Perinatal factors associated with neonatal thyroid-stimulating hormone in normal newborns

Seong Yong Lee, MD

Department of Pediatrics, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

Purpose: This study was to evaluate the effect of neonatal, maternal, and delivery factors on neonatal thyroid-stimulating hormone (TSH) of healthy newborns.

Methods: Medical records of 705 healthy infants born through normal vaginal delivery were reviewed. Neonatal TSH levels obtained by neonatal screening tests were analyzed in relation to perinatal factors and any associations with free thyroxine (FT4) and 17-α hydroxyprogesterone (17OHP) levels.

Results: An inverse relationship was found between TSH and sampling time after birth. Twin babies and neonates born by vacuum-assisted delivery had higher TSH levels than controls. First babies had higher TSH levels than subsequent babies. Birth weight, gestational age, maternal age and duration from the rupture of the membrane to birth were not related to neonatal TSH. There were no significant differences in TSH level according to sex, Apgar scores, labor induction, the presence of maternal disease and maternal medications. There was a positive association between TSH and 17OHP level but not between TSH and FT4 level. Multiple linear regression analyses showed that sampling time, mode of delivery, birth order, and 17OHP level were significant factors affecting neonatal TSH level.

Conclusion: Neonatal TSH levels of healthy normal newborns are related with multiple factors. Acute stress during delivery may influence the neonatal TSH level in early neonatal period.

Keywords: Thyrotropin, Neonatal screening, Newborn infant

Introduction

Thyroid hormone is essential for somatic growth and neurodevelopment. Early infancy is a critical period in which adequate levels of thyroid hormone are required for normal brain development. Otherwise, irreversible neurological sequelae will ensue. Therefore, early diagnosis and proper treatment for congenital hypothyroidism (CH) are important to prevent deleterious consequences such as mental retardation and growth failure.

As it is difficult to diagnose CH with clinical symptoms at birth, most patients with CH were diagnosed by laboratory results; low serum thyroid hormones and high serum thyroid-stimulating hormone (TSH) levels except for central hypothyroidism.

To avoid a delayed diagnosis, a neonatal screening test (NST) using capillary blood has been introduced in many countries. In Korea, a neonatal screening program for CH was initiated early in the 1990s. Most centers in Korea evaluate TSH levels but some examine both TSH and free thyroxine (FT4) levels to screen for CH. If the TSH level is above the cutoff level at initial NST, a repeat NST or an evaluation of serum levels of TSH will be done. Thus, the initial neonatal TSH level is an important clue to decide on further evaluation and initiation of treatment.

TSH level is influenced by various factors. However, some of the results are controversial and most of these studies investigated subjects including neonates with pathologic or
Abnormal conditions, such as preterm and sick babies. Prematurity itself, neonatal illness, and neonatal and maternal medications may influence neonatal TSH and thyroid hormone levels.2,9

This study aimed to evaluate perinatal factors affecting neonatal TSH of healthy neonates born through normal vaginal delivery, excluding the effects of severe neonatal problems such as prematurity and pathologic conditions.

Materials and methods

1. Subjects

We performed a retrospective review of the medical records of 726 babies who were born through normal vaginal delivery at Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center, Seoul, Korea from January 2013 to December 2014 and discharged from the nursery. Of 726 newborns, 4 had a TSH level above 10 mIU/mL, which is the cutoff level for reevaluation. Follow-up TSH levels were at normal levels in 3 of them and they were included in this study. One of the 4 infants whose TSH levels were above 10 mIU/mL was diagnosed with CH. Two infants whose initial TSH levels were at normal levels had been taking thyroid hormone replacement under the suspicion of CH or transient TSH elevation. Seven infants whose sampling time was before 24 hours after birth and one baby whose sampling time was after 96 hours after birth were excluded. Ten neonates had congenital anomalies or perinatal problems (2 congenital heart disease, 3 renal anomaly, 1 syndactyly, 1 achondroplasia, 1 pineal cyst, 1 chromosomal anomaly, and 1 hypocalcemia). After excluding these 10 infants, 8 infants whose sampling time was early or late, and 3 others who were diagnosed with or suspected of having CH, 705 subjects were included in this study.

2. Methods

Dried capillary blood spots were obtained by heel prick to measure TSH, FT4, and 17-α hydroxyprogesterone (17OHP) levels. Neonatal TSH levels were measured using an AutoDELFIA Neonatal hTSH kit (PerkinElmer, Waltham, MA, USA). Neonatal FT4 levels were measured using Microplate Neonatal FT4 (Bio-Rad, Hercules, CA, USA). An AutoDELFIA Neonatal 17α-OH-progesterone kit (PerkinElmer, Waltham, MA, USA) was used to measure neonatal 17OHP levels.

The normal levels of NST were as follows: TSH <10.0 mIU/mL; FT4 >0.7 ng/dL; 17OHP <12.0 ng/mL.

Data on various factors were collected. Infant-related factors included sex, gestational age, birth weight, birth length, head circumference, sampling time, and Apgar scores (ASs). Delivery-related factors included mode of delivery, labor induction, and duration of the rupture of the membrane (ROM). Maternal factors included twin delivery, parity, maternal age, maternal disease, and maternal medication. Neonatal TSH levels were analyzed in relation to these perinatal factors and any associations with FT4 and 17 OHP levels.

3. Statistics

Statistical analyses were performed with IBM SPSS version 20.0 (IBM Co., Armonk, NY, USA). Variables were tested for a normal distribution. Levels of TSH, FT4, and 17OHP were log-transformed to normalize each distribution. Student t-test was used to compare TSH levels according to differences in perinatal factors. Pearson correlation analysis and stepwise linear regression analysis were applied to evaluate the relationship between TSH levels and continuous variables. A P-value of <0.05 was considered statistically significant.

Table 1. Descriptive data on the subjects

| Variable          | Mean±SD | Range     |
|-------------------|---------|-----------|
| TSH (mIU/mL)      | 3.78±1.91 | 0.05–13.9 |
| FT4 (ng/dL)       | 2.36±0.94 | 0.7–5.4   |
| 17OHP (ng/mL)     | 3.54±2.59 | 0.5–31.2  |
| Gestational age (wk) | 38.86±1.22 | 35.0–42.9 |
| Birth weight (kg) | 3.10±0.39 | 1.84–4.27 |
| Birth length (cm) | 49.85±2.15 | 41.0–57.0 |
| Head circumference (cm) | 33.77±1.24 | 30.0–38.0 |
| Maternal age (yr) | 32.69±5.02 | 17.50–49.92 |
| Apgar score at 1 min | 7.90±0.63 | 3–9       |
| Apgar score at 5 min | 8.94±0.39 | 7–10      |
| Sampling time (hr) | 44.69±8.95 | 24–95    |
| Duration of ROM (hr) | 5.28±9.09 | <0.5–128 |

SD, standard deviation; TSH, thyroid stimulating hormone; FT4, free thyroxine; 17OHP, 17-α hydroxyprogesterone; ROM, rupture of membrane.

Table 2. Pearson correlation analysis between TSH and perinatal factors

| Variable       | TSH | InTSH |
|----------------|-----|-------|
| Gestational age| −0.024 | 0.518 | −0.001 | 0.972 |
| Birth weight   | −0.062 | 0.101 | −0.051 | 0.179 |
| Birth length   | −0.054 | 0.152 | −0.040 | 0.288 |
| Head circumference | −0.058 | 0.125 | −0.037 | 0.323 |
| Sample time    | −0.089 | 0.018 | −0.100 | 0.008 |
| ROM            | 0.017 | 0.651 | 0.022 | 0.555 |
| Maternal age   | 0.026 | 0.483 | −0.003 | 0.945 |
| 17OHP          | 0.164 | <0.001 | 0.170 | <0.001 |
| In17OHP        | 0.208 | <0.001 | 0.220 | <0.001 |
| FT4            | 0.020 | 0.611 | 0.027 | 0.487 |
| InFT4          | 0.020 | 0.601 | 0.023 | 0.540 |

TSH, thyroid stimulating hormone; InTSH, log transformed TSH; 17OHP, 17-α hydroxyprogesterone; In17OHP, log transformed 17OHP; FT4, free thyroxine; InFT4, log transformed free T4; ROM, rupture of membrane.
4. Ethics statement

This study was approved by the Institutional Review Board of SMG-SNU Boramae Medical Center (IRB No. 16-2016-91/081). Informed consent was waived by the Board.

Results

Clinical data and results of NSTs are shown in Table 1. TSH and 17OHP levels were examined in 705 newborns and FT4 was analyzed in 610 newborns. Of 705 neonates, 3 had an abnormal level of 17OHP (>12.0 ng/mL) initially and a normal level subsequently. Of 610 newborns, no one had an abnormal FT4 level.

1. Infant factors

Log transformed TSH level (lnTSH) was not related to gestational age, birth weight, birth length, or head circumference at birth (Table 2). There were no significant differences in TSH level according to the sex of the baby (Table 3). When subjects were divided into 2 groups by AS at 1 minute (<7 vs. ≥7) and at 5 minutes (<9 vs. ≥9), there were no differences in TSH level between the 2 groups (Table 3).

Table 3. Comparison of TSH level according to perinatal factors

| Variable                        | No. (%) | TSH     | P-value | InTSH  | P-value |
|---------------------------------|---------|---------|---------|--------|---------|
| Sex                             |         |         |         |        |         |
| Male                            | 373 (52.9) | 3.85±1.90 | 1.22±0.52 |         |         |
| Female                          | 332 (47.1) | 3.69±1.92 | 1.17±0.53 | 0.200  |         |
| Multiple delivery               |         |         |         |        |         |
| Singleton                       | 679 (96.3) | 3.75±1.89 | 1.19±0.52 |         |         |
| Twin                            | 26 (3.7)  | 4.57±2.37 | 1.42±0.42 | 0.026  |         |
| Birth order                     |         |         |         |        |         |
| 1st baby                        | 433 (61.4) | 3.89±1.92 | 1.24±0.49 |         |         |
| 2nd or later baby               | 272 (38.6) | 3.60±1.88 | 1.14±0.56 | 0.011  |         |
| Apgar score at 1 min            |         |         |         |        |         |
| <7                              | 18 (2.6)  | 3.56±1.51 | 1.17±0.48 |         |         |
| ≥7                              | 687 (97.4) | 3.78±1.92 | 1.20±0.52 | 0.811  |         |
| Apgar score at 5 min            |         |         |         |        |         |
| 7, 8                            | 65 (9.2)  | 4.12±1.93 | 1.30±0.50 |         |         |
| 9, 10                           | 640 (90.8) | 3.74±1.91 | 1.19±0.52 | 0.099  |         |
| Delivery type                   |         |         |         |        |         |
| Spontaneous                     | 571 (81.0) | 3.72±1.91 | 1.18±0.53 |         |         |
| Vacuum assisted                 | 134 (19.0) | 4.01±1.91 | 1.28±0.49 | 0.048  |         |
| Labor type                      |         |         |         |        |         |
| Spontaneous                     | 218 (30.9) | 3.60±1.79 | 1.15±0.52 |         |         |
| Induced                         | 487 (69.1) | 3.85±1.96 | 1.22±0.52 | 0.115  |         |
| Maternal diabetes               |         |         |         |        |         |
| Normal                          | 653 (92.6) | 3.75±1.89 | 1.19±0.52 |         |         |
| GDM/DM                          | 52 (7.4)  | 4.14±2.10 | 1.29±0.53 | 0.191  |         |
| Maternal hypertension           |         |         |         |        |         |
| Normal                          | 688 (97.6) | 3.77±1.92 | 1.20±0.52 |         |         |
| PIH                             | 17 (2.4)  | 4.00±1.64 | 1.30±0.45 | 0.439  |         |
| Maternal thyroid disease        |         |         |         |        |         |
| Normal                          | 646 (91.6) | 3.76±1.94 | 1.19±0.53 |         |         |
| Hypothyroidism<sup>a</sup>       | 52 (7.4)  | 3.98±1.70 | 1.28±0.47 | 0.245  |         |
| Hyperthyroidism<sup>a</sup>      | 7 (1.0)   | 3.71±1.02 | 1.28±0.29 | 0.675  |         |
| Maternal medication             |         |         |         |        |         |
| None                            | 587 (83.3) | 3.78±1.92 | 1.20±0.52 |         |         |
| Insulin<sup>b</sup>             | 22 (3.1)  | 3.79±2.23 | 1.16±0.62 | 0.693  |         |
| L-thyroxine<sup>b</sup>         | 41 (5.8)  | 4.07±1.78 | 1.31±0.46 | 0.205  |         |
| Steroid<sup>b</sup>             | 2 (0.0)   | 2.55±0.35 | 0.93±0.14 | 0.461  |         |

Values are presented as mean±standard deviation unless otherwise indicated.

TSH, thyroid stimulating hormone; lnTSH, log transformed TSH; GDM, gestational diabetes mellitus; DM, diabetes mellitus; PIH, pregnancy induced hypertension.

<sup>a</sup>Maternal thyroid diseases in comparison with normal thyroid function.

<sup>b</sup>Maternal medication in comparison with no medication.
An inverse relationship was found between lnTSH and sampling time after birth ($r=-0.100$, $P=0.008$) (Table 2). There was a positive association between lnTSH and log transformed 17OHP level (ln17OHP) ($r=0.22$, $P<0.001$) (Table 2) but not between lnTSH and log transformed FT4 level (lnFT4) (Table 2).

2. Delivery factors

Infants born by vacuum-assisted delivery had higher lnTSH values than those born by spontaneous vaginal delivery ($P=0.048$) (Table 3). There were no significant differences in lnTSH according to labor induction (Table 3). Duration from ROM to birth was not associated with lnTSH (Table 2).

3. Maternal factors

Maternal age was not related to lnTSH (Table 2). Twin newborns had higher values than singleton babies ($P=0.026$) (Table 3), and first babies had higher values than subsequent babies ($P=0.011$) (Table 3). There were no significant differences in TSH level according to the presence of maternal disease such as diabetes, hypertension, and thyroid disease. In addition, TSH level did not differ according to any medications being taken by mothers, such as insulin and L-thyroxine (Table 3).

4. Stepwise multiple linear regression

In stepwise multiple linear regression analyses including twin delivery, mode of delivery, birth order, sampling time, and ln17OHP as independent variables and lnTSH as the dependent variable, mode of delivery, birth order, sampling time, and ln17OHP were significant factors affecting lnTSH (Table 4).

Discussion

This study showed that the TSH level of normal neonates born through vaginal delivery was influenced by mode of delivery and birth order. Vacuum-assistance delivery and first delivery were associated with higher neonatal TSH levels compared to spontaneous delivery and being a second or later child. TSH levels had a positive relationship with 17OHP levels and a negative relationship with sampling time, and were not related to neonatal FT4 levels.

Previous studies have reported that TSH levels in cord blood are higher in infants born through vaginal delivery than in those born through cesarean section$^{5,10-12}$, and higher in those born through vacuum-assisted delivery than in those born through spontaneous vaginal delivery$^{6,10,14}$. Our results support these studies, although we investigated capillary blood TSH, not cord blood TSH, and infants born through cesarean section were excluded. In contrast, two studies have shown no difference in neonatal TSH level according to mode of delivery$^{8,13}$. However, the subjects in one study included preterm and sick babies, and the authors did not consider vacuum-assisted delivery$^{13}$. The other study also reported higher TSH levels in infants born with vacuum assistance compared to spontaneous vaginal delivery, although the difference was not significant$^{8}$. Therefore, vacuum-assisted delivery itself or the condition prompting vacuum assistance is likely to increase neonatal TSH levels.

Many studies have reported that first babies have higher TSH levels than subsequent babies$^{8,13,14}$. In contrast, one study from Belgium (where iodine insufficiency is common) reported no differences in TSH level according to birth order$^{8}$. Herbstman et al.$^{8}$ assumed that this pattern might be related to environmental exposure, as some persistent chemicals are found at higher levels in firstborn children. In addition, the relatively more difficult labor associated with a first delivery compared to subsequent deliveries could increase TSH levels.

Glucocorticoid treatment may decrease serum levels of TSH through a direct inhibitory effect on thyrotropin releasing hormone (TRH); however, chronic high-dose glucocorticoids or cortisol excess in severe Cushing’s syndrome do not have a significant effect$^{16}$. 17OHP is a precursor of cortisol and its levels are higher in preterm and sick newborns$^{17}$. When levels are high in term newborns without congenital adrenal hyperplasia, it may reflect some sort of stress. Therefore, a positive relationship between 17OHP and TSH may imply that stress during labor increases neonatal levels of TSH.

At birth, TSH levels surge in response to exposure to cold; they peak about 30 min after birth and then gradually decrease$^{8}$. Generally, NSTs are performed 2 days after vaginal birth and 4 or 5 days after cesarean section in Korea. The sampling time of NST depends on the duration of hospital stay of mother and baby. Thus, we excluded neonates born through cesarean section, whose sampling times were much later than those of neonates born through vaginal delivery, from this study. As expected, the later the sampling time, the lower the level of TSH in babies born through normal vaginal delivery. This result is in accordance with previous studies on preterm infants and term infants$^{8,19}$.

Although the increased levels of FT4 after birth that we observed was due to increased levels of TRH and TSH, the lack of a correlation between TSH and FT4 implies an immature hypothalamic pituitary thyroid (HPT) axis in the early neonatal period.

Blunted TSH surges and delayed elevation of TSH levels
are often observed in preterm babies who have an impaired hypothalamic pituitary responsiveness at birth. Term babies also may have an immaturity of HPT axis in the early neonatal period. However, further studies about HPT axis in normal term babies will be required.

TSH level was not related to gestational age in this study. Many previous studies have reported that TSH levels increase with increasing gestational age; however, an inverse relationship has also been reported, another study reported higher TSH levels in preterm than in term babies, and several other studies have reported no difference in TSH levels according to gestational age.

Although some studies have reported that low birth weight is related to high TSH levels, we did not find any association between birth weight and TSH level, in line with two previous reports. Therefore, the relationship between TSH level and gestational age or birth weight seems to be different according to the study population.

Twin delivery is generally related to relative low birth weight, low gestational age, and increased maternal and fetal stress during labor. In our study, twin babies had higher TSH levels than singletons, but the difference was not significant in multivariate analyses, in line with previous works.

We did not find any significant differences in TSH level according to sex, in line with many previous studies. However, a few studies have reported higher TSH levels in boys.

One study reported that neonates with asphyxia (AS at 1 minute<3, and 5 minutes<5) had higher TSH levels than neonates with 1 minute AS≥8 and 5 minutes AS≥9. Another study reported high TSH levels with 1 minute AS<6, but no difference in TSH level according to 5 minutes AS. In contrast, Herbstman et al. reported that infants with 5 minutes AS<8 had higher TSH levels, but there were no differences in TSH level according to 1 minute AS. Some studies have reported no differences in TSH level according to AS, as we found.

Maternal disease such as overt and gestational diabetes, essential or pregnancy-induced hypertension, and hypothyroidism did not affect TSH levels, in agreement with many previous studies and in disagreement with one study in which the authors reported an increased TSH level in maternal diabetes and preeclampsia. In addition, the use of medications to mothers did not affect TSH levels in our study. All of the infants in this study were born through a normal vaginal delivery. This means that any maternal diseases were well controlled with proper medications. These results suggest that a well-controlled maternal disease during pregnancy is not likely to influence neonatal TSH levels. Therefore, acute stress during labor may have caused the increases in TSH levels.

There were some limitations to this study. First, this is a cross-sectional retrospective study. Second, the NST was not as accurate as that of a serologic test for assessing TSH levels. Third, all of the factors possibly affecting TSH levels were not analyzed. For example, maternal and fetal levels of iodine were not evaluated. Iodine deficiency of mother and fetus could cause CH or an elevation of TSH level. Factors not included in this study may influence neonatal TSH levels.

Nonetheless, this study, conducted on normal babies without pathologic conditions, suggests that stress during labor may influence TSH levels even in normal newborns. In addition, this study is unique in that the relationship between neonatal TSH and 17OHP level was analyzed.

In conclusion, TSH levels of healthy, normal newborns are related to multiple factors. Acute stress during delivery may influence the neonatal TSH level in the early neonatal period. We should consider various perinatal conditions when evaluating neonatal TSH levels.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Bongers-Schokking JJ, de Muinck Keizer-Schrama SM. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. J Pediatr 2005;147:768-74.
2. Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Arch Dis Child 2011;96:374-9.
3. Léger J, Olivier A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. Horm Res Paediatr 2014;81:80-103.
4. Lee DH. Newborn screening of inherited metabolic disease
5. Kim EY, Park SK, Song CH, Lim SC. Perinatal factors affecting thyroid stimulating hormone (TSH) and thyroid hormone levels in cord blood. Korean J Pediatr 2005;48:143-7.

6. Herbstman J, Apelberg BJ, Witter FR, Panny S, Goldman LR. Maternal, infant, and delivery factors associated with neonatal thyroid hormone status. Thyroid 2008;18:67-76.

7. Ryckman KK, Spracklen CN, Dagle JM, Murray JC. Maternal factors and complications of preterm birth associated with neonatal thyroid stimulating hormone. J Pediatr Endocrinol Metab 2014;27:929-38.

8. Trumpff C, Vandevijvere S, Moreno-Reyes R, Vanderpas J, Tafforeau J, Van Oyen H, et al. Neonatal thyroid-stimulating hormone level is influenced by neonatal, maternal, and pregnancy factors. Nutr Res 2015;35:975-81.

9. Pereira DN, Procianoy RS. Effect of perinatal asphyxia on thyroid-stimulating hormone and thyroid hormone levels. Acta Paediatri 2003;92:339-45.

10. Miyamoto N, Tsuji M, Imataki T, Nagamachi N, Hirose S, Hamada Y. Influence of mode of delivery on fetal pituitary-thyroid axis. Acta Paediatri Jpn 1991;33:363-8.

11. McElduff A, McElduff P, Wiley V, Wilcken B. Neonatal thyrotropin as measured in a congenital hypothyroidism screening program: influence of the mode of delivery. J Clin Endocrinol Metab 2005;90:6361-3.

12. Lakshminarayana SG, Sadanandan NP, Mehaboob AK, Gopaliah LR. Effect of maternal and neonatal factors on cord blood thyroid stimulating hormone. Indian J Endocrinol Metab 2016;20:317-23.

13. Armanian AM, Hashemipour M, Esnaashari A, Kelishadi R, Farajzadegan Z. Influence of perinatal factors on thyroid stimulating hormone level in cord blood. Adv Biomed Res 2013;2:48.