Effect of Maternal and Neonatal Factors on Neonatal Thyroid Screening Results

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SUMMARY

Background: Thyroid-stimulating hormone (TSH) levels are an important parameter in screening for congenital hypothyroidism (CH). This study aimed to analyze the effects of birth weight, gestational age, and delivery mode on the incidence of neonatal CH.

Methods: A retrospective cohort study of neonates born in 2015 at a maternity hospital in Xiamen, China and their mothers was conducted. Differences in TSH levels, CH positivity at baseline, and the incidence of CH according to gestational age, birth weight, and delivery mode were assessed using matched neonatal and maternal data.

Results: Of the 15,615 enrolled neonates, 150 had positive CH screening results at baseline and nine had confirmed CH. Premature and low-birth-weight neonates had a significantly higher incidence of CH and lower TSH levels when compared to full-term neonates and normal-to-high birth weight neonates, respectively. Neonates delivered vaginally had significantly lower TSH levels and a reduced incidence of baseline CH positivity; cesarean section delivery (odds ratio [OR] = 2.06, p = 0.006) and a maternal TSH level >2.5 mIU/L (OR = 2.37, p = 0.002) were risk factors for CH positivity at baseline.

Conclusions: In this study, the incidence of CH in neonates was associated with gestational age and birth weight. Neonatal baseline CH positivity was positively associated with cesarean delivery and an early-pregnancy maternal TSH level >2.5 mIU/L.


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KEY WORDS
neonate, thyroid-stimulating hormone, baseline screening positivity, risk factors, premature birth, congenital hypothyroidism

What is already known on this topic?
Congenital hypothyroidism (CH) results from thyroid hormone deficiencies during various stages of fetal development and causes neurological and skeletal defects in neonates. Abnormal maternal thyroid function also causes miscarriages, stillbirths, intrauterine growth restriction, premature birth, and congenital deformities. The peripheral blood thyroid-stimulating hormone level is an important CH screening marker.

What this study adds?
Few studies have examined correlations between maternal and newborn TSH levels. Therefore, the current study screened neonates born at a single center to determine the effects of birth weight, gestational age and delivery mode and investigate risk factors for baseline CH positivity and correlations between maternal and neonatal TSH levels.

INTRODUCTION
Congenital hypothyroidism (CH) is caused by a lack of exposure to thyroid hormones during various stages of fetal development, and results in developmental defects in the nervous and skeletal systems of neonates [1]. Abnormal maternal thyroid function can also cause miscarriage, stillbirth, intrauterine growth restriction, premature birth, and congenital deformities [1,2]. The peripheral blood thyroid-stimulating hormone (TSH) level is considered an important CH screening marker. Although significant advances in the field of CH research have recently been made, few studies have investigated the effects of birth weight, gestational age, mode of delivery, and other factors in neonates on CH incidence and TSH levels, and even fewer have subjected these factors to multifactorial analyses. Other studies have investigated the association between maternal TSH levels during early pregnancy and mental development in children [3], but few have evaluated correlations between maternal and newborn TSH levels, and the results of existing studies are somewhat controversial. Therefore, the present study aimed to subject neonates born in 2015 at the Xiamen Maternity and Child Care Hospital in China to CH screening and to analyze the effects of birth weight, gestational age, and delivery mode on the CH screening results. Additionally, this study aimed to investigate the risk factors for baseline CH positivity and evaluate the correlation between maternal and neonatal TSH levels.

MATERIALS AND METHODS

Study Population
This study included neonates born in 2015 at the Xiamen Maternity and Child Care Hospital, Fujian Province, China for whom complete data on gestational age, birth weight, and delivery mode were available. The study also included a sub-analysis of neonates whose mothers had registered at the hospital and had undergone TSH testing during early pregnancy (gestation: 1 - 3 months) to ascertain risk factors for CH positivity at baseline. This study was approved by the Ethics Committee of Xiamen Maternity and Child Care Hospital and conducted according to the principles of the Declaration of Helsinki.

Sample collection
Blood samples were obtained from neonates from 48 hours up to 7 days post-birth. The collected blood spots were 1.5 - 2.0 cm in diameter without clots and were dried for 4 - 6 hours at room temperature prior to storage in sealed plastic bags in a 4°C refrigerator. Venous blood was drawn from mothers during early pregnancy for serum TSH measurements.

Initial screening of neonates
As a marker of CH, the TSH values in blood spots were measured using a time-resolved fluorescence immunoassay (TRFIA) and a DELFIA-1420 TRFIA analyzer (Perkin-Elmer, Waltham, MA, USA). A TSH value > 9 mIU/L was considered to indicate CH positivity at baseline.

Confirmatory CH diagnosis in neonates and maternal TSH levels
Mothers of neonates who received positive CH screening results at baseline were informed within 24 hours for a review and confirmation of the diagnosis. At that time, venous blood was obtained and the serum levels of TSH and free thyroxine (FT4) were measured using chemical fluorescence assays and a UniCel® DxI 800 Immunoassay System (Beckman Coulter, Brea, CA, USA) and the attached reagent box, respectively. CH was diagnosed if the neonate had a TSH level > 9 mIU/L and FT4 level < 0.6 ng/dL [4]. Chemical fluorescence was used to measure the maternal serum TSH level during early pregnancy, using a reference range of 0.1 - 2.5 mIU/L based on the early gestation guidelines of the American Thyroid Association [5].

Definitions of gestational age and birth weight
The neonates were stratified by gestational age, birth weight, and delivery mode (vaginal versus cesarean). Gestational ages of < 37 weeks, 37 - 42 weeks, and > 42 weeks were defined as premature, full-term, and post-term, respectively. Birth weights of < 2,500 g, 2,500 - 4,000 g, and > 4,000 g were defined as low, normal, and high birth weights, respectively.
CH screening results
In 2015, 15,697 neonates were born at the Xiamen Maternity and Child Care Hospital; of these, 82 were excluded because of incomplete data on the gestational age, birth weight, and delivery mode. A total of 15,615 (54.3% male [n = 8,485]) neonates were enrolled in the study; 9,680 (62.0%) were delivered vaginally, and the median gestational age and birth weight were 39.2 weeks (IQR: 38.3 - 40.1 weeks) and 3,205 g (IQR: 2,995 - 3,514 g), respectively. Of the 150 neonates who screened positive for CH at baseline (positivity rate: 1/104), nine were confirmed to have CH (incidence: 1/1,495). The maternal and neonatal data associated with the neonates with confirmed CH are shown in Table 2.

The results of the multiple logistic regression analysis to determine the factors influencing baseline CH positivity in neonates are shown in Table 4. Caesarean section as a delivery mode and a maternal TSH level > 2.5 mIU/L were identified as risk factors for baseline CH positivity in neonates (p < 0.05). Neonatal gender, gestational age, birth weight, and maternal age were not statistically significant risk factors for baseline CH positivity in neonates (p > 0.05).

Correlation between newborn TSH levels and maternal TSH levels during early pregnancy
Data from 4,804 matched cases of normal maternal and neonatal TSH levels were subjected to a correlation analysis and linear regression. The results showed that maternal TSH levels correlated positively with newborn TSH levels (r = 0.05, p = 4.3 \times 10^{-5}; \beta = 0.13 (0.04) mIU/L, p = 0.001). This correlation remained after correcting for neonatal gender, gestational age, birth weight, delivery mode, and maternal age (\beta = 0.13 (0.04) mIU/L, p = 0.001).

DISCUSSION
In this study, we aimed to investigate the correlation between CH positivity in neonates and maternal TSH levels, as well as the relationship between neonate and maternal TSH levels. We observed a CH incidence of 1/1,735 among neonates born in 2015 at the Xiamen Maternity and Child Care Hospital, which was higher than the incidence reported in China in 2004 (1/3,009) [6]. A neonatal TSH value > 5 mIU/L was used to define CH positivity in accordance with the joint recommendations of the World Health Organization (WHO), United Nations Children's Fund (UNICEF), and International Council for the Control of Iodine Deficiency Disorders.
Table 1. Congenital hypothyroidism screening results and TSH levels in neonates stratified by gestational age, birth weight, and mode of delivery (n = 15,615).

<table>
<thead>
<tr>
<th>Strata</th>
<th>Screened (n = 15,615)</th>
<th>Baseline CH&lt;sup&gt;a&lt;/sup&gt; positivity (n)</th>
<th>Baseline CH&lt;sup&gt;a&lt;/sup&gt; positivity rate</th>
<th>Confirmed CH&lt;sup&gt;a&lt;/sup&gt; diagnosis (n)</th>
<th>Incidence</th>
<th>Median TSH&lt;sup&gt;b&lt;/sup&gt; levels (mIU/L) (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature</td>
<td>1,232</td>
<td>11</td>
<td>1/112</td>
<td>3</td>
<td>1/411</td>
<td>1.61 (0.96 - 2.56)</td>
</tr>
<tr>
<td>Full-term</td>
<td>14,378</td>
<td>139</td>
<td>1/103</td>
<td>6</td>
<td>1/2,396</td>
<td>1.84 (1.04 - 3.12)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-term</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.42 (0.72 - 1.98)</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1,214</td>
<td>11</td>
<td>1/110</td>
<td>3</td>
<td>1/405</td>
<td>1.61 (0.96 - 2.59)</td>
</tr>
<tr>
<td>Normal</td>
<td>13,875</td>
<td>130</td>
<td>1/101</td>
<td>6</td>
<td>1/2,313</td>
<td>1.84 (1.04 - 3.11)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>High</td>
<td>526</td>
<td>9</td>
<td>1/58</td>
<td>0</td>
<td>0</td>
<td>1.96 (1.09 - 3.44)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Delivery mode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>9,680</td>
<td>75</td>
<td>1/129</td>
<td>6</td>
<td>1/1,613</td>
<td>1.77 (1.00 - 2.98)</td>
</tr>
<tr>
<td>Cesarean</td>
<td>5,935</td>
<td>75</td>
<td>1/79</td>
<td>3</td>
<td>1/1,978</td>
<td>1.93 (1.09 - 3.29)</td>
</tr>
</tbody>
</table>

<sup>a</sup> - CH: congenital hypothyroidism, <sup>b</sup> - TSH: thyroid-stimulating hormone; IQR: interquartile rate; <sup>*</sup> p < 0.001, compared with premature neonates, <sup>**</sup> p < 0.001, compared with low-birth-weight neonates.

Table 2. Neonates with confirmed congenital hypothyroidism diagnosis and matched maternal data (n = 4/5,979 screened subjects).

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Newborn gender</th>
<th>Gestational age (weeks)</th>
<th>Newborn weight (g)</th>
<th>Newborn FT4&lt;sup&gt;a&lt;/sup&gt; (ng/dL)</th>
<th>Newborn TSH&lt;sup&gt;b&lt;/sup&gt; (mIU/L)</th>
<th>Maternal age (years)</th>
<th>Maternal TSH&lt;sup&gt;b&lt;/sup&gt; levels during early pregnancy (mIU/L)</th>
<th>Gestational diabetes</th>
<th>Gestational hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>32.3</td>
<td>1,760</td>
<td>0.40</td>
<td>&gt; 100.0</td>
<td>32</td>
<td>0.91</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>40.4</td>
<td>3,300</td>
<td>&lt; 0.25</td>
<td>&gt; 100.0</td>
<td>31</td>
<td>2.17</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>40.0</td>
<td>3,515</td>
<td>&lt; 0.25</td>
<td>&gt; 100.0</td>
<td>31</td>
<td>1.87</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>41.4</td>
<td>3,375</td>
<td>&lt; 0.25</td>
<td>&gt; 100.0</td>
<td>22</td>
<td>5.33</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> FT4 - free thyroxine, <sup>b</sup> TSH - thyroid-stimulating hormone.

Table 3. Risk factors and assignment method and stratification for the multiple unconditional logistic regression analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Assignment method and stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender of infant</td>
<td>Male = 0; Female = 1</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Premature birth (&lt; 37 weeks) = 0, non-premature birth (≥ 37 weeks) = 1</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Normal birth weight (2,500 - 4,000 g) = 1, low birth weight (&lt; 2,500 g) = 2, high birth weight (≥ 4,000 g) = 3</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>Vaginal delivery = 0, Cesarean section = 1</td>
</tr>
<tr>
<td>Maternal age</td>
<td>&lt; 30 years = 1, 30 - 35 years = 2, ≥ 35 years = 3</td>
</tr>
<tr>
<td>Maternal TSH&lt;sup&gt;a&lt;/sup&gt; level</td>
<td>≤ 2.5 mIU/L = 0, &gt; 2.5 mIU/L = 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> TSH - thyroid-stimulating hormone.
Maternal TSH and Neonatal CH Screening

Table 4. Results of a multiple unconditional logistic regression analysis of factors influencing baseline congenital hypothyroidism positivity in neonates.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>B value</th>
<th>Standard error</th>
<th>Wald value</th>
<th>Odds Ratio</th>
<th>95% CI a</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.066</td>
<td>0.264</td>
<td>0.062</td>
<td>0.936</td>
<td>0.558</td>
<td>1.570</td>
</tr>
<tr>
<td>Non-premature birth</td>
<td>-0.013</td>
<td>0.700</td>
<td>0.000</td>
<td>0.987</td>
<td>0.250</td>
<td>3.891</td>
</tr>
<tr>
<td>Normal birth weight</td>
<td></td>
<td></td>
<td>2.329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.079</td>
<td>0.701</td>
<td>0.013</td>
<td>1.082</td>
<td>0.274</td>
<td>4.276</td>
</tr>
<tr>
<td>High birth weight</td>
<td>0.731</td>
<td>0.479</td>
<td>2.326</td>
<td>2.076</td>
<td>0.812</td>
<td>5.309</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>0.724</td>
<td>0.266</td>
<td>7.444</td>
<td>2.064</td>
<td>1.226</td>
<td>3.473</td>
</tr>
<tr>
<td>Maternal age &lt; 30 years</td>
<td></td>
<td></td>
<td>0.109</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age 30 - 35 years</td>
<td>-0.094</td>
<td>0.291</td>
<td>0.104</td>
<td>0.910</td>
<td>0.514</td>
<td>1.612</td>
</tr>
<tr>
<td>Maternal age ≥ 35 years</td>
<td>0.000</td>
<td>0.485</td>
<td>0.000</td>
<td>1.000</td>
<td>0.387</td>
<td>2.588</td>
</tr>
<tr>
<td>Maternal TSH b &gt; 2.5 mIU/L</td>
<td>0.862</td>
<td>0.280</td>
<td>9.455</td>
<td>2.368</td>
<td>1.367</td>
<td>4.103</td>
</tr>
</tbody>
</table>

CCI - Confidence interval, b TSH - thyroid-stimulating hormone.

(ICCIDD) [7]. A CH incidence < 3.0% indicates acceptable iodine uptake within a given region, whereas incidences of 3.0 - 19.9% suggest mild iodine deficiency. In our study, 8.5% of the 15,619 included neonates had a TSH value > 5 mIU/L, indicating that the Xiamen region faces mild iodine deficiency. La Franchi [8] reported that the thyroid gland matures more slowly at lower gestational ages, which affects the development of the hypothalamus-pituitary gland-thyroid axis and increases the risk of CH development. Upon premature birth, a negative iodine balance during the first few weeks of life results in the use of brown fat for heat production and immature tissue responses to thyroid hormones [9]. Similarly, we observed lower levels of TSH and a higher incidence of CH in premature neonates relative to full-term neonates. However, our study included only a small number of post-term neonates, potentially because pregnant mothers with at > 42 weeks' gestation selected cesarean section as the delivery mode, and we lacked confirmed cases in this group for comparison.

Waller et al. [10] observed a higher CH incidence among neonates with both low and high birth weights. Those with low birth weights mostly had intrauterine developmental defects that may have been accompanied by abnormal thyroid development [11]. Another study by Larson et al. also proved that low birth weight is a risk factor for CH [12]. Similarly, we observed a higher CH incidence among neonates with low birth weights, compared to those with normal birth weights; by contrast, no confirmed cases of CH positivity were observed among the high-birth-weight neonates, and thus could not be included in the statistical analysis. Low-birth-weight neonates also had lower TSH levels, compared with normal- and high-birth-weight neonates. Primary screening for congenital hypothyroidism might not be able to identify neonates with delayed rise in TSH, and a recent guideline recommended repeating screening in premature and low-birth-weight neonates [13]. In our study, the repeated specimens were collected at 2 weeks of age, or 2 weeks after the first screening.

Bird et al. [14] found that vaginally delivered neonates had significantly lower TSH and thyroid hormone levels when compared with their counterparts delivered via cesarean section. This finding was attributed to physical compression during vaginal delivery, which increases the production of TSH and thyroid hormone levels within a half-hour to an hour after birth, as well as subsequent negative feedback regulation, which causes the TSH levels to decrease thereafter. In our study, the baseline CH positivity rate and TSH levels were significantly lower in vaginally delivered neonates than in neonates delivered via cesarean section. Our multiple logistic regression analysis supported these findings and indicated that the risk of baseline CH positivity increased by 2.06 times among neonates delivered via cesarean section, compared to those delivered vaginally. During early development, the fetus generally derives thyroid hormones from the mother; the pituitary gland-thyroid axis becomes functionally active and matures later during development. Therefore, maternal thyroid functionality during early pregnancy can directly influence the early development of the fetal thyroid gland [15]. Bajoria and Fisk [16] were the first to discover that small amounts of TSH could be transferred through the placenta wall, and Shields et al. [17] were the first to identify a positive correlation between maternal FT4 levels at 28 weeks of gestation and newborn cord blood FT4 levels in 616 matched pairs. Although a similar correlation was not observed for TSH levels in the latter study, the sample size was small, and matched maternal and child subjects with abnormal TSH levels were not excluded. However, Medici et al. [18] observed a positive correlation between maternal and neonatal TSH levels in 2,424 matched pairs with normal TSH levels.
We demonstrated an association of the incidence of CH with gestational age and birth weight in a cohort of neonates, as well as an association of baseline CH positivity with cesarean delivery and a maternal TSH level > 2.5 mIU/L. Furthermore, we identified a positive correlation between neonatal and maternal TSH levels during early pregnancy. The specific mechanisms behind this correlation should be explored in greater detail in future studies.

CONCLUSION

We demonstrated an association of the incidence of CH positivity when compared to neonates whose mothers had TSH levels < 2.5 mIU/L. This finding could be explained by the ability of FT4 to cross the placenta, thus impacting thyroid function, or by the mutual dependence of the mother and neonate on the iodine supply [19]. There were several limitations of note in this study. Given the small number of confirmed cases, a multiple logistic regression was not used to analyze risk factors for the incidence of CH. Additionally, the current study was performed at a single center. More comprehensive data could be obtained if future studies included multiple sites.

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Declaration of Interest:
All authors declare no competing financial interests.

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