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Thyroid hormone levels in late preterm, early term and term infants: a study with healthy neonates revealing reference values and factors affecting thyroid hormones

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Abstract

Background: Thyroid function tests in neonates have been challenging to interpret because their levels are affected by several neonatal and delivery-related factors. The aim of the study was to evaluate reference values of thyroxine (T4) and thyrotropin (TSH) levels in different gestational age groups and to demonstrate the affect of perinatal factors on thyroid hormones.

Methods: Medical records of 7616 neonates whose gestational age ranges between 34 and 42 weeks were analyzed retrospectively. Gender, mode of delivery, gestational age, postnatal age and birth weight were noted together with TSH and T4 levels.

Results: Gestational age ($r=0.14$, $p<0.001$) and birth weight ($r=0.12$, $p<0.001$) had positive correlation with T4 levels, whereas they had no effect on TSH levels. Males had higher TSH and lower T4 levels ($p=0.001$ for both) compared with females. T4 levels of babies born via vaginal delivery were lower than the ones born via cesarean section ($p=0.01$). Multivariable analysis yielded gestational age as the only factor affecting T4 levels ($p<0.001$). T4 and TSH levels based on 2.5–97.5 percentile cutoffs according to gestational age were presented.

Conclusions: The thyroid hormone ranges given in this study can help pediatricians to interpret the thyroid hormone results with ease.

Keywords: gender; gestational age; mode of delivery; preterm; term; thyroid hormones.

Introduction

Thyroid function in postnatal period has been challenging to interpret for pediatricians because it is subject to variations in gestational age [1–3], postnatal age at which blood samples are collected [4, 5], birth weight [2], mode of delivery [5, 6] and gender [7]. Thyrotropin (TSH) levels rise and peak at first 30 min and decline rapidly during the first 24 h of life followed by slower decrease over the next 48 h in full-term infants [8, 9]. The peak observed in TSH levels is partially explained by cold exposure and stress after birth [9]. Thyroid hormone levels of term infants are well determined, but there is still lack of knowledge about those of late preterm and early term infants in the literature. Late preterm infants (34–36⁶ weeks) and early term infants (37–38⁶ weeks) have higher morbidity and mortality rates compared with term infants [10, 11]. In fetal life, the hypothalamus-hypophysis-thyroid axis continues to develop, so the problems seen in late preterm and early term babies may stem from this interruption of development in the axis. There has been no study comparing thyroid hormone levels in late preterm, early term and term infant in the literature. The objective of this study is to compare thyroid hormone levels in late preterm, early term and term neonates, to provide reference ranges of TSH and thyroxine (T4) values according to gestational age and to help pediatricians to interpret thyroid hormone results accurately. We also aim to identify the impact of gestational age, birth weight, gender and mode of delivery on thyroid function in late preterm and early term neonates.

Subjects and methods

Subjects

In this retrospective study, newborn data were collected from the electronic archive system of American Hospital, Istanbul, Turkey, between 1 January 2008 and 31 December 2013. Gender, mode of delivery, birth weight, postnatal age at which blood samples were collected and gestational age were noted together with TSH and T4 levels.

The total number of neonates born in this period was 8164. After excluding the newborns with a gestational age below 34 weeks

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($n=110$), the ones who had sampling on the days other than postnatal 2–4 days ($n=433$), and five newborns without T4 values recorded in the system, total 7616 healthy newborns were included in the study. Neonates with the gestational age less than 34 weeks are directly admitted to the Neonatal Intensive Care Unit in American Hospital regardless of their health status. Blood collection is performed at the end of first week for those babies, so we excluded those with gestational age <34 weeks from the study to standardize the time of blood collection in the study group. Neonates with special conditions requiring more than 4 days of hospitalization ($n=312$ out of which four neonates with major congenital anomalies and five neonates with perinatal asphyxia) were already excluded from the study as their samples were collected after 4 days of life. Neonates were categorized according to their gestational ages as late preterm babies (34–36⁶ weeks), early term babies (37–38⁶ weeks) and term babies (39–42 weeks).

Gestational age was calculated from the beginning of the last menstrual period of mothers and verified by first trimester ultrasonography. Neonates were weighed naked with an electronic scale (Sartorius AG, Gottingen, Germany) accurate to ± 5 g.

Blood samples for T4 and TSH are collected via venepuncture between 03.00 and 06.00 am during the morning care routine for newborn screening in American Hospital for years. Additionally, one sample taken to filter paper is sent to the Ministry of Health, which only measures TSH, and calls the families back for the neonates with TSH levels equal to or above 5.5 mIU/L to repeat the test [12]. Although the Ministry of Health National Screening Program performs the neonatal hypothyroidism screening only with TSH levels by using heel lancing, we routinely include T4 levels in our hospital's screening program not to overlook any patient with secondary hypothyroidism. Venous blood TSH level is about twice that of heel prick TSH level [13]. Therefore, we have categorized TSH levels in two different groups as the ones below 11 μ IU/mL and the ones equal to or above 11 μ IU/mL for interpretation of the data.

The Local Ethics Committee approved the study protocol (2015.146.IRB2.052). Informed consent was obtained from every patient/parent hospitalized in American Hospital permitting the use of anonymized patient data in clinical studies.

Laboratory analyses

TSH and T4 levels were analyzed via electrochemiluminescence immunoassay system (Cobas®, Roche Diagnostics GmbH, Mannheim, Germany). Undiluted serum samples for T4 levels were analyzed via competitive immunoassay, and TSH levels were analyzed on the basis of sandwich principle (Cobas®, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analyses

Statistical analyses were performed by using the IBM SPSS Statistics Software (SPSS, Chicago, IL, USA). The variables were investigated using visual histograms, probability plots and Shapiro-Wilk test to determine whether or not they are normally distributed. Descriptive analyses were presented by using means $\pm$ SD for normally distributed variables, as medians (25 p–75 p) for the nonhomogeneously distributed variables and as percentages for categorical variables. Normally distributed variables were compared by one-way ANOVA, nonparametric variables by Mann-Whitney U-test and categorical variables by χ^2 -test. Correlations were evaluated by using the Spearman correlation coefficient. Two-way ANOVA test was performed to see the effect of previously determined factors on T4. Reference ranges for T4 and TSH values were presented based on 2.5th and 97.5th percentile cutoffs. The univariate analyses for TSH levels equal to or above 11 μ IU/mL was performed by using χ^2 -test. For multivariable analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of having TSH level equal to or above 11 μ IU/mL. Mode of delivery, sex and birth weight were controlled in multivariable analysis. A p value less than 0.05 was considered to be statistically significant.

Results

A total of 7616 neonates were included in the study. Characteristics of the study population and T4 and TSH levels according to the gestational age groups are given in Table 1. Thyroxine levels were the highest in term neonates and the lowest in late preterm infants (Figure 1).

In neonates born via vaginal delivery, T4 levels were lower than T4 levels of neonates born via cesarean section (13.2 ± 2.2 vs. 13.4 ± 2.2 , $p=0.001$). Additionally, gender was found to affect T4 values with males having lower T4 levels than females (13.27 ± 2.3 vs. 13.43 ± 2.16 , $p=0.001$). There were positive correlations between T4 levels and gestational age ($r=0.14$, $p<0.001$) and between T4 levels and birth weight ($r=0.12$, $p<0.001$). After performing multivariable analysis, only gestational age was demonstrated to affect T4 levels ($p<0.001$). Tables 2 and 3 show T4 and TSH levels according to the gestational age of

Table 1: Characteristics of the study population, and T4 and TSH levels according to the gestational age groups.

Gestational age categories	Late preterm (n=678)	Early term (n=3383)	Term (n=3555)	p-Value
Female, n (%)	347 (51.2%)	1615 (47.7%)	1799 (50.6%)	0.036
Cesarean section, n (%)	591 (87.2%)	2866 (84.7%)	2319 (65.2%)	<0.001
Birth weight, g, mean $\pm$ SD	2436 $\pm$ 424	3250 $\pm$ 423	3466 $\pm$ 390	<0.001
Gestational age, week, mean $\pm$ SD	35.6 $\pm$ 0.7	37.8 $\pm$ 0.4	39.5 $\pm$ 0.6	<0.001
T4, μ g/dL, mean $\pm$ SD	12.6 $\pm$ 2.3	13.2 $\pm$ 2.2	13.6 $\pm$ 2.2	<0.001
TSH, μ IU/mL, median (25–75 p)	5.8 (3.6–9.3)	5.6 (3.4–8.9)	5.6 (3.4–9.1)	0.24

neonates and TSH levels of all neonates based on 2.5 to 97.5 percentile cutoffs.

In our analysis, there was no significant effect of gestational age on TSH levels ($p=0.24$). TSH levels of males were found to be higher than females (7.2 ± 5.4 vs. 6.7 ± 5.03 , $p < 0.001$). However, mode of delivery had no effect on TSH levels. A total of 1254 neonates (16.5%) had TSH levels equal to or above $11 \mu\text{IU/mL}$. Out of 1254 neonates, 560 (44.7%) were female and 694 (55.3%) were male. Overall, 14.9% of females and 18% of males had TSH levels equal to or above $11 \mu\text{IU/mL}$ ($p < 0.001$). Male gender increased the risk of having TSH level equal to or above $11 \mu\text{IU/mL}$ by 1.25 times (95% CI = 1.11–1.41, $p < 0.001$). TSH and T4 tests were repeated for control purposes in 407 (32.5%) of 1254 neonates who had TSH levels equal to or above $11 \mu\text{IU/mL}$ on first analysis. They were normal except two neonates

Table 3: TSH levels ($\mu\text{IU/mL}$) according to gestational age.

Gestational age, week	2.5 p	10 p	25 p	Median	75 p	90 p	97.5 p
34 (n=76)	0.8	2.2	3.3	5.8	9.9	14.9	28.1
35 (n=183)	1.6	2.5	3.9	6.3	9.3	13.5	20.1
36 (n=419)	1.2	2.1	3.5	5.7	9	14.5	22.8
37 (n=787)	1.2	2.3	3.6	5.9	9.4	13.7	20
38 (n=2596)	1.1	1.9	3.3	5.5	8.7	13.4	20.4
39 (n=2198)	1	1.9	3.3	5.6	8.9	12.8	19.6
40 (n=1104)	1.1	2.2	3.5	5.7	9.5	14.5	21.5
41 (n=253)	1	2	3.7	5.6	9.6	14.3	19.6
Total (n=7616)	1.1	2.1	3.4	5.6	9	13.5	20.4

for whom thyroid replacement therapy was initiated (2.6 in 10000 or 1/3846). There was no diagnosis of secondary hypothyroidism in our patient population.

Figure 1: Box plot showing plasma T4 level distribution of late preterm, early term and term infants (the horizontal line shows median values, and the error bars indicate the lowest and highest non-outlier observations).

T4 levels were the highest in term and the lowest in late preterm infants.

Table 2: T4 levels ($\mu\text{g/dL}$) according to gestational age.

Gestational age, week	2.5 p	10 p	25 p	Median	75 p	90 p	97.5 p
34 (n=76)	7.3	9.1	10.6	12	14.2	15.2	17.6
35 (n=183)	8.5	10	10.9	12.6	14	15.2	17.7
36 (n=419)	8.4	9.8	11.1	12.5	14.1	15.7	17.1
37 (n=787)	9	10.5	11.6	13	14.6	15.9	17.6
38 (n=2596)	9	10.5	11.9	13.2	14.7	16	17.6
39 (n=2198)	9.4	10.9	12.1	13.4	14.8	16.4	18.1
40 (n=1104)	9.4	10.9	12.4	13.7	15.2	16.6	18.4
41 (n=253)	10.1	11.5	12.5	14.1	15.4	16.9	19.6

Discussion

In this study, T4 levels were mostly affected by gestational age; however, TSH levels remained unchanged with respect to gestational age. Thyroxine levels were demonstrated to increase with gestational age in other studies performed previously [7, 14–16] similar to our study. Thyroxine levels were also shown to increase with gestational age during fetal life [7]. However, T4 levels were reported to plateau at 35–37 gestational weeks in some studies [17–20] in contrast to our study, where T4 levels did not plateau at any gestational age. The increase in T4 levels was observed even at 41 weeks of gestational age in our study population. Therefore, we suggest that T4 levels of late preterm, early term and term infants can be evaluated separately for the accuracy of interpretation of the results.

Serum T4 concentrations were previously reported to plateau at about $10 \mu\text{g/dL}$, which is lower than the T4 levels found in our study [19]. Many articles use different time frames (at birth from cord blood or different postnatal days) to collect blood samples for the assessment of thyroid hormones in neonates [2, 4, 6]. The variations in timing of blood sample collection may explain the difference between T4 levels reported previously and T4 levels in our study. After TSH surge in 30 min of life, TSH decreases as the postnatal age increases in term and preterm neonates [21]. The initial surge of TSH causes T4 to rise and eventually peak at 24–36 h of life. T4 levels are higher in the first week of life and gradually decrease thereafter, as the postnatal age progresses [22, 23]. Therefore, the timing of blood collection to evaluate thyroid hormones is important in newborns because it is a complicated physiological axis that continues to mature even after birth. For this

reason, collection of the blood samples at different predetermined time points can lead to diverse thyroid hormone levels. Furthermore, American Academy of Pediatrics and American Thyroid Association reports that the specimens collected in the first 24–48 h of life may result in false positive TSH elevations with any screening technique used. Optimal time for the collection of blood specimens is recommended to be in 2–4 days of life before discharge [24]. Thus, to prevent misinterpretation of the data and to eliminate postnatal age as a confounding factor, samples collected only in postnatal 2–4 days were included in this study.

There is contradictory information about the relation of TSH and T4 levels to gestational age in the literature. Similar to our findings, Herbstman et al. [7] reported positive correlation between gestational age and T4 levels. However, both Herbstman et al. [7] and Korevaar et al. [2] reported lower TSH levels with increasing gestational age, which is not consistent with our results. This difference could be explained by the sample size of the study groups. The number of infants included in mentioned studies ($n=298$ in Herbstman et al. [7] and $n=3339$ in Korevaar et al. [2]) is much lower than the sample size of our study ($n=7616$). The larger sample size strengthens the accuracy of the results found in our study. Moreover, similar to our findings, there are many other studies which did not show any correlation between TSH levels and gestational age [1, 3, 4, 16, 20].

Not only the effect of gestational age but also the effect of mode of delivery on thyroid hormones have not been established yet. TSH levels were reported to be higher [6, 25] or lower [2, 3, 7, 26] in babies born via cesarean section compared with the ones born via normal spontaneous vaginal delivery. However, some other studies could not be able to show any effect of mode of delivery on TSH similar to our study [4, 27, 28]. Turan et al. [5] proposed that postnatal TSH levels were not influenced by the mode of delivery, type of anesthesia used during procedure or type of cesarean section performed, that is, whether it is an elective or an emergent cesarean section. In contrast to this, stress factor such as labor via vaginal delivery versus elective cesarean section was reported to be a significant factor that may affect TSH levels in neonates in some other studies [3, 26].

T4 levels were lower in babies born via normal spontaneous vaginal delivery than the ones born via cesarean section in this study, yet it was not statistically significant in multivariable analysis. Although some studies reported no association between T4 levels and mode of delivery [3, 4, 26, 29] similar to our study, Turan et al. [5] found higher T4 levels in neonates born via vaginal delivery. Different results regarding the effect of mode of delivery on both T4

and TSH levels may reflect the impact of stress factor on the process of labor. The information whether the labor had started before cesarean section or not in either our study population or previous studies reported in the literature is not available. Although the labor can be planned to be an elective cesarean section, the process of labor might have already started, which may change the stress factor in that particular situation.

The limitation of our study is that it is a retrospective study in which the electronic archive system was used. Therefore, it was not possible to document details about delivery such as the type of cesarean section (elective or emergent), instrumental delivery or type of anesthesia (general or local) administered to the mother during birth, which may also affect thyroid hormone levels of neonates. Even different types of anesthetic agents were shown to have various effects on T4 levels after surgery. Intraoperative increase in T4 levels was reported in patients having anesthesia with enflurane but not with isoflurane or fentanyl-droperidol [30]. Furthermore, Korevaar et al. [2] suggested that maternal TSH and T4 levels might determine neonatal TSH and T4 levels. Therefore, any factor that affects maternal hormone levels, such as the anesthesia type as in the mentioned study above, can also influence neonatal thyroid hormone levels. Further studies can be valuable to explore this interaction.

Thyroid hormone levels were not affected by gender in this study after applying multivariable analysis. Males tend to have lower T4 and higher TSH levels than female neonates in several studies [7, 31, 32]. A study [33] from Belgium classifying patients by using gender and TSH values reported lower verbal IQ levels in children with neonatal TSH values found between 10 and 15 mIU/L. Moreover, male gender was shown to be a predictor of lower IQ scores (less than 85), when they used the same infants' data at preschool age [33]. In our study, 18% of males and 14.9% of females had TSH values equal to or above 11 μ IU/mL. Therefore, to evaluate whether the results found in our study is a predictor of IQ scores, further studies are essential to follow the neonates whose TSH levels are equal to or above 11 μ IU/mL. In our patient population, two neonates (1/3846) were diagnosed with congenital hypothyroidism, similar to hypothyroidism prevalence in Turkey which is 1/3500 [34].

Additionally, although we found lower T4 levels in males compared with females, when we performed two-way ANOVA test, the only significant factor affecting T4 levels was gestational age ($p<0.001$). Therefore, we suggest to interpret T4 values by using gestational age as the only parameter without considering the gender of the newborn.

In conclusion, reference ranges of T4 and TSH for late preterm, early term and term neonates were presented in this study, which can help pediatricians to interpret the thyroid hormone results with ease. Further studies evaluating IQ scores of healthy neonates with TSH levels higher than the predetermined reference value can contribute to the literature.

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