Thyroid Function in Early Pregnancy in Japanese Healthy Women: Relation to Urinary Iodine Excretion, Emesis, and Fetal and Child Development

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Context: The effect of constant rich iodine intake, especially during pregnancy, has not been well understood.

Objective: The objective was to examine urinary iodine excretion and thyroid function in early pregnancy in Japanese healthy women. We also studied fetal maturation and child development in these women.

Design and Setting: This study was an observational, prospective study conducted at a maternity hospital.

Subjects: Subjects were 622 pregnant women who visited a maternity hospital consecutively in early gestation. Subjects with positive thyroid antibodies were excluded, and finally 514 subjects were examined. Offspring subjects were infants born to the maternal subjects.

Main Outcome Measures: Thyroid function, serum thyroperoxidase antibodies, and urinary concentrations of iodine were measured at the initial obstetrical visit. The fetal maturation scores estimated by the Dubowitz and Ballard methods in newly born infants were assessed. A child developmental test was performed using the Enjoji Scale up to 12 months of age.

Results: The distribution of urinary iodine concentrations was large, and the average was extremely high. There were significant positive correlations between urinary iodine and serum TSH ($r = 0.1326$; $P < 0.005$). Serum TSH during early pregnancy in mothers had no relevance to parameters in neonates, scores of fetal maturation, or child developmental testing in their infants.

Conclusions: Iodine excess during early pregnancy seems to have no adverse effects on the fetus in healthy Japanese women. To avoid hypothyroidism, reducing excess dietary iodine intake to moderate intake may be beneficial for pregnant woman in Japan. **(*J Clin Endocrinol Metab* 94: 1683–1688, 2009)**

Worldwide, iodine deficiency is still a major problem in public health (1). Because hypothyroidism due to iodine deficiency in pregnant women has an adverse effect on the fetus, they should increase their intake of iodine. The ideal dietary allowance of iodine recommended by the World Health Organization (WHO) and the International Council for Control of Iodine Deficiency Disorders has been 200 μg/d for pregnant women since 1996 (2). Recently, it was recommended to increase the iodine intake of pregnant and lactating women to 250 μg/d (range 200–300) by the WHO (3). The Clinical Guidelines committee of The Endocrine Society has the same recommendation (4).

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Abbreviations: Cr, Creatinine; FT_4, free FT_4; FT_3, free T_3; TBII, TSH binding inhibitor immunoglobulin; TPOAb, thyroperoxidase antibody; WHO, World Health Organization.

On the other hand, the effect of constant excess iodine intake on the human body is known to induce hypothyroidism. It has been reported that when 27 mg iodine was given daily to 10 normal males for 4 wk, subclinical hypothyroidism developed in two subjects (5). Konno *et al.* (6) reported that hypothyroidism is more prevalent and marked in subjects consuming further excessive amounts of iodine. However, its effect in pregnancy has not been studied. The upper limit of dietary iodine intake is variable because it is affected by the level of iodine intake before exposure to iodine excess and age. Thyroids with a moderate iodine deficiency and neonatal thyroids are sensitive to the Wolff-Chaikoff effect and may be more likely to develop iodine-induced hypothyroidism (7). The WHO recommended an upper limit of iodine intake of 1.5 to three times higher than the average intake in premature infants in areas of moderate iodine deficiency (8). They also stated that the probable safe upper limits are 15–20 times higher than the recommended intakes (40 μg/kg · d in pregnant women) in areas of iodine sufficiency. The guideline of The Endocrine Society indicated that iodine intake during pregnancy should not exceed twice the daily recommended nutritional intake for iodine, *i.e.* 500 μg iodine/d (4). The Health, Labor and Welfare Ministry in Japan recommended an upper limit of iodine intake for adults and pregnant women of 3000 μg iodine/d in Japan, which is known to have an iodine-rich dietary culture (9). However, evidence for the upper limit of iodine intake during pregnancy is unclear.

To test the hypotheses that excess iodine intake may increase hypothyroidism or subclinical hypothyroidism in normal pregnant women and may influence their babies' maturation and development, we studied urinary iodine excretion and thyroid function in early pregnancy in Japanese healthy women. We also studied fetal maturation of newly born infants and child development in the subjects' offspring. This is the first study to examine the relation between urinary iodine excretion and thyroid function in pregnant women exposed to dietary iodine excess.

Subjects and Methods

Subjects

A total 622 consecutive pregnant women newly visited the Palmore hospital (for obstetrical advice: Kobe, Japan) for their first checkup during early pregnancy between July 2005 and January 2006. There were 54 women who were not Japanese or who had complications, including thyroid disorders, excluded. All subjects were at 7–15 wk gestation calculated from the last menstrual period and verified by ultrasonography. Informed consent was obtained from each subject. Protocols were approved by the ethics committees of the Palmore and Kuma hospitals.

Mothers

Serum concentrations of TSH, free T_4 (FT_4), free T3 (FT_3), and thyroperoxidase antibodies (TPOAbs) were measured at the initial obstetrical visit. Urinary iodine and creatinine (Cr) concentrations in single-voided urinary specimens were measured simultaneously. Serum TSH binding inhibitor immunoglobulin (TBII) levels were measured in subjects who showed suppressed TSH (<0.60 μU/ml). Subjects with positive TPOAbs and positive TBII were excluded. We were not able to obtain urine from six subjects, who were also excluded. There were 514 final subjects who were considered thyroid disorder free (normal pregnant subjects). We studied the relationship between serum TSH concentration and urinary iodine concentration in these 514 subjects. A total of 346 of the normal pregnant subjects were checked for emesis. We defined women who had nausea and vomiting as having hyperemesis, and defined those who had only nausea as having mild emesis.

Infants

A total of 509 infants was born from these normal pregnant subjects. Spontaneous abortion occurred in 10 subjects, and five bore twins. Weight, height, head circumference, chest circumference, Apgar score (n = 371), and score of fetal maturation estimated by the Dubowitz (10) and Ballard methods (11) in newly born infants were measured (n = 66). We used the external score, neurological score, and combined total score in the Dubowitz method for statistical analysis. Similarly, physical score, neuromuscular score, and total score were used in the Ballard method. A child developmental test was performed using the Enjoji Scale at 3 (n = 162), 6 (n = 216), 9 (n = 247), and 12 months (n = 177) after birth. The Enjoji Scale (12) consists of physical abilities of the whole body, skilled hand motor activities, behavior, interpersonal skills, speech ability, and language comprehension.

In addition, we compared thyroid function between the infants whose mothers had low-serum TSH (n = 30, TSH <0.05 μU/ml) in early pregnancy and those whose mothers had high-serum TSH (n = 6, TSH >4.9 μU/ml) in early pregnancy.

Biochemical analyses

TSH, FT_4, and FT_3 concentrations were measured by electrochemiluminescent immunoassays (ECLusys TSH, ECLusys FT_4, and ECLusys FT_3, respectively; Roche Diagnostics K.K., Tokyo, Japan) (13). We established normal reference ranges using 59 normal Japanese nonpregnant pregnancy aged women who did not have thyroid antibodies because we had to take racial and cultural differences into consideration. The normal reference ranges we used were 0.60–4.90 μU/ml for TSH, 1.07–1.66 ng/dl for FT_4, and 2.07–3.65 pg/ml for FT_3. TPOAbs were measured by a highly sensitive RIA system (TPOAb Cosmic 2; Cosmic Co., Tokyo, Japan). The normal range for TPOAb is less than 0.3 U/ml. TBII levels were measured by a solid-phase immunoradioreceptor assay kit (TRAb CT Cosmic; Cosmic). The normal range is less than 15% for TBII. Urinary iodine concentrations were measured by a microplate method using the Sandell-Kolthoff reaction (14). Urinary concentrations of Cr (normal range 1.0–1.5 g/d) were measured using a routine automated analyzer (Hitachi 7170S Clinical Analyzer; Hitachi, Ltd., Tokyo, Japan).

Statistics

TSH data were log transformed before analyses. Correlation analyses between serum thyroid hormones and urinary concentrations of iodine were performed using Spearman's rank correlation test. Multiple regression analysis was performed to explore the association of parameters in neonates and concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers with explanatory variables such as weight, height, head circumference, chest circumference, and Apgar scores for neonates. Multiple regression analysis was also performed to explore the association of fetal maturation scores estimated by the Dubowitz and Ballard methods and concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers with explanatory variables, including external score, neurological score, combined total score in the Dubowitz method, physical score, neuromuscular score, and total score in the Ballard method. Similarly, the association of the child developmental test (Enjoji Scales) and concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers, along with physical abilities of the whole body, skilled hand motor activities, behavior, interpersonal skills, speech abilities, and language comprehension scores were analyzed by multiple regression. Serum concentrations of TSH, FT_4, FT_3, and urinary concentrations of iodine in each subject group were compared using the Mann-Whitney *U* test. We did not correct for the impact of multiple

TABLE 1. Serum TSH and FT_4 in the normal pregnant subjects

TSH (μU/ml)		FT_4 (ng/dl)		
		<1.07	1.07–1.66	<1.66
<4.90	8 (1.6%)	2	6	0
0.60–4.90	308 (60.5%)	60	246	2
0.05–0.60	147 (28.9%)	4	132	11
<0.05	46 (9.1%)	1	28	17
Total	509			

Five subjects were excluded because they bore twins.

statistical tests on the data. Two tailed cutoffs were used to determine statistical significance.

Results

Study population

The age of the normal pregnant subjects was 30.88 ± 4.22 yr (mean ± SD, n = 514). Gestational age at screening was 10.54 ± 4.84 wk (mean ± SD). There were 38 (6.7% of 568) subjects with positive TPOAbs, 11 (1.9%) with positive TBII, and three (0.5%) were positive for both. A total of 193 (38.0% of 509) subjects showed suppressed TSH levels. The prevalence of gestational thyrotoxicosis defined as elevated FT_4 and suppressed TSH levels was 28 (5.5% of 509) (Table 1). Five subjects were excluded from the 514 because they bore twins.

Urinary iodine and serum TSH in mothers

The distribution of urinary iodine concentrations was large, and the average was extremely high (Fig. 1). The median urinary iodine concentration was 328.0 (25.0–78487) μg/liter [259.5 (16.0–5353) μg/g Cr)]. There was a significant positive correlation between concentrations of urinary iodine and serum concentrations of TSH (r = 0.1326; $P < 0.005$) (Fig. 2A). On the other hand, there was a significant negative correlation between concentrations of urinary iodine and serum concentrations of both FT_4 (r = −0.1801; $P < 0.0001$) and FT_3 (r = −0.1701; $P < 0.0005$) (Fig. 2, B and C). The number of subjects by TSH level is shown in Fig. 3. There were 61 (11.9%) subjects with serum TSH concentrations higher than 2.50 μU/ml. There were six (1.2%) subjects who showed subclinical hypothyroidism (serum TSH higher than 4.90 μU/ml and normal serum FT_4) and two (0.4%) who showed overt hypothyroidism. The highest TSH value was 7.99 μU/ml. Only seven (1.36%) women had a urinary iodine level less than 50 μg/liter in our subjects.

Table 2 shows the follow-up observation in subjects whose serum TSH concentrations were higher than 4.90 μU/ml in the first trimester. They were instructed to reduce iodine intake by obstetricians in the first trimester. TSH levels decreased in most subjects as gestation progressed, but remained high in a few subjects.

Parameters in neonates

No correlations were found between the parameters of weight, height, head circumference, chest circumference, and Apgar scores in neonates or concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers. Neither were there any correlations between fetal maturation scores estimated by the Dubowitz and Ballard methods, and concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers.

Child developmental test

There were no correlations between Enjoji Scales at 3, 6, 9, and 12 months after birth, and concentrations of urinary iodine or serum concentrations of TSH during early pregnancy in their mothers.

Thyroid hormones in cord blood and 5 d after birth

We compared thyroid function between the infants whose mothers had low-serum TSH (n = 30, TSH <0.05 μU/ml) in early pregnancy and those whose mothers had high-serum TSH (n = 6, TSH >4.9 μU/ml) in early pregnancy, as previously stated. As for TSH and FT_4 levels in cord blood and serum FT_4 levels in the infants 5 d after birth, no significant differences were found between the two groups. However, only serum TSH levels in the infants 5 d after birth whose mothers had high-serum TSH in their early pregnancy were significantly higher (7.10 ± 2.80 *vs.* 4.64 ± 3.82 μU/ml; $P < 0.05$) than the infants whose mothers had low-serum TSH in their early pregnancy.

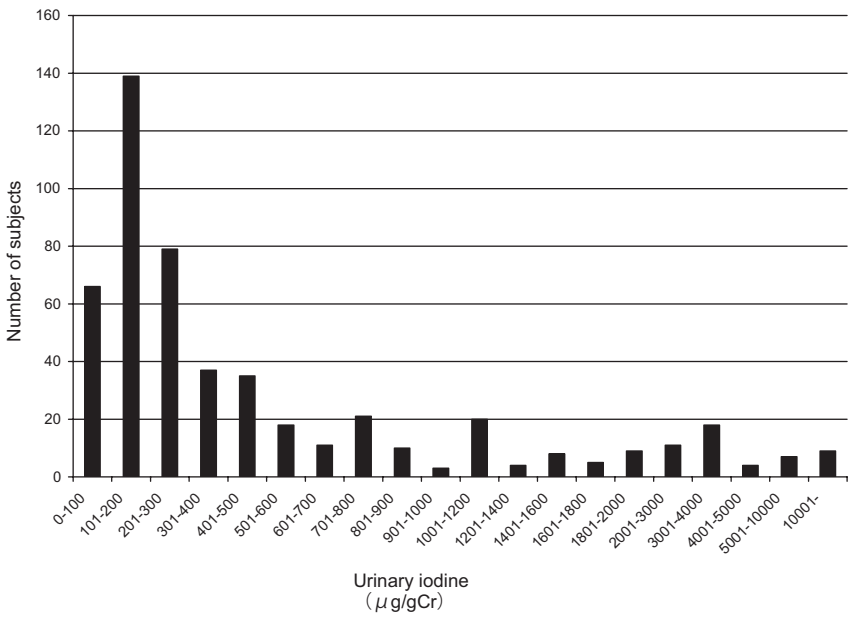

FIG. 1. Distribution of urinary iodine concentrations.

Emesis, serum TSH, and urinary iodine

Of 346 subjects, 267 had no emesis, 45 had mild emesis, and 34 had hyperemesis. Serum concentrations were 1.25 ± 1.13 μU/ml in the no emesis group, 0.94 ± 1.30 μU/ml in the emesis group, and 0.84 ± 0.95 μU/ml in the hyperemesis group. Serum TSH concentrations in the subjects who had emesis were

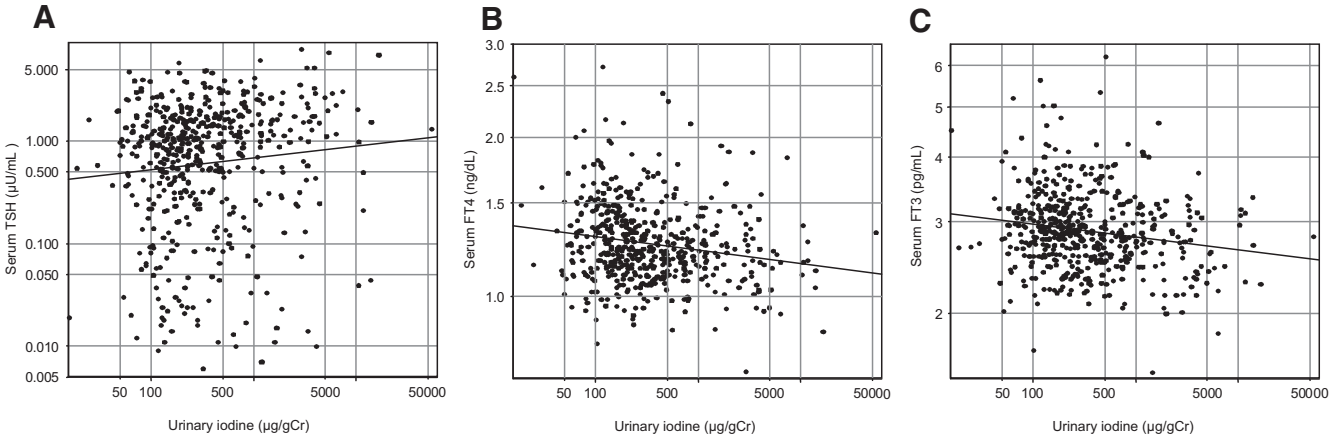

FIG. 2. A, Relationship between concentrations of urinary iodine and serum concentrations of TSH (r = 0.1326; $P = 0.00259$). B, Relationship between concentrations of urinary iodine and serum concentrations of FT_4 (r = −0.1801; $P = 0.00004$). C, Relationship between concentrations of urinary iodine and serum concentrations of FT_3 (r = −0.1701; $P = 0.00011$).

lower than in those who did not ($P < 0.005$). There was no significant difference in urinary iodine concentrations in each group. Four subjects were excluded because they bore twins.

TPOAb and thyroid function

Serum TSH in TPOAb-positive subjects was significantly higher than that in TPOAb-negative subjects (1.69 ± 1.34 *vs.* 1.17 ± 1.16 μU/ml; $P < 0.01$), and serum FT_4 in TPOAb-positive subjects was significantly lower than that in TPOAb-negative subjects (1.19 ± 0.20 *vs.* 1.28 ± 0.25 ng/dl; $P < 0.05$).

Discussion

Japanese dietary culture is unique, and many Japanese eat seaweed and make soup stock from kelp on a daily basis. There are several reports of high urinary iodine concentrations in Japanese adults and children (6, 15–18). However, there have been no reports about urinary iodine concentration in Japanese pregnant women. In this study our results showed high urinary iodine concentrations in Japanese pregnant women. In fact, seaweed intake is believed to be good for pregnancy in Japan. Although the serum concentration of TSH correlated with urinary iodine concentration, the highest value of TSH was 7.99 μU/ml, and 1.6% of subjects showed subclinical and overt hypothyroidism. Young age, negative TPOAbs, and escaping from the Wolff-Chaikoff effect may contribute to the low prevalence of subclinical and overt hypothyroidism. When Japanese thyroidologists encounter subclinical hypothyroid nonpregnant patients, they first routinely recommend reducing excess iodine intake for patients before starting l-T_4 treatment. This is completely different from other countries. We included this procedure in our study protocol.

Subclinical hypothyroidism in the first trimester improved by reducing iodine intake in most of the subjects. The improvement seemed to be greater in the subjects whose urinary iodine concentration was high in the first trimester. Excess iodine intake probably contributed to the elevation in serum TSH levels. Reducing iodine intake may be useful in Japanese pregnant women whose urinary iodine concentrations are high.

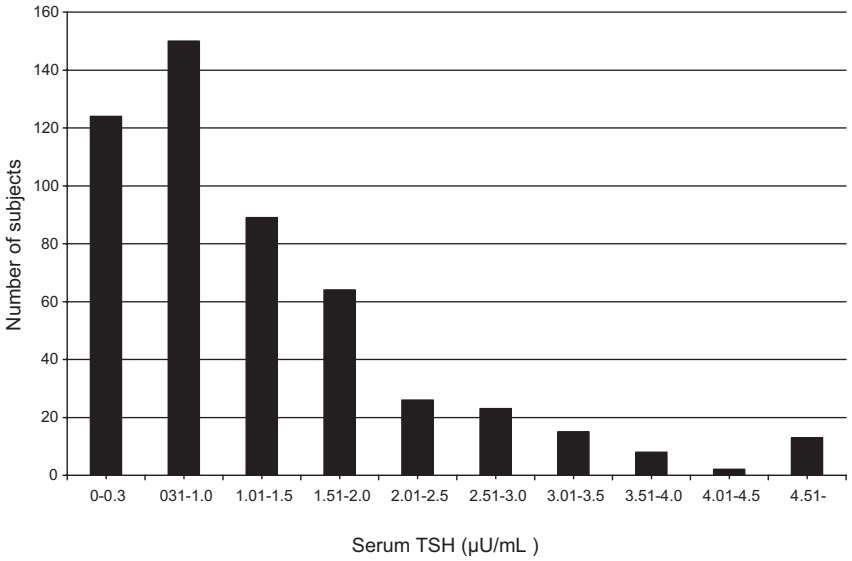

FIG. 3. Serum TSH distribution in the normal pregnant subjects.

Recently, it was proposed that the true normal upper limit for the serum TSH level is 2.5 μU/ml (19). The American Endocrine Society recommends adjustment of the T_4 dose to reach a TSH level not higher than 2.5 μU/ml if hypothyroidism has been diagnosed before pregnancy (4). It is well known that hypothyroidism develops when women with potential iodine deficiency become pregnant, and it can have serious adverse effects on the fetus (20, 21). In our study about 12% of normal pregnant subjects showed serum TSH levels higher than 2.5 μU/ml. However, serum concentrations of TSH during early pregnancy in normal women had no relevance to parameters in neonates, fetal maturation scores, and child developmental tests in their infants. It is necessary to keep in mind that the developmental test was performed only up to 12 months of age. We have to

TABLE 2. Follow-up observation of serum TSH in the subjects (TSH >4.90 μU/ml in the first trimester)

Subject no.	TSH (μU/ml)			Urinary iodine (μg/g Cr)
	First trimester	Second trimester	Third trimester	First trimester
1	4.93	2.26	ND	345
2	5.23	1.77	2.51	3,277
3	5.25	3.04	ND	3,876
4	5.87	4.81	6.11	187
5	6.19	3.48	ND	1,163
6	7	3.05	2.08	16,444
7	7.35	8.99	4.87	5,379
8	7.99	ND	ND	2,908

ND, Not determined.

follow the babies until school age before making a final conclusion. It should also be added that not all mothers brought their babies for regular checkups and that the sample size of infants was, therefore, smaller. If there are any differences between the infants who complied with follow-up visits and the infants who did not attend follow-up visits, there will be family income, presence of mother's occupation, and accessibility to the maternity hospital. We believe that these factors did not affect our results, and there was little selection bias in these groups. Thus, it is likely that subclinical hypothyroidism and dietary iodine excess during early pregnancy have no adverse effects on the fetuses of Japanese women without thyroid autoantibodies.

Haddow *et al.* (22) reported that hypothyroidism in pregnant women can adversely affect their children's subsequent performance on neuropsychological tests, even if the hypothyroidism is mild. There are two differences between the study reported by Haddow *et al.* (22) and our study. Whereas 77% of TSH-elevated women were TPOAb positive in their study, none of our subjects was TPOAb positive. Recently, it was reported that iodine status was still poor in a segment of the U.S. population (23). They showed that 15.1% women had a urinary iodine level less than 50 μg/liter among all women of reproductive age. In contrast, 1.36% women had a urinary iodine level less than 50 μg/liter in our subjects. Maternal urinary iodine concentrations were not measured in the study reported by Haddow *et al.* (22). Therefore, we assumed that the results of their study could not be applied to normal Japanese women. Iodine deficiency itself, rather than subclinical hypothyroidism, in pregnant women may be a problem in other countries.

It has been reported that hypothyroxinemia during early gestation could be harmful to the offspring (24–26). However, our results also suggested that serum FT_4 levels during early pregnancy in mothers had no relevance to child development. Strangely, only serum TSH levels in the infants 5 d after birth whose mothers had high-serum TSH in early pregnancy were higher than the other group. This may be due to iodine-rich breast milk. Although the frequency of breast-feeding was not defined in this study, this is the practice of most mothers in Japan.

On the other hand, overt thyrotoxicosis was found in 5.5% of our normal pregnant subjects. There have been reports that gestational thyrotoxicosis was found in 2.4% of European women, 11% of Singaporean women, and 6.7% of Japanese women in early pregnancy (27–29). Price *et al.* (30) reported that gestational thyrotoxicosis is more frequent in Asian than in European women. The difference is possibly due to differences in ethnicity. However, there were no significant differences in urinary iodine concentrations between the gestational thyrotoxicosis group and nonthyrotoxic group in this study; thus, the difference in prevalence in gestational thyrotoxicosis between Singaporean and Japanese women may be due to the difference in iodine intake.

There have been several reports of a relationship between gestational thyrotoxicosis and hyperemesis gravidarum (31–34). Our results also showed a relationship between serum TSH concentrations and emesis. We assumed that excess iodine intake decreases the prevalence of emesis, but there was no significant difference in urinary iodine concentrations between the groups that had emesis and that did not.

A major issue is the determination of the upper limit of iodine intake during pregnancy in iodine-rich areas. If Japanese dietary habits in pregnant women are a problem, we will have to educate them not to consume too much iodine. Because there were weak positive correlations between concentrations of urinary iodine and serum levels of TSH, it is difficult to determine the upper limit of iodine intake during pregnancy from this study. Although subclinical hypothyroidism with dietary iodine excess during early pregnancy seems to have no adverse effects on infants, it is preferable to normalize the serum TSH level because of the methodological limitations of our study. In fact, we start l-T_4 replacement therapy for pregnant women once they are identified as having subclinical hypothyroidism. However, we do not generally use any thyroid screening (serum TSH, TPOAb, thyroglobulin antibody, or urinary iodine) for pregnant women in Japan, and, thus, we cannot identify all pregnant women with subclinical hypothyroidism. Ideally, a screening program in early pregnancy in Japan should be introduced.

Because changing dietary habits is not easy for many people, we would like to minimize the restriction of dietary iodine. Considering all the various factors together, the limit of iodine intake for healthy Japanese pregnant women should be around 3000 μg iodine/d, as recommended by the Japanese Health, Labor and Welfare Ministry (9). As for TPOAb-positive women identified by chance, restriction of dietary iodine intake should be recommended.

In summary, concentrations of urinary iodine varied widely, and the median value was extremely high in early pregnancy in 514 Japanese healthy women. There were significant positive correlations between concentrations of urinary iodine and serum TSH levels in these women: 1.2% of subjects showed subclinical hypothyroidism, 0.4% of the subjects showed overt hypothyroidism, and the highest value of TSH was 7.99 μU/ml. Subclinical hypothyroidism with dietary iodine excess during early pregnancy seems to have no adverse effects on the fetus in healthy Japanese women from our results. However, we have to consider our conclusion carefully because controversial conclusions have been reported. To avoid hypothyroidism, reducing excess di-

etary iodine intake to moderate levels may be beneficial for healthy pregnant woman in Japan.

Acknowledgments

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