 and free T4 levels (2).

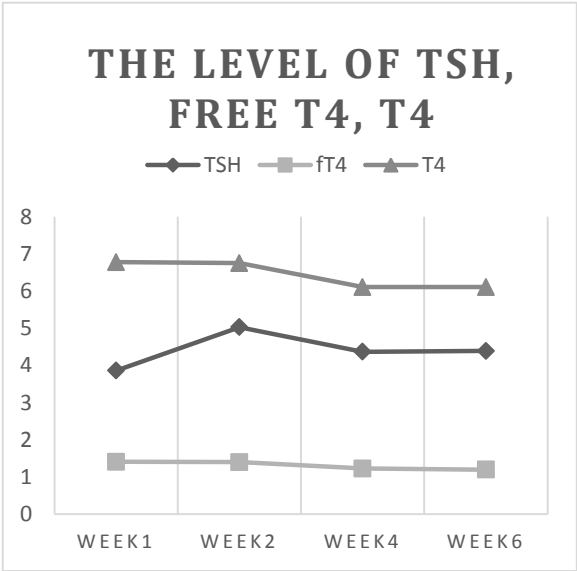

Figure 2. Levels of thyroid-stimulating hormone (TSH), free T4, and T4 during six weeks after birth

Statistical analysis

Data analysis was performed in SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution and categorical data were presented as mean ± standard deviation and numbers and percentages, respectively. Moreover, numerical data were compared using Chi-square, independent t-test or Mann-Whitney U test as appropriate. Comparison of continuous variables was carried out using one-way analysis of variance (ANOVA), and $\alpha < 0.05$ was considered statistically significant.

Ethical considerations

This article was extracted from a research project conducted in Isfahan University of Medical Sciences, Isfahan, Iran (code: 190112). Study Review Board of the university, and written protocol was approved by the regional Ethical informed consent was obtained from all the parents prior to the study.

Results

In total, 126 infants were enrolled in this study, including 65 males (51.6%) and 61 females (48.4%) with mean gestational age of 30.51±2.29 weeks and mean birth weight of 1246.90±193.58 g on day five of birth. With increased age, we reduced the number of infants in this study.

Some of the infants were excluded from the study due to different factors, such as the unwillingness of parents for participation, lack of compliance of the attending neonatologist with the study protocol, transfer of infants to other wards, and no blood sampling. Eventually, 115 and 99 infants were evaluated in weeks two and four of birth, respectively, and 72 neonates completed the study in week six of birth (Table 3).

Gestational age of 15 infants was less than 28 weeks, while it was 28-30 weeks in 50 neonates, and 57 neonates had gestational age of more than 30 weeks. Levels of TSH, free T4, and T4 increased with gestational age, which was considered significant in terms of T4 serum level (Table 1). Moreover, mean TSH level significantly increased during the second week of birth, while it showed a slight increase after four and six weeks. On the other hand, levels of free T4 and T4 gradually decreased within six weeks after birth (tables 2 & 3) (Figure 1).

In this study, 100 neonates (78.7%) received treatment for respiratory distress syndrome (RDS) with nasal continuous positive airway pressure (NCPAP). Furthermore, surfactant administration (INSURE method) was used in 58 infants (45.7%). Intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA) and clinical sepsis were detected in 9 (7.1%), 21 (16.5%), and 3 infants (2.4%), respectively (Table 4). In the first week of birth, mean concentration of bilirubin was

Table 1. Levels of TSH, free T4 and T4 based on gestational age

Gestational age (weeks^{days})	<28 (n=15)	$28^{0/7}$-$29^{6/7}$ (n=50)	$30^{0/7}$-$31^{6/7}$ (n=28)	>32 (n=29)	P-value
TSH (Mean±SD)	2.25±1.34	3.81±3.15	4.17±1.99	4.42±3.34	0.09
Free T4 (Mean±SD)	1.25±0.24	1.40±0.54	1.42±0.31	1.53±0.47	0.25
T4 (Mean±SD)	5.04±2.62	6.23±2.26	8.11±3.04	7.47±2.50	0.01

Table 2. Mean levels of TSH, free T4 and T4 during six weeks after birth

	Day 5 of birth	Week 2	Week 4	Week 6
TSH (Mean±SD)	3.86±2.84	5.03±4.74	4.37±2.69	4.39±2.41
Free T4 (Mean±SD)	1.41±0.45	1.40±0.69	1.23±0.37	1.20±0.47
T4 (Mean±SD)	6.78±2.72	6.75±2.87	6.11±2.43	6.11±1.74

Table 3. Levels of TSH, free T4 and T4 during six weeks after birth

		Week 1 (day 5 of birth) N (%)	Week 2 N (%)	Week 4 N (%)	Week 6 N (%)
TSH (mU/L)	<5	97 (77)	79 (68.7)	70 (70.7)	51 (70.8)
	5-7	18 (14.2)	21 (18.3)	12 (12.1)	12 (16.7)
	7-10	7 (5.5)	6 (5.2)	13 (13.1)	8 (11.1)
	10-30	4 (3.1)	9 (7.8)	4 (4.1)	1 (1.4)
	Total	126 (100)	115 (100)	99 (100)	72 (100)
Free T4 (ng/dL)	<0.7	0 (0)	3 (2.7)	0 (0)	1 (1.4)
	>0.7	126 (100)	112 (97.3)	99 (100)	71 (98.6)
	Total	126 (100)	115 (100)	99 (100)	72 (100)
T4 (mg/dL)	<7	75 (59.6)	68 (59.2)	72 (72.7)	58 (80.6)
	>7	51 (40.4)	47 (40.8)	27 (27.3)	14 (19.4)
	Total	126 (100)	115 (100)	99 (100)	72 (100)

Table 4. Frequency of clinical events

Clinical events	Infants with thyroid function disorders (n=74; 58.73%) N (%)	Infants without thyroid function disorders (n=52; 41.27%) N (%)	Total (n=126) N (%)	P-value
RDS	59 (79.72)	41 (78.84)	100 (79.36)	0.001
INSURE method	34 (45.94)	25 (48.07)	59 (46.82)	0.023
NCPAP	59 (79.72)	41 (78.84)	100 (79.36)	0.001
Mechanical ventilation	2 (2.72)	2 (3.84)	4 (3.17)	0.15
IVH	5 (6.75)	6 (11.53)	11 (8.73)	0.26
PDA	12 (16.21)	7 (13.46)	19 (15.07)	0.14
Suspected NEC	3 (4.05)	1 (1.92)	4 (3.17)	0.5
Documented sepsis	2 (2.72)	2 (3.84)	4 (3.17)	0.79
Clinical sepsis	7 (9.45)	9 (17.30)	16 (12.69)	0.19

RDS: respiratory distress syndrome; INSURE: intubation-surfactant-extubation; NCPAP: nasal continuous positive airway pressure; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis

estimated at 6.86±1.76 mg/dl, which showed a slight reduction in the second and third measurements (5.51±1.58 and 5.38±2.12 mg/dl in weeks two and four, respectively).

Among the studied neonates, 74 cases (58.73%) presented with different types of thyroid function disorders. Transient hypothyroxinemia (Free T4 levels are low but TSH levels are normal) was the most prevalent thyroid disorder, which was detected in 42 infants (33.33%) (Table 5). Two of these neonates had gestational age of <28 weeks, who received treatment, according some references (2)

Table 5. Frequency of congenital hypothyroidism, transient hypothyroxinemia, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia

Thyroid function disorders	N (%)
Congenital hypothyroidism	8 (6.34)
Transient hypothyroxinemia	42 (33.33)
Transient primary neonatal hypothyroidism	15 (11.90)
Transient hyperthyrotropinemia	9 (7.14)

Moreover, Neonatal hypothyroidism (elevated TSH level with low levels of Free T4 and T4) was observed in eight infants (6.34%). In the second week of birth, four neonates had TSH level of >20 mU/L, while in week four of birth, four neonates had TSH level of >10 mU/L and low levels of free T4 and T4 (Table 5). Therefore, levothyroxine treatment was initiated in all these infants.

Transient primary neonatal hypothyroidism (Free T4 is low or steadily decreases while TSH remains moderately elevated) was observed in 15 neonates (11.90%) (Table 5), who received levothyroxine treatment in case TSH level remained above 5 mU/L on serial testing during the first month of birth (2).In addition, transient hyperthyrotropinemia (elevated TSH level during the neonatal period despite normal T4 and free T4 levels) was diagnosed in 9 neonates (7.14%) (Table 5).

Neonatal clinical events in infants with thyroid dysfunction are presented in tables 4 and 6. According to our findings, these clinical events were similar between infants with and without thyroid function disorders. Furthermore, RDS, INSURE and NCPAP were observed in 59 (79.72%), 34 (45.94%), and 59 neonates (79.72%) with thyroid function disorders, as well as 41 (78.84%), 24 (46.15%), and 41 (78.84%) infants without thyroid dysfunction, respectively.

Incidence of IVH, PDA, suspected necrotizing enterocolitis (NEC), and sepsis was found to be similar in neonates with and without thyroid function disorders in this study. On the other hand, incidence of these clinical events was similar between infants with different types of thyroid dysfunction (Table 6). Although, in the first, it was seemed that the duration of need to NCPAP was more longer in transient hypothyroxinemia (e.g. 6, 8 or even 11 days) but the median (range) of NCPAP dependency was 1 [1- 11] days in transient hypothyroxinemia and 2

[1- 6] days in others kind of thyroid function disorders (Table 6).

Discussion

In the present study, 126 infants with mean gestational age of 30.51 weeks and mean birth weight of 1246 g were evaluated in terms of thyroid function disorders. Gestational age of the majority of the neonates was more than 30 weeks. According to our findings, frequency of hypothyroxinemia and CHT was 2.4%, which is lower compared to the study by Chung et al. In the mentioned cohort, incidence of hypothyroidism was estimated at 12%. This discrepancy might be due to the higher gestational age of infants in the current research compared to the study by Chung et al. (30.51 versus 28.5 weeks) (28).

Table 6. Characteristics of infants with congenital hypothyroidism, transient hypothyroxinemia, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia

	Congenital hypothyroidism (n=8) N (%)	Transient hypothyroxinemia (n=42) N (%)	Transient primary neonatal hypothyroidism (n=15) N (%)	Transient hyperthyrotropinemia (n=9) N (%)	P-value
RDS	7 (87.5)	35 (83.3)	9 (60.0)	8 (88.8)	0.16
INSURE method	4 (50.0)	19 (45.2)	5 (33.3)	6 (66.6)	0.46
NCPAP	7 (87.5)	35 (83.3)	9 (60.0)	8 (88.8)	0.19
Mechanical ventilation	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)	>0.99
IVH	0 (0.0)	3 (7.1)	1 (6.6)	1 (11.1)	0.67
PDA	0 (0.0)	9 (21.4)	0 (0.0)	3 (20.0)	0.02
Suspected NEC	0 (0.0)	3 (7.1)	0 (0.0)	0 (0.0)	0.49
Documented sepsis	0 (0.0)	1 (2.3)	1 (6.6)	0 (0.0)	0.71
Clinical sepsis	4 (50.0)	2 (4.7)	0 (0.0)	1 (11.1)	0.001

In this regard, a large-scale study was performed by Hashemipour et al. (2004) in Isfahan (Iran), which indicated the incidence of CHT to be one case per 349 live births (9). Low incidence of CHT in the mentioned research could be due to the inclusion of term, preterm, and LBW neonates and infants with normal weight. Therefore, our findings seem to be more reliable in the case of preterm LBW neonates.

In another study by Mandel et al., incidence of CHT in VLBW newborns was reported to be 0.75%, which is lower than the present study (29). Similarly, Larson et al. (30) estimated the incidence of neonatal thyroid function disorders at 0.25%, which is lower compared to two studies performed in Belgium (CHT incidence: 5% and 18% due to iodine deficiency in premature infants) (30).

According to the results of the current study, incidence of transient hypothyroidism and hyperthyrotropinemia was 7.8% and 16%, respectively. Consistent with our findings, previous reports have suggested that transient hypothyroxinemia is a prevalent condition in preterm neonates, the severity of which rises in newborns with lower gestational age. Some researchers have attributed this to the developmental complications in neonates (31, 32).

Furthermore, several studies have emphasized the high prevalence of transient hypothyroidism in preterm and LBW infants. Correspondingly, neonates with transient hypothyroidism are more susceptible to neurodevelopmental disorders. In these infants, levothyroxine treatment could prevent possible complications (33-35).

According to the literature, premature infants with CHT are highly likely to experience various complications, as Chung et al. (21) reported RDS, IVH, and NEC in these neonates. In line with previous studies in this regard, we detected PDA, RDS, and NEC in preterm newborns.

The interpretation of our results is subject to some limitations such as relatively small sample size and short duration of follow-up (six weeks) that hindered significance in our analyses. According to increasing of premature births (36) which is the most common cause of disability and even death (37), prevalence determination of the complications of prematurity such as thyroid function disorders seem essential in any society. Hence, further investigations are recommended with longer follow-up and larger series to validate the findings reported here.

Conclusion

According to the results of this study, thyroid function disorders are relatively common in preterm LBW neonates. In addition, serum level of T4 is correlated with gestational age in these infants. Therefore, thyroid function tests must be performed with a consistent protocol on premature infants. Furthermore, it is recommended that future studies in this regard be carried out on larger sample sizes.

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Conflicts of interests

The authors declare no conflicts of interest.

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