Subclinical Hypothyroidism in Korean Preterm Infants Associated with High Levels of Iodine in Breast Milk

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Context: The dietary iodine intake of lactating women has been reported to be high in Korea.

Objectives: The aim of this study was to assess iodine balance and to determine its relationship with thyroid function in preterm infants.

Design: Thyroid functions of preterm infants born at 34 wk gestation or less were evaluated in the first (n = 31) and third (n = 19) weeks. Mothers’ breast milk (BM) and random urine samples of infants were taken on the same days for thyroid function tests.

Results: Iodine concentrations in BM were very high (198–8484 μg/liter), and one third of the infants had an iodine intake of more than 100 μg/kg per day at the third week after birth (excessive iodine intake group). At that time, the levels of TSH were positively correlated with urinary iodine (r = 0.622; P = 0.004). The frequencies of subclinical hypothyroidism were high in the excessive iodine intake group at the third and sixth weeks. The estimated daily iodine intake at the third week (51.2 ± 45.5 vs. 149.0 ± 103.8 μg/kg per day; P = 0.033), urinary iodine at the third week (913.2 ± 1179.7 vs. 1651.3 ± 1135.2 μg/liter; P = 0.051), and estimated daily iodine intake at the sixth week (32.8 ± 35.5 vs. 92.1 ± 51.2 μg/kg per day; P = 0.032) were significantly higher in infants with subclinical hypothyroidism than in controls.

Conclusions: Excessive iodine intake from BM contributed to subclinical hypothyroidism in these preterm Korean infants. (J Clin Endocrinol Metab 94: 4444–4447, 2009)
Iodine contents in the breast milk (BM) of lactating mothers have been reported to be higher in Korea than in other iodine-sufficient countries because postpartum women traditionally have consumed brown seaweed soups, which contain abundant iodine (3, 12). The effects of excessive iodine from BM on the thyroid function of preterm infants have not yet been elucidated. Therefore, the aims of this study were to assess iodine intake and urinary excretion patterns in preterm Korean infants and to determine the relationship between iodine balance and thyroid function.

Subjects and Methods

Of 69 preterm infants born at 34 wk gestation or less and admitted to the neonatal intensive care unit of Seoul National University Bundang Hospital between October 2007 and June 2008, 31 infants whose parents gave consent for study and who underwent thyroid function tests at the first week after birth were included in this study. The mean gestational age (GA) of the study group was 30.1 ± 2.8 (range, 24.1–34.0) wk, and the mean birth weight (BW) was 1.34 ± 0.46 (0.60–2.37) kg. Infants born to mothers who had been diagnosed previously with thyroid disease or who had used iodine-containing medications were excluded. Thyroid function tests were repeated in 19 and 10 babies at the third and sixth weeks, respectively; and 12 and 9 babies who were discharged, who expired, or who were administered l-thyroxine supplementation dropped out from the study at the third and sixth weeks. Clinical data, such as GA, BW, Apgar score at 5 min, the development of respiratory distress syndrome requiring surfactant supplementation, and chronic lung disease (duration of oxygen requirement ≥ 4 wk) were analyzed. This study was approved by the Institutional Ethics Committee of the participating institution.

Thyroid function tests

Serum-free thyroxine (FT₄) was measured using a RIA kit (RIA-gnost FT₄; CIS Bio International, Gif-Sur-Yvette, France) and TSH by an immunoradiometric assay (TSH-CKT-3; Dia-Sorin, Saluggia, Italy) at the first, third, and sixth weeks after birth. Random samples of urine from the infants and BM from the mothers were collected for measuring iodine concentrations on the same days as the thyroid function tests, and the specimens were frozen at −20 °C until analyzed.

Measurement of iodine concentrations

Urinary iodine (UI) concentrations and iodine concentrations in BM (BMI) were measured colorimetrically using the Sandell–Kolhoff reaction (13, 14). Each sample was measured in duplicate (coefficient of variation, 3.9%). Estimated daily iodine intake (EDI) was calculated from the amount of BM taken and the iodine concentration in the milk. The amount of feeding was calculated as the mean volume of intake between 2 d before sampling and the day of sampling because daily amounts of feeding varied markedly in some infants. The mean iodine concentration of the formulas fed to premature infants was estimated to be 75 μg/liter, based on the composition of standard formulas for preterm infants provided by manufacturing companies in Korea. Any iodine intake from parenteral fluid was neglected because it has an extremely low concentration of iodine.

TABLE 1. Comparison of thyroid function according to EDI and UI concentration

<table>
<thead>
<tr>
<th>Postnatal age</th>
<th>EDI (μg/kg per day)</th>
<th>UI concentration (μg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30</td>
<td>30–100</td>
</tr>
<tr>
<td>First week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA (wk)</td>
<td>n = 21</td>
<td>n = 3</td>
</tr>
<tr>
<td>FT₄ (ng/dl)</td>
<td>29.5 ± 2.9</td>
<td>31.6 ± 3.0</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>4.37 ± 2.70</td>
<td>5.99 ± 3.42</td>
</tr>
<tr>
<td>Third week</td>
<td>n = 6</td>
<td>n = 7</td>
</tr>
<tr>
<td>GA (wk)</td>
<td>29.1 ± 4.0</td>
<td>28.5 ± 1.7</td>
</tr>
<tr>
<td>FT₄ (ng/dl)</td>
<td>1.26 ± 0.42</td>
<td>1.61 ± 0.41</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>4.37 ± 2.26</td>
<td>10.64 ± 6.65</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>(0%)</td>
<td>(57%)</td>
</tr>
<tr>
<td>Sixth week</td>
<td>n = 5</td>
<td>n = 2</td>
</tr>
<tr>
<td>GA (wk)</td>
<td>27.4 ± 2.0</td>
<td>28.1 ± 0.2</td>
</tr>
<tr>
<td>FT₄ (ng/dl)</td>
<td>1.40 ± 0.40</td>
<td>1.15 ± 0.13</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>5.64 ± 3.27</td>
<td>10.07 ± 8.58</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>(20%)</td>
<td>(50%)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD. The percentage of subjects with subclinical hypothyroidism was calculated from the number of infants with subclinical hypothyroidism and the total number of infants in each respective group.

EDI was grouped based on Ref. 2.
UI was grouped based on the suggestion in Ref. 3.
P comparing EDI less than 30 and 30–100 μg/kg/day.
P comparing EDI 30–100 and more than 100 μg/kg/day.
The median BMi values were 25.29 (range, 35.5–84.84), 11.53 (198–3791), and 82.2 (236–183.6) μg/liter at the first, third, and sixth weeks, respectively. The values of FT₄, TSH, and the frequency of subclinical hypothyroidism according to EDi and UI are shown in Table 1. Subclinical hypothyroidism was frequently observed in infants who had excessive iodine intake or excretion.

At the first week, the FT₄ level was positively correlated with GA (r = 0.726; P < 0.001) and with BW (r = 0.535; P = 0.002) but was not significantly correlated with the UI or EDi. TSH levels were positively correlated with GA (r = 0.380; P = 0.035), UI (r = 0.381; P = 0.034), and EDi (r = 0.366; P = 0.043). However, the TSH level was not significantly correlated with UI or EDi after adjusting for GA.

At the third week, the FT₄ level was not significantly correlated with GA, BW, UI, or estimated iodine intake. The TSH level at the third week was positively correlated with UI (r = 0.622; P = 0.004) and with the mean iodine intake over 3 wk (r = 0.509; P = 0.026) but was not significantly correlated with GA or BW.

When EDi and UI were compared between infants with subclinical hypothyroidism and controls, the EDi at the third week, UI at the third week, and EDi at the sixth week were significantly higher in infants with subclinical hypothyroidism than in controls (Fig. 1).

**Discussion**

The iodine concentrations in BM were very high, and a subclinical hypothyroidism was prominent in these preterm infants with excessive iodine intake from BM. The daily iodine requirement of preterm infants is more than twice that of term infants because they show a much lower retention of iodine (2). In contrast to the previous results which most lactating Korean mothers ingest brown seaweed (Undaria pinnatifida) soup daily, their iodine intake or excretion was not significantly correlated with UI or EDi after adjusting for GA.

When EDi and UI were compared between infants with subclinical hypothyroidism and controls, the EDi at the third week, UI at the third week, and EDi at the sixth week were significantly higher in infants with subclinical hypothyroidism than in controls (Fig. 1).
iodine in the lactating mother can be transferred directly to the baby. The thyroid-suppressive effect of excessive iodine in preterm infants is known to be remarkable because the Wolff-Chaikoff effect can be increased by the impairment of iodine organification in the human fetus (17, 18). Additionally, the escape phenomenon does not occur in third trimester fetuses before 35 wk of GA (18).

This study had limitations in that the low number of subjects resulted in weak statistical power. Moreover, there was potential impact of selection bias because of the limited initial inclusion of subjects among all the infants admitted into the neonatal intensive care unit, and the limited follow-up at the third and sixth weeks. Nevertheless, this study clearly showed that excessive iodine intake from BM can cause subclinical hypothyroidism in preterm infants.

It is known that iodine deficiency can also cause thyroid dysfunction and is partially responsible for the hypothyroxinemia found in preterm infants (19), although there is no evidence of the effect of iodine supplementation on thyroid hormone levels of preterm infants (20). Because our results showed that the thyroid function of infants with a low iodine intake was not impaired significantly, it can be postulated that transient iodine deficiency might not influence thyroid function among preterm infants, especially in iodine-sufficient areas.

UI showed a good positive correlation with EDi and the levels of TSH in this study. We did not correct UI for urinary creatinine level because the urinary iodine/creatinine ratio is unreliable, particularly when protein intake is low (2) and because urinary creatinine has no significant correlation with the GA, BW, or body length of preterm infants (4). The UI might be a simple and reliable marker for the evaluation of iodine balance in preterm infants, although the optimal ranges of UI are not clear in term and preterm neonates (3), and the present study could not clarify the ranges because of the small number of subjects.

This study showed that excessive iodine intake from BM caused subclinical hypothyroidism in these preterm Korean infants. Optimizing the dietary iodine intake of lactating mothers is necessary, and further studies are warranted to elucidate the optimal ranges of iodine intake and excretion in preterm and term infants.

Acknowledgments

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References