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 is a rate-limiting element for the synthesis of thyroid hormones. During gestation, iodine is transferred through the placenta (1), and milk appears to be the major source of iodine after birth, especially during the neonatal period (2). Because thyroid hormone plays an important role in the neurodevelopment of fetuses and neonates, an adequate iodine supply is important for preterm infants, and the recommended iodine intake for preterm infants ranges from 30 to 100 μg/kg per day (2, 3). However, a high incidence of iodine deficiency in preterm infants has been reported, because such infants have been permitted to ingest a small amount of milk during the early postnatal period and the parenteral fluid provided contained only small amounts of iodine (3–5). On the other hand, preterm infants are sensitive to thyroid suppression by iodine excess, and sporadic cases of hypothyroidism in preterm infants caused by excessive iodine have been reported (6–9).

In our previous study of thyroid function of 105 preterm infants, the incidence of thyroid dysfunction was high. In addition, a TSH elevation after 1 wk of postnatal age was prominent in preterm infants of more than 30 wk gestation (10), which was contrary to the result of a study conducted in Europe in which such TSH elevation was higher and longer in duration in infants at less than 28 wk than for at least 28 wk gestation (11).

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Abbreviations: BM, Breast milk; BMi, iodine concentrations in BM; BW, birth weight; EDi, estimated daily iodine intake; FT_4, free thyroxine; GA, gestational age; UI, urinary iodine.

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 (FT_4) 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; DiaSorin, 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–Kolthoff 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

	EDi (μg/kg per day)[a]				UI concentration (μg/liter)[b]			
Postnatal age	<30	30–100	>100	*P*	<180	180–225	>225	*P*
First week	n = 21	n = 3	n = 7		n = 20	n = 0	n = 11	
GA (wk)	29.5 ± 2.9	31.6 ± 3.0	31.2 ± 1.7	0.256	29.4 ± 2.7		31.2 ± 2.7	0.066
FT_4 (ng/dl)	1.42 ± 0.49	1.93 ± 1.01	1.55 ± 0.47	0.542	1.40 ± 0.50		1.68 ± 0.61	0.239
TSH (μU/ml)	4.37 ± 2.70	5.99 ± 3.42	5.30 ± 4.50	0.615	4.03 ± 2.69		6.01 ± 3.69	1.07
Third week	n = 6	n = 7	n = 6		n = 3	n = 0	n = 16	
GA (wk)	29.1 ± 4.0	28.5 ± 1.7	30.3 ± 2.1	0.539	29.1 ± 2.7		29.3 ± 2.8	0.154
FT_4 (ng/dl)	1.26 ± 0.42	1.61 ± 0.41	1.31 ± 0.48	0.238	1.08 ± 0.37		1.47 ± 0.44	0.314
TSH (μU/ml)	4.37 ± 2.26	10.64 ± 6.65	14.98 ± 12.13	0.074	3.06 ± 2.77		11.34 ± 8.87	0.025
Subclinical hypothyroidism	n = 0 (0%)	n = 4 (57%)	n = 4 (67%)	0.070[c] 1.000[d] 0.061[e]	n = 0 (0%)	n = 0 (0%)	n = 8 (50%)	0.228
Sixth week	n = 5	n = 2	n = 3		n = 1	n = 0	n = 9	
GA (wk)	27.4 ± 2.0	28.1 ± 0.2	28.7 ± 4.3	0.844	28.3		27.9 ± 2.6	0.860
FT_4 (ng/dl)	1.40 ± 0.40	1.15 ± 0.13	0.82 ± 0.04	0.049	1.13		1.18 ± 0.40	0.862
TSH (μU/ml)	5.64 ± 3.27	10.07 ± 8.58	23.90 ± 9.93	0.072	8.24		12.43 ± 10.80	0.862
Subclinical hypothyroidism	n = 1 (20%)	n = 1 (50%)	n = 3 (100%)	1.000[c] 0.400[d] 0.143[e]	n = 0 (0%)	n = 0 (0%)	n = 5 (56%)	1.000

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.

[a] EDi was grouped based on Ref. 2.

[b] UI was grouped based on the suggestion in Ref. 3.

[c] *P* comparing EDi less than 30 and 30–100 μg/kg/day.

[d] *P* comparing EDi 30–100 and more than 100 μg/kg/day.

[e] *P* comparing EDi less than 30 and more than 100 μg/kg/day.

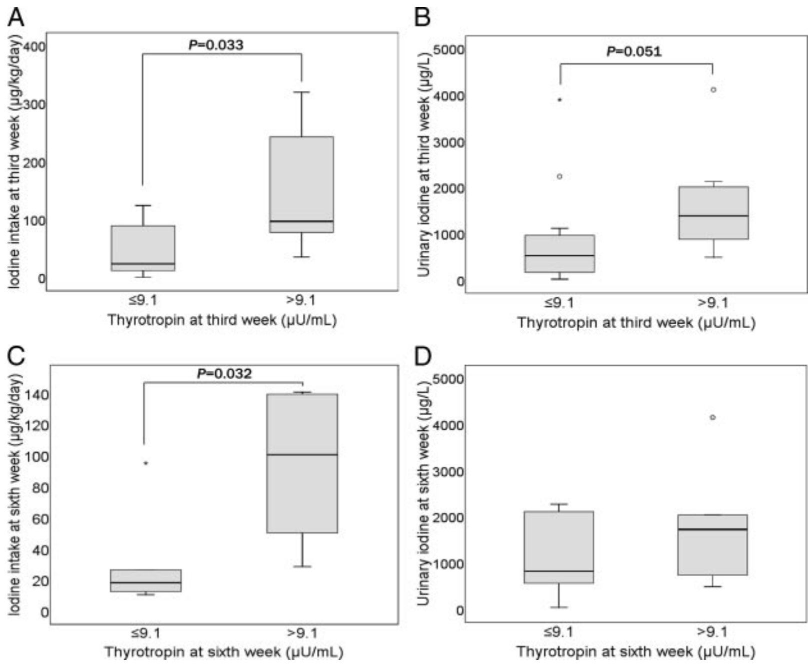

FIG. 1. Comparison of EDi and UI at the third and sixth week in infants with subclinical hypothyroidism and in controls. At the third week, EDi (51.2 ± 45.5 *vs.* 149.0 ± 103.8 μg/kg per day) (A) and UI (913.2 ± 1179.7 *vs.* 1651.3 ± 1135.2 μg/liter) (B) were significantly higher in infants with subclinical hypothyroidism (n = 11) than in controls (n = 8), respectively. At the sixth week, EDi values (32.8 ± 35.5 *vs.* 92.1 ± 51.2 μg/kg per day) (C) were significantly higher in infants with subclinical hypothyroidism (n = 5) than in controls (n = 5), respectively, and UI values (1166.1 ± 982.9 *vs.* 1831.9 ± 1450.8 μg/liter) (D) were not significantly different between the two groups.

Definitions

Subclinical hypothyroidism was defined as a normal FT_4 level in conjunction with a TSH level of more than 9.1 μU/ml after 1 wk of postnatal age (15). Low iodine intake was defined when the estimated iodine intake was less than 30 μg/kg per day, and high iodine intake was defined when the estimated iodine intake was at least 100 μg/kg per day, based on a report by the Food and Agriculture Organization of the United Nations/World Health Organization (2). The range of 180–225 μg/liter of UI concentrations was considered optimal based on a report by the International Council for Control of Iodine Deficiency Disorder (3).

Statistical analysis

Data are expressed as the mean ± SD or as medians and ranges. Differences between groups were compared using the Mann-Whitney nonparametric *U* or Kruskal-Wallis tests. Spearman correlation and partial correlation tests were used to test for any correlation between two variables such as UI, EDi, and BMi. All calculations were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL), and $P < 0.05$ was considered statistically significant.

Results

The median BMi values were 2529 (range, 355–8484), 1153 (198–3791), and 822 (236–1836) μg/liter at the first, third, and sixth weeks, respectively. The values of FT_4, 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 FT_4 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 FT_4 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 that most preterm infants show iodine deficiency (4, 5), a third of the subjects in the present study had excessive iodine intake at the third and sixth weeks after birth, which is unusual among preterm infants in other countries. Because most lactating Korean mothers ingest brown seaweed (*Undaria pinnatifida*) soup daily, their iodine intakes are more than 2000 μg/d during the early postpartum period (12). The intake of brown seaweed soup typically decreases gradually during the postpartum period, and the mothers return to a normal diet after about 1 month. The changes in the iodine concentration of BM in our study might be attributed to this dietary preference among postpartum Korean mothers. Because the sodium/iodide symporters are expressed in the mammary gland, iodide can be concentrated in the BM (16), and the excessive 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.

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