Cord Blood Thyroid Hormones and Neurodevelopment in 2-Year-Old Boys and Girls

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Objective: Thyroid hormones are essential for neurodevelopment in early life. However, the impact of mild alterations in neonatal thyroid hormones on infant neurodevelopment and its sex dimorphism is unclear. We aimed to assess whether mild variations in neonatal thyroid hormones of term-born newborns with maternal euthyroid are related to neurodevelopment in 2-year-old boys and girls.

Methods: This study used data from 452 singleton term-born infants of mothers with normal thyroid function in Shanghai, China, and their follow-up measure at the age of 2 years. Cord serum concentrations of free thyroxine (FT4), free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), and thyroid peroxidase antibody (TPOAb) were measured by chemiluminescent microparticle immunoassays and classified into three groups: the low (1st, Q1), middle (2nd−4th, Q2−Q4), and high (5th, Q5) quintiles. Neurodevelopment indices were assessed using the Ages and Stages Questionnaire, third edition (ASQ-3), at 24 months of age.

Results: Compared to infants with thyroid hormones in the middle (Q2−Q4), boys with FT4 in the lowest quintile had 5.08 (95% CI: 1.37, 8.78) points lower scores in the communication domain, 3.25 (0.25, 6.25) points lower scores in the fine motor domain, and 3.84 (0.04, 7.64) points lower scores in the personal-social domain, respectively. Boys with FT3 in the highest quintile had 4.46 (0.81, 8.11) points increase in the personal-social domain. These associations were not observed in girls. No associations were observed between cord blood serum TSH and ASQ-assessed neurodevelopment in the boys or the girls.

Conclusions: Mild alterations in thyroid hormones of newborns were associated adversely with neurodevelopment in boys, suggesting the importance of optimal thyroid hormone status for neurodevelopment in early life.

Keywords: thyroid hormones, neurodevelopment, cord blood, ASQ-3, infancy, boys and girls
INTRODUCTION

An adequate supply of thyroid hormones is essential for healthy neurodevelopment in utero and during infancy (the first 2 years of postnatal life) (1, 2). During early gestation, fetal thyroid hormones are of maternal origin, and from mid gestation onward, fetal thyroid gland begins to secrete thyroxine (T4) and triiodothyronine (T3) under the control of the hypothalamic-pituitary-thyroid axis, and the thyroid hormone axis becomes fully functional around the time of term birth (3). In early postnatal period, continuing maturation of the brain is dependent on neonatal thyroid hormones (2). The developing brain may be susceptible to even mild thyroid hormone deficiency (4). However, it is unclear whether mild variations in neonatal thyroid hormones may affect subsequent neurodevelopment during infancy.

Neonatal levels of thyroid hormones have been related to gestational brain development as well as postnatal neurodevelopment (5, 6). Studies in recent decades have showed that variations in the lower and higher ranges of neonatal thyroid hormone levels may be associated with neurodevelopment, but data are limited and contradictory (7). Some studies showed that higher neonatal thyroid-stimulating hormone (TSH) levels, although below normal screening thresholds, were associated with poorer cognitive or behavioral development (8–11), while no association was reported in other studies (12–14) or the association might be dependent on TSH levels (15). Lower free thyroxine (FT4) concentrations have been related to worse neurodevelopment in preterm babies (6, 16, 17). However, there were also reports of no significant associations (18–21) or age-dependent associations (22). There are several randomized controlled trials (RCTs) addressing the effect of thyroid hormone supplementation during infancy on neurodevelopment and reporting that T4 supplementation does not improve mental or motor development in preterm infants (23) and in infants with Down syndrome (24). It remains unclear whether mild variations in neonatal thyroid hormones, within normal ranges, may affect neurodevelopment during infancy. In addition, the brain undergoes substantial organization and sexual differentiation during infancy (25), and it is unclear whether sex has an impact on the association between neonatal thyroid hormones and neurodevelopment.

Cord blood thyroid hormones levels are proxy for in utero thyroid functional status (26). In this prospective cohort study, we tested the hypothesis that relatively low cord blood FT4 and free triiodothyronine (FT3) levels in term-born infants of euthyroid mothers may reflect suboptimum thyroid function during gestation and may have an impact on neurodevelopment during infancy.

METHODS

Study Design and Participants

The study participants were from the Shanghai Obesity and Allergy Cohort described previously (27). Briefly, between 2012 and 2013, women with singleton pregnancy at late trimester (close to delivery) were recruited in two tertiary hospitals in Shanghai, China. The study was approved by the Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from the parents of the infants.

In this cohort, there were 1,051 mother-infant pairs with data on cord blood serum FT4, FT3, TSH, or thyroid peroxidase antibody (TPOAb). Neurodevelopment assessments were completed in 494 infants at 24 months of age. We excluded infants of mothers with thyroid diseases (hyperthyroidism, n = 5; hypothyroidism, n = 12) and syphilis (n = 3), and infants with artificial fertilization (n = 10), and preterm births (n = 14), among whom two had both artificial fertilization and preterm births. Thus, the final study sample included 452 mother-infant pairs. No infants included were diagnosed with congenital hypothyroidism or congenital anomalies.

Cord Serum FT4, FT3, TSH, and TPOAb Assays

Immediately after delivery, cord blood sample was collected. Aliquots of serum samples were stored at −80 °C until the assays. Cord blood serum FT4, FT3, TSH, and TPOAb concentrations were measured by chemiluminescent microparticle immunoassays using the ARCHITECT System (Abbott Laboratories, Abbott Park, IL, United States) in the clinical biochemistry laboratory of Shanghai International Peace Maternity and Child Health Hospital of Chinese Welfare Foundation; the laboratory is certified by the National Accreditation Board of China. QA/QC procedures were performed for all the assays in accordance with the system’s instructions. Inter- and intra assay coefficients of variation were 2.5–6.3 and 3.5% for FT4, 5.9 and 5–5.1% for FT3, and 2.5–4.1 and 2.2–2.9% for TSH. The limits of detection (LOD) for FT4, FT3, TSH, and TPOAb were 5.15 pmol/L, 1.54 pmol/L, 0.01 mIU/L, and 0.5 IU/ml, respectively. The cross-reactivity was 0.002% between the T3 and T4 assays for FT4 > 1,000,000 pg/ml, and 0.0035% for FT3 > 12,000 ng/dl. Therefore, the assays showed virtually no cross-reactivity between FT3 and FT4. The TPOAb positive was defined as TPOAb ≥ 5.61 IU/ml (28).

Neurodevelopment Assessment

Neurodevelopment during infancy was assessed (at 24 months of age) using the Ages and Stages Questionnaires, third edition (ASQ-3) (29). This standardized developmental screening tool is designed for children 1–66 months of age. Each of the age-specific questionnaires contains 30 items over five domains: communication, gross motor, fine motor, problem solving, and personal-social skills. The answer to each item is one of the following: “yes,” “sometimes,” and “not yet” and was scored 10, 5, and 0 points, respectively. Scores in each subscale ranged from 0 to 60. Suspected developmental delay was indicated by a domain score of 1–2 SD below the mean, while developmental delay was defined as domain score > 2 SD below the mean using the reference norms (29). More than 92% of the questionnaires were completed by the parents of the infants. The high inter-rater reliability of the ASQ-3 questionnaires was confirmed in a Chinese population, with a coefficient of between 0.8 and 0.84 (30, 31).
Maternal and Infant Factors
Maternal and infant characteristics included maternal age, education, infant sex, gestational age at birth, birth weight, 5-min Apgar score, age at ASQ-3 assessment, infant feeding pattern during the first 6 months of life, and infant exposure to passive smoking in the first 2 years of postnatal life. There were three infant feeding categories: (1) exclusive breastfeeding, (2) formula feeding, and (3) mixed feeding. Birth weight for gestational age was defined according to the Chinese birth weight references for male and female newborns separately, and categorized as small for gestational age (SGA, <10th percentile), appropriate for gestational age (AGA, 10th–90th percentile), and large for gestational age (LGA, >90th percentile).

Statistical Analysis
Student's t-test and Chi-square test were performed to assess the differences in continuous and categorical variables. Considering that cord serum levels of thyroid hormones differ between infants born by vaginal and cesarean section deliveries, and the non-linear associations with neurodevelopment, FT4, FT3, and TSH levels were categorized into mode-of-delivery specific quintiles in comparisons of neuro-developmental outcomes. For cord serum thyroid hormone, the middle 60% (2nd–4th quintiles, Q2–Q4) was set as the reference group to analyze the effects of low (1st quintile, Q1) or high (5th quintile, Q5) levels on neurodevelopment. Associations between neonatal thyroid hormone levels and ASQ-3 scores in boys and girls were assessed in generalized linear models. Adjusted analyses were controlled for maternal age (<30, 30–34, ≥35 years), education (high school or lower, college/university), birth weight for gestational age (SGA, AGA, LGA), infant feeding pattern during the first 6 months of life (exclusive breastfeeding, formula feeding, mixed feeding), any passive smoking in the first 2 years of postnatal life (yes, no), and age at ASQ-3 assessment. In multivariable regression models, we coded the missing values as a separate category for the covariate-infant feeding pattern during the first 6 months. P < 0.05 were considered statistically significant. Data analyses were conducted using the Statistical Analysis System (SAS), version 9.4 (SAS Institute, Inc, Cary, NC, United States).

RESULTS
Study Population Characteristics
Average mother age was 29 ± 3.4 (mean ± SD) years. About 97.8% of the mothers were Han Chinese, 86.3% had college or university education, and 76.1% of the infants were cesarean section deliveries. All the newborns were full term and had normal 5-min Apgar score (≥8). Average age at ASQ-3 assessment was 24.17 ± 0.71 months. The prevalence of exclusive breastfeeding in the first 6 months of life was 38.6%. Exposure to passive smoking in the first 2 years of postnatal life was 58.6% in the infants. The boys had higher birth weight and cord blood TSH concentration than the girls (Table 1).

Infant Neurodevelopment at 24 Months of Age
The mean scores were 43–54 for the communication, gross motor, fine motor, problem solving, and personal-social domains at 24 months of age for the boys, and 48–56 for the girls (Table 2). Compared with the girls, the boys had a higher proportion of delay and suspected delay in the communication (17.3 vs. 7.9% for boy vs. girl, p = 0.003), and personal-social (19 vs. 5.1%, p < 0.0001; Table 2) domains.
### Cord Blood Thyroid Hormones and Infant Neurodevelopment

Cord serum FT4, FT3, and TSH concentrations were categorized into mode-of-delivery-specific quintiles (Supplementary Table 1). Low cord serum FT4 levels were associated with lower ASQ-3 scores. Compared to the boys with FT4 in the middle 60%, those with FT4 in the lowest quintile (Q1) had 5.08 (95% CI: 1.37, 8.78) points lower scores in the communication domain, 3.25 (0.25, 6.25) points lower scores in the fine motor domain, 3.84 (0.04, 7.64) points lower scores in the personal-social domain. Compared to the boys with cord serum FT3 in the middle 60%, those with FT3 in the highest quintile (Q5) had 4.46 (0.81, 8.11) points higher scores in the personal-social domain (Table 3).

For the girls, compared to those with cord serum FT3 in the middle 60%, both those with FT3 in the highest and lowest quintiles had higher scores in the communication domain, with 3.06 (0.24, 5.88) points and 3.26 (0.46, 6.06), respectively, increase in points (Table 4).

There was no significant association between cord blood TSH and TPOAb positivity with ASQ-3 scores at 24 months of age in both boys and girls (Tables 3, 4).

### DISCUSSION

In this birth cohort conducted in term-born infants of euthyroid mother, for boys, lower levels of cord blood FT4 was associated with lower ASQ-3 scores in the communication, fine motor, and personal-social domains, and higher FT3 levels was associated with higher scores in the personal-social domain in boys at age 24 months. These associations were not observed in the girls.

Cord blood TSH and TPOAb positivity were not associated with ASQ-3 scores during infancy.

In contrast, negative or no association between neonatal T4 and cognitive outcomes were also reported (18, 19). Before mid-gestation, maternal supply is the only source of fetal FT4, and there is lack of a compensatory regulation of cerebral enzyme type 2 deiodinase (D2) bioactivity (38) involved in the local conversion of T4 to active T3 in the brain (38). Therefore, lower maternal T4, even within the normal range, could lead to lower FT4 supply to fetus; thus, lower T3 is available for brain development (39). Neonatal T4 and T3 levels may partly reflect maternal T4 levels during gestation (40). The brain regions primarily affected by FT4 are the hippocampus, cortex, and cerebellum, involved in memory, learning, cognition, and motor abilities (41). Our findings suggest that even mild alternations in fetal thyroid hormone levels of euthyroid mother may affect neurodevelopment during infancy.

In this study, no associations were observed between cord blood serum TSH and ASQ-assessed neurodevelopment in boys or girls. This finding was consistent with previous studies (42). In traditional views, TSH could reflect mild and subclinical variations of thyroid hormones. This study was limited to term-born infants of euthyroid mothers. T3 is the bioactive form of thyroxine and essential for fetal cerebral cortex development (39). A substantial part of intracellular T3 supply in the brain depends on circulating T4 transport and local conversion by the D2 enzyme (43). A cross-sectional study on 4-year-old children found no association between serum FT3 concentration and mental or motor development (11). Few studies had examined cord blood T3 and infant neurodevelopment. A previous study on preterm infants found that a decrease between cord blood T3 and infant serum T3 levels at the end of the first week of life was associated with an increased risk of disturbed mental...
TABLE 3 | Associations between cord blood thyroid hormones and ASQ-3 scores in boys at 24 months of age.

| Thyroid related hormones | Communication | Gross motor | Fine motor | Problem solving | Personal-social |
|--------------------------|---------------|-------------|------------|----------------|-----------------|
|                          | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) |
| FT4 (pmol/L)             |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 44)    | 47.73 ± 11.88 | −5.08 (−8.78, −3.17)** | 51.82 ± 9.09 | −2.32 (−4.78, 0.13) | 47.34 ± 11.42 | −3.25 (−6.25, −0.25)* | 48.18 ± 10.24 | −2.07 (−5.02, 0.89) |
| 5th quintile (n = 43)    | 53.84 ± 8.15 | 1.17 (−2.54, 4.88) | 56.63 ± 4.04 | 2.27 (−0.19, 4.73) | 53.26 ± 7.31 | 1.93 (−1.07, 4.94) | 50.27 ± 7.68 | Ref                |
| FT3 (pmol/L)             |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 49)    | 53.98 ± 9.35 | 3.59 (−0.01, 7.19) | 54.39 ± 7.82 | 0.30 (−2.14, 2.74) | 51.33 ± 9.34 | 0.84 (−2.13, 3.81) | 51.12 ± 8.80 | 2.28 (−0.60, 5.15) |
| 5th quintile (n = 43)    | 50.58 ± 11.12| Ref          | 53.98 ± 7.79 | Ref             | 50.12 ± 8.70 | Ref              | 48.94 ± 8.77 | Ref                |
| TSH (mIU/L)              |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 48)    | 52.60 ± 9.28 | 1.40 (−2.24, 5.04) | 53.75 ± 7.89 | −0.76 (−3.18, 1.68) | 51.67 ± 7.67 | 1.73 (−1.21, 4.67) | 50.63 ± 8.46 | 1.94 (−0.90, 4.78) |
| 5th quintile (n = 57)    | 52.98 ± 10.04| 1.99 (−1.48, 5.46) | 55.26 ± 6.15 | 0.43 (−1.87, 2.74) | 51.96 ± 8.40 | 1.86 (−0.95, 4.66) | 51.58 ± 7.27 | 2.67 (−0.04, 5.38) |
| TPOAb                    |               |             |            |                |                |                      |                |                  |
| Negative (n = 205)       | 52.02 ± 10.48| Ref          | 54.29 ± 7.06 | Ref             | 50.62 ± 8.83 | Ref              | 50.17 ± 8.02 | Ref                |
| Positive (n = 29)        | 52.59 ± 11.15| 0.52 (−3.74, 4.78) | 54.48 ± 10.03| 0.98 (−1.90, 3.85) | 50.69 ± 9.89 | 0.45 (−3.04, 3.93) | 47.76 ± 10.99| 2.29 (−5.69, 1.10) |

FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody. TPOAb positive: ≥5.61 IU/ml, CI; confidence interval.

The regression coefficients were adjusted for maternal age (<30, 30–34, ≥35 years), education (high school or lower, college/university), birth weight for gestational age (SGA, AGA, LGA), infant feeding pattern during the first 6 months of life (exclusive breast-feeding, mixed feeding, formula feeding), infant passive smoking in the first 2 years (yes, no), and infant age at ASQ-3 assessment.

*p < 0.05, **p < 0.01.

TABLE 4 | Associations between cord blood thyroid hormones and ASQ-3 scores in girls at 24 months of age.

| Thyroid related hormones | Communication | Gross motor | Fine motor | Problem solving | Personal-social |
|--------------------------|---------------|-------------|------------|----------------|-----------------|
|                          | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) | Mean ± SD     | Adjusted β (95% CI) |
| FT4 (pmol/L)             |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 47)    | 55.21 ± 9.44 | −0.31 (−3.08, 2.45) | 53.30 ± 8.42 | −2.20 (−5.01, 0.62) | 51.81 ± 7.55 | −0.26 (−3.03, 2.51) | 51.49 ± 8.00 | −0.05 (−2.92, 2.82) |
| 5th quintile (n = 45)    | 58.00 ± 5.05 | 2.00 (−0.79, 4.80) | 53.78 ± 9.12 | −1.67 (−4.51, 1.18) | 51.78 ± 7.40 | −0.95 (−3.74, 1.85) | 51.67 ± 8.73 | −0.08 (−2.97, 2.82) |
| FT3 (pmol/L)             |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 43)    | 58.49 ± 3.19 | 3.26 (0.46, 6.06)* | 55.33 ± 9.20 | 0.86 (−2.05, 3.77) | 53.37 ± 7.05 | 1.39 (−1.45, 4.23) | 53.26 ± 8.69 | 1.22 (−1.73, 4.16) |
| 5th quintile (n = 39)    | 57.69 ± 5.24 | 3.06 (0.24, 5.88)* | 55.13 ± 7.30 | 0.78 (−2.14, 3.71) | 50.90 ± 8.65 | −0.68 (−3.54, 2.17) | 50.64 ± 8.82 | −0.18 (−3.14, 2.76) |
| TSH (mIU/L)              |               |             |            |                |                |                      |                |                  |
| 1st quintile (n = 43)    | 55.93 ± 8.54 | −0.27 (−3.04, 2.50) | 53.95 ± 7.91 | −0.93 (−3.76, 1.90) | 52.44 ± 7.67 | 0.10 (−2.66, 2.85) | 52.79 ± 7.81 | 1.05 (−1.81, 3.91) |
| 5th quintile (n = 32)    | 57.50 ± 4.92 | 1.72 (−1.39, 4.84) | 54.50 ± 8.71 | −0.35 (−3.53, 2.84) | 50.78 ± 8.43 | −1.87 (−4.97, 1.23) | 51.09 ± 9.13 | −0.40 (−3.61, 2.82) |
| TPOAb                    |               |             |            |                |                |                      |                |                  |
| Negative (n = 196)       | 55.97 ± 7.95 | Ref          | 54.69 ± 8.04 | Ref             | 52.07 ± 7.92 | Ref              | 51.40 ± 8.61 | Ref                |
| Positive (n = 19)        | 57.37 ± 4.82 | 0.93 (−3.00, 4.85) | 54.74 ± 7.67 | −1.04 (−5.05, 2.96) | 49.47 ± 7.24 | −2.18 (−6.08, 1.72) | 53.42 ± 4.43 | 1.68 (−2.37, 5.72) |

FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody. TPOAb positive: ≥5.61 IU/ml, CI; confidence interval.

The regression coefficients were adjusted with maternal age (<30, 30–34, ≥35 years), education (high school or lower, college/university), birth weight for gestational age (SGA, AGA, LGA), infant feeding pattern during the first 6 months of life (exclusive breast-feeding, mixed feeding, formula feeding), infant passive smoking in the first 2 years (yes, no), and infant age at ASQ-3 assessment.

*p < 0.05.
development at 9 months but not at 24 months of age (44). In this study, a “U”-shaped relationship was found between cord blood FT3 levels and scores in the communication domain in girls. Future confirmation studies are needed.

In general, relatively lower neonatal FT4 levels are associated with suboptimal performance in the communication, fine motor, and personal-social domains in boys. Brain structure and function affected by thyroid hormones may not be global but involve subregions (41). During gestation and the first 2 years of postnatal life, thyroid hormone availability in the brain is under a complex temporal and spatial regulation, exquisitely tailored by the iodothyronine deiodinase system; D2 generates T3 from T4, and the enzyme type 3 deiodinase (D3) protects brain regions from excessive T3 until differentiation is required (38). Thyroid hormone T3 also affects neurodevelopment through activation of the phosphatidylinositol 3-kinase 3-kinase protein kinase AKT (PI3K/AKT) pathway by affecting nitric innervation function (45–47).

It is assumed that TPOAb/thyroglobulin (TgAb) in newborns is of maternal origin, but there is limited information on the association between cord TPOAb/TgAb and neurodevelopment (18). We observed that there was no association between cord blood TPOAb positivity and infant neurodevelopment. Williams et al. also reported no association between the McCarthy score and cord TPOAb, but the Perceptual Performance subscale score was significantly lower in infants with cord TgAb positivity (18). The association between maternal TPOAb positivity and child IQ may partially depend on iodine status (48). A previous study has shown that term-born infants with positive thyroid antibodies had normal thyroid function (18). More studies with larger cohorts are needed to clarify the association between cord TPOAb/TgAb and neurodevelopment in infants.

Our study had some limitations. We did not measure maternal urinary iodine status, but iodine is known to be adequate in this study population because of ubiquitous consumption of iodine salt (49). The study participants are all Chinese, and the findings may not be generalizable to other populations.

CONCLUSION

Mild alterations in thyroid hormones of newborns with maternal euthyroid may affect neurodevelopment during infancy in boys. The results of this study suggest the importance of optimal thyroid hormones status for neurodevelopment in early life.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request for the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FO conceived, designed, conducted the study, analyzed and interpreted the data, and drafted and revised the manuscript. PF analyzed and interpreted the data and drafted the manuscript. Z-CL and JZ contributed to data interpretation and intensively revised the manuscript. YC, LS, WW, and ZL contributed in study conduct and critically revised the manuscript for important intellectual content. All the authors have reviewed and approved the final version of the manuscript as submitted and agree to be accountable for all aspects of the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.773965/full#supplementary-material

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