Iodine Status of Pregnant and Postpartum Japanese Women: Effect of Iodine Intake on Maternal and Neonatal Thyroid Function in an Iodine-Sufficient Area

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Background: Iodine deficiency in pregnant and lactating women results in serious damage to their fetuses, newborns, and weaning infants. The effect of dietary iodine intake on maternal and infantile thyroid function has not been well studied in iodine-sufficient areas, and there are few data on appropriate gestational age-specific reference ranges for urinary iodine excretion during pregnancy and lactation.

Objectives: The aim of the study was to characterize the gestational change of urinary iodine excretion in Japanese women and to assess the effects of iodine status on thyroid function in mother and infant.

Methods: A total of 934 Japanese women and their 722 newborn infants were enrolled in the study. Iodine and creatinine concentrations were determined in spot urine samples in the three trimesters of pregnancy and the postpartum period at 34.0 d after delivery. Serum thyroperoxidase antibody and thyroglobulin antibody, TSH, and free T_4 were measured in each trimester, and neonatal TSH was measured on postnatal d 4.

Results: The overall median urinary iodine concentration (UIC) during pregnancy was 219.0 μg/liter, higher than that in postpartum women (135.0 μg/liter). The prevalence of pregnant women with low UIC less than 100 μg/liter or high UIC greater than 500 μg/liter was 16.1 and 22.2%, respectively. Urinary iodine excretion increased from 220.0 μg/liter in the first trimester to 258.0 μg/liter in the second trimester, decreased to 195.0 μg/liter in the third trimester, and then remained at 137.0 μg/liter postpartum. The maternal UIC correlated positively with serum TSH during pregnancy. There was no significant difference in UIC between subjects with positive thyroid autoantibodies and those with negative antibodies.

Conclusions: Iodine intake assessed by UIC in Japanese pregnant women is regarded as sufficient and not excessive according to World Health Organization criteria. Although the data are local, our results provide additional information on the reference range for UIC throughout gestation in iodine-sufficient areas. **(*J Clin Endocrinol Metab* 96: 3846–3854, 2011)**

In pregnancy, thyroid hormone and iodine requirements increase from early gestation to term due to three separate events that stimulate the thyroid gland (1). They are: the progressive rise in serum T_4-binding globulin under the influence of elevated estrogen, the direct stimulation of the thyroid gland by elevated concentrations of human chorionic gonadotropin, and modifications in the peripheral metabolism of maternal thyroid hormones, mainly at the

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Abbreviations: CI, Confidence interval; Cr, creatinine; FT_4, free T_4; IDD, iodine deficiency disorder; IQR, interquartile range; TgAb, thyroglobulin antibody; ThAb, thyroid autoantibody; TPOAb, thyroperoxidase antibody; UI, urinary iodine; UIC, UI concentration.

placental level. Iodine requirements increase due to increased renal blood flow and glomerular filtration, which lead to increased iodine clearance and iodine loss in the urine. In later pregnancy, fetal demands for iodine increase, and iodine deprivation occurs due to the passage of iodine from the maternal circulation to the fetal-placental unit. In the postpartum period, an additional iodine intake is needed to compensate the iodine loss into the breast milk. The most serious adverse effect of iodine deficiency in pregnant and lactating women is damage to their fetuses, newborns, and weaning infants (2). Based on the proportion of household consumption of adequately iodized salt, the United Nations Children's Fund (UNICEF) estimates that every year about 38 million newborns in developing countries remain unprotected from the lifelong consequences of brain damage associated with iodine deficiency disorders (IDD) (3).

Recently, there have been increasing concerns about pregnant and lactating women, weaning infants, and older children who do not receive enough iodine in the countries that have been iodine sufficient for several decades (4–6). The World Health Organization (WHO), UNICEF, and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) endorse the policy of iodine supplementation for pregnant and breastfeeding women in iodine-deficient countries where salt iodization is not regulated or is ineffective (7). In the United States and Canada, the American Thyroid Association and The Endocrine Society recommended iodine supplementation during pregnancy and lactation (8, 9).

In contrast to iodine deficiency, excess exposure to iodine through foods, dietary supplements, or iodine-containing drugs during pregnancy may cause fetal and neonatal thyroid dysfunction (10). However, the effect of dietary iodine intake during pregnancy on maternal and infantile thyroid function has not been well studied in iodine-sufficient areas, and there are few data on appropriate gestational age-specific reference ranges for urinary iodine (UI) excretion during pregnancy and lactation (11).

Japan is a nongoitrous country without iodine fortification, due to the regular intake of iodine-rich food such as seaweeds and kelp (12); however, no national data assessing iodine status is currently available. For pregnant and lactating women, only one study on UI excretion and thyroid function has been reported in early pregnancy (13). The aim of this study is to examine the pattern of maternal UI excretion throughout gestation and to assess the influence of iodine status on maternal and neonatal thyroid function in an iodine-sufficient area.

Subjects and Methods

Subjects

Between November 2005 and January 2007, healthy pregnant and postpartum women without previous history of thyroid disease were consecutively recruited when they attended a routine antenatal clinic at Yamaguchi Hospital in Funabashi City, Chiba Prefecture, Japan. The study was approved by the local ethics committee, and written informed consent was obtained from each of the participants. These women were prospectively studied during the three trimesters of pregnancy and the late puerperium at 5–6 wk postpartum. Gestational dates were confirmed by ultrasound in the first trimester.

After their body weight was measured, blood and urine samples were taken from the participants once in each trimester and 1 month after birth. As part of the National Neonatal Screening Program, a heel-prick blood sample was taken between 72 and 120 h after birth from all infants. Casual urine samples were collected and kept frozen at −30 C until they were analyzed.

The study group comprised 701 pregnant women, 545 postpartum women, and 722 newborn infants (365 boys and 350 girls). The mean (SD) ages of the pregnant and postpartum women were 30.9 (4.1) and 31.0 (4.1) yr, respectively. Three hundred twelve of the 545 postpartum women were the same individuals from the group of 701 pregnant women, and 492 of the 722 newborn infants were those born to the 701 pregnant women.

A total of 1662 urine samples obtained at obstetric visits included multiple measurements from the same subjects (246 women provided single samples, 151 women provided two samples, 141 women provided three samples, 128 women provided four samples, and 35 women provided five or more samples). Serum TSH, free T_4 (FT_4), and two thyroid autoantibodies (ThAb) [*i.e.* thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb)] were measured in 729 serum samples obtained from 456 subjects in each trimester (253 women provided single samples, 133 women provided two samples, and 70 women provided three samples).

Assays

Maternal serum TSH and FT_4 were measured by electrochemiluminescence immunoassay using ECLusys TSH and FT_4 (Roche Diagnostics K.K., Tokyo, Japan). Detection limits and laboratory reference ranges in Japanese healthy adults were: TSH, 0.0022 mU/liter, 0.500–5.00 mU/liter; and FT_4, 0.01 ng/dl, 0.90–1.70 ng/dl, respectively. TPOAb and TgAb were measured by RIA using TPOAb Cosmic II (500) and TgAb Cosmic II (RSR Limited, Cardiff, UK). The normal reference range for both ThAb was less than 0.3 U/ml. Neonatal blood TSH was measured in the dried heel-prick blood spot samples by ELISA using Enzaplate N-TSH (detection limit, 0.5 mU/liter; Bayer Medical Ltd., Tokyo, Japan).

UI was measured by the ammonium persulfate digestion on microplate method based on the Sandell-Kolthoff reaction. The analytical sensitivity of this assay was 1.39 μg/dl. The creatinine (Cr) concentration in urine was estimated by colorimetric enzymatic assay. All urine samples were assayed in duplicate. UI concentration (UIC) was expressed relative to Cr excretion (UI/Cr; micrograms per gram Cr) or as a concentration in micrograms of iodine per 1000 ml of urine (μg/liter). Because WHO guidelines for IDD status use micrograms per liter for cutoff points in IDD surveillance, we gave SI units (micromoles per liter)

in *parentheses*. (For conversion to SI units, 1 μg/liter = 0.0079 μmol/liter).

Statistics

The results are presented as mean, 95% confidence interval (CI) of mean, SD, median, interquartile range (IQR), or observed range. Because the UIC and serum TSH concentration were distributed asymmetrically and skewed, their logarithmically transformed values were used to normalize the distribution. Differences between paired data or groups were examined using one-way ANOVA with Tukey's multiple comparison test, the Kruskal-Wallis test, and Dunn's multiple comparison test. Differences between two unmatched groups for normally and non-normally distributed data were tested using the unpaired *t* test and Mann-Whitney test, respectively. The significance of differences in ThAb prevalence between the groups was determined using Fisher's exact test. Simple linear regression analysis was used to test for correlations between UI and serum TSH or FT_4 concentrations. A *P* value less than 0.05 was considered significant. Data processing and statistical analysis were performed using GraphPad Prism 5.0 from GraphPad Software Inc. (San Diego, CA).

Epidemiological criteria of IDD in pregnant and lactating women

WHO/UNICEF/ICCIDD-recommended epidemiological criteria based on median UIC for assessing iodine intake in pregnant women are as follows: insufficient, below 150 μg/liter; adequate, 150–249 μg/liter; more than adequate, 250–499 μg/liter; and excessive, 500 μg/liter or higher. Criteria for lactating women and children less than 2 yr of age are: insufficient, below 100 μg/liter; and adequate, 100 μg/liter or higher (14).

Results

UIC in pregnant and postpartum women

The overall UIC in spot urine samples obtained at the time of study enrollment were highly variable, ranging from 6.0 μg/liter (0.047 μmol/liter) to 16,300 μg/liter (128.8 μmol/liter); the median UIC in pregnant women was 219.0 μg/liter (1.7 μmol/liter), significantly higher than that in postpartum women, which was 135.0 μg/liter (1.1 μmol/liter) (Table 1).

The rates of the pregnant and postpartum women who excreted iodine less than 100 μg/liter (0.79 μmol/liter) were 16.1% (110 of 684 women) and 35.7% (190 of 532 women), respectively ($P < 0.0001$). High iodine excretion greater than 500 μg/liter (4.0 μmol/liter) was found in 22.2% (152 of 684) of pregnant women and 14.1% (75 of 532) of postpartum women ($P = 0.0003$). Extremely high UI values exceeding 1000 μg/liter (7.9 μmol/liter) were found in 13.5% (92 of 684) of pregnant women and 6.6% (35 of 532) of postpartum women ($P < 0.0001$). The differences of prevalence were significant between the pregnant and postpartum women.

When the subjects were divided into two age groups with a cutoff value of 30 yr, higher UIC and UI/Cr were observed in the older age group; however, the difference for UIC was not significant in postpartum women (Table 2).

TABLE 1. UIC of pregnant and postpartum women

	Pregnant women	Postpartum women
n	683	532
Age (yr)[a]	30.9 (4.1)	30.9 (4.2)
Gestational weeks[a]	21.2 (10.6)	
Postpartum days[a]		34.0 (3.4)
UIC (μg/liter)		
Median	219[b]	135.0
IQR	124.0–436.0	78.0–262.0
Range	18.0–16,300	6.0–12,200
Geometric mean	262.4[b]	157.0
95% CI	240.9, 285.8	143.3, 172.0
UI/Cr (μg/g Cr)		
Median	234.8[b]	173.8
IQR	144.8–510.1	104.9–406.0
Range	33.1–16,471	27.0–19,636
Geometric mean	302.7[b]	217.2
95% CI	302.7, 328.7	198.8, 237.3

Urine samples were obtained at initial obstetric visit, at the time of study enrollment.

[a] Values are expressed as means (SD); 1 μg/liter = 0.0079 μmol/liter.

[b] Different from postpartum women ($P < 0.0001$).

Trimester-specific changes of UI excretion

The median and mean UIC during pregnancy were significantly higher than those in postpartum; however, there were no significant differences in UIC values among the three trimesters (Table 3 and Fig. 1). In contrast, the median UI/Cr increased from 185.4 μg/g Cr in the first trimester to 258.9 μg/g Cr in the second trimester, and decreased slightly to 237.9 μg/g Cr in the third trimester but remained above the postpartum value (173.8 μg/g Cr). A similar pattern was observed for the mean UI/Cr.

Gestational changes of UI, Cr, and UI/Cr stratified by a 4-wk interval

The median UIC increased as early as the eighth week and fluctuated from 193.5 to 266.0 μg/liter (15.5 to 21.0 μmol/liter) during pregnancy, and it remained significantly higher than that in the postpartum period [135.0 μg/liter (10.7 μmol/liter)] (Table 4). The mean UIC values, except in the 17–20th and 25–28th weeks, were significantly higher than the postpartum value. However, there were no significant changes among the mean UIC values during pregnancy.

The mean urinary Cr concentration was highest at the eighth week (137.4 mg/dl). It then decreased steadily to 120.4 mg/dl in the 13–16th weeks and remained stable until the postpartum period.

The median UI/Cr increased before the eighth week (184.0 μg/g Cr) and made a first peak at the 17–20th weeks (296.3 μg/g Cr), decreased during the 21–36th

TABLE 2. UI excretion of pregnant and postpartum women divided in two age groups

	Pregnant women			Postpartum women		
	Age (yr)			Age (yr)		
	20–29	30–39	*P*	20–29	30–39	*P*
n	246	422		189	323	
Age (yr)[a]	26.8 (2.2)	33.2 (2.4)	<0.0001	26.8 (2.3)	33.2 (2.4)	<0.0001
Gestational weeks[a]	21.0 (10.1)	21.5 (10.9)	0.617			
Postpartum days[a]				33.8 (2.8)	34.2 (3.8)	0.1208
Body weight (kg)[a]	54.4 (8.0)	55.6 (7.7)	0.0562	56.6 (8.2)	55.9 (8.0)	0.4915
UIC (μg/liter)						
Median[b]	190.5	226.5	0.007	127.0	140.0	0.4446
IQR	113.0–383.0	134.0–486.5		104.9–406.0	76.0–285.0	
Range	18.0–10,000	19.0–16,300		19–4,600	6.0–12,200	
Geometric mean[a]	227.6	288.9	0.0092	149.8	161.9	0.4295
95% CI	199.2, 260.0	258.2, 323.4		130.8, 171.5	142.9, 183.4	
Cr (mg/dl)						
Mean (SD)	109.0 (66.4)	106.9 (64.3)	0.6938	96.2 (59.8)	83.5 (48.9)	0.0099
UI/Cr (μg/g Cr)						
Median[b]	205.6	249.1	0.0039	161.2	183.7	0.0149
IQR	128.6–461.3	152.8–572.7		93.3–324.3	116.7–436.3	
Range	33.1–16,472	44.4–11,711		27.0–4,596	27.5–19,636	
Geometric mean[a]	258.6	333.9	0.002	190.4	236.9	0.0227
95% CI	227.3–294.2	299.5–372.1		165.1, 219.5	210.8, 266.2	

Values are expressed as means (SD).

[a] Unpaired *t* test.

[b] Mann Whitney test; 1 μg/liter = 0.0079 μmol/liter.

weeks, and increased again in the 37th week or later making a second peak (312.5 μg/g Cr), although the difference of UI/Creat was not significant. The median and mean UI/Cr values after the 17th week were significantly higher than in the postpartum period.

UIC in micrograms per liter was positively correlated with UI expressed as micrograms per gram of Cr (UI/Cr) in pregnant and postpartum women (Pearson's r = 0.6983; $P < 0.0001$; n = 1562).

Relationship between serum ThAb and UI concentration

Serum TgAb and TPOAb were found in 57 subjects (11.7%) and 33 subjects (6.8%), respectively, whereas

TABLE 3. Trimester-specific change of UI excretion

	First trimester	Second trimester	Third trimester	Postpartum
n	243	541	466	533
Age (yr)*	30.9 (4.5)	30.8 (4.1)	31.2 (4.1)	30.9 (4.2)
Gestational weeks*	9.3 (1.8)	24.9 (4.7)	35.1 (2.3)	34.0 (3.4)**
UIC (μg/liter)				
Median	221.0[a]	208.0[a]	193.0[a]	135.0
IQR	140.0–436.0	110.0–399.5	113.0–383.5	78.0–262.0
Range	19.0–16,300	17.0–10,000	7.0–10,800	6.0–12,200
Geometric mean	277.3[a]	229.6[a]	225.7[a]	157.0
95% CI	240.1, 320.3	209.3, 251.9	203.8, 249.9	143.3, 172.0
UI/Cr (μg/g Cr)				
Median	185.4[b,c]	258.9[a]	237.9[a]	173.8
IQR	113.0–350.0	152.1–556.0	144.7–529.3	104.9–406.0
Range	33.1–9,166	44.4–16,472	36.0–11,711	27.0–19,636
Geometric mean	248.4[b]	318.8[a]	298.1[a]	217.2
95% CI	214.9, 287.1	292.8, 347.1	271.5–327.3	198.8, 237.3

* Values are expressed as means (SD).

** Postpartum days; 1 μg/liter = 0.0079 μmol/liter.

[a] Different from postpartum ($P < 0.001$).

[b] Different from second trimester ($P < 0.001$).

[c] Different from third trimester ($P < 0.001$).

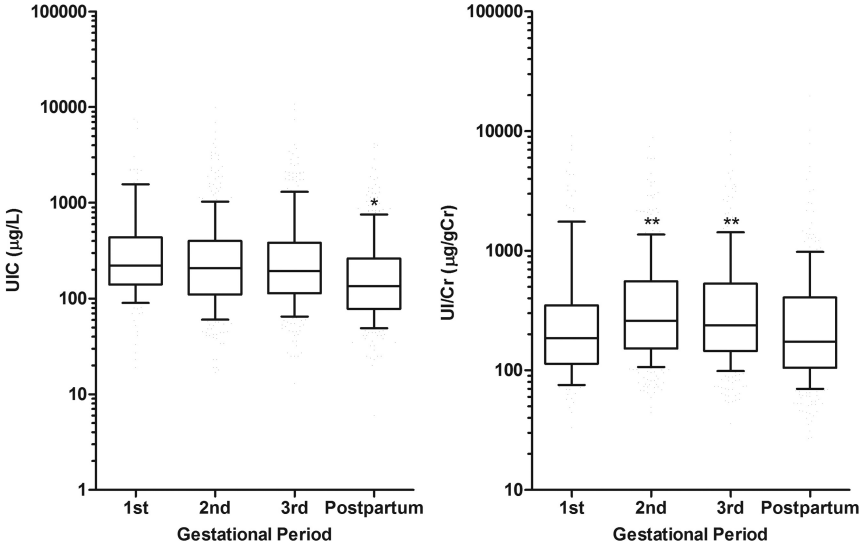

FIG. 1. Trimester-specific changes of UIC. The *boxes* represent median UIC with IQR. *Whiskers* denote 10th-90th percentiles. For conversion to SI units: 1 μg/liter = 0.0079 μmol/liter. *, $P < 0.05$ *vs.* first, second, and third trimesters. **, $P < 0.05$ *vs.* first trimester and postpartum.

both TgAb and TPOAb were positive in 27 subjects (5.2%) and either TgAb or TPOAb was positive in 63 subjects (12.9%).

The median and mean UIC in the ThAb-positive subjects (n = 77) were 213.0 and 267.6 μg/liter, respectively, and were not significantly different from those in ThAb-negative subjects (n = 653; 217.1 and 279.6 μg/liter).

When the samples were divided into two groups according to UIC with a cutoff value of 500 μg/liter, the prevalence of positive ThAb in the higher UIC group (n = 596) was 11.4% and was not significantly different from that (13.4%) in the lower UIC group (n = 134). The same results as UIC were observed between UI/Cr and ThAb.

Relationship between UI and serum TSH or FT_4 concentrations

There were no significant direct correlations of UIC or UI/Cr with both serum TSH and FT_4 concentrations in any of the three trimesters or in each gestational period stratified by a 4-wk interval and postpartum (data not shown).

When the subjects were divided into two groups according to the serum TSH with a cutoff value of 2.5 mU/liter, the mean UIC and UI/Cr in the groups with TSH of at least 2.5 mU/liter had higher values compared with the groups with less than 2.5 mU/liter of TSH in each trimester. The difference was statistically significant in the first trimester (n = 201; 9.0 ± 1.6 wk) for both UIC (424.0 *vs.* 256.3 μg/liter) and UI/Cr (371.1 *vs.* 230.1 μg/g Cr) and in the second trimester (n = 238; 28.6 ± 0.9 wk) for UI/Cr (183.1 *vs.* 140 μg/g Cr).

The mean serum TSH and FT_4 concentrations were compared among the five groups divided according to UIC, *i.e.* less than 150, 150–249, 250–499, 500–999 and at least 1000 μg/liter. The mean TSH value in the group at least 1000 μg/liter of UIC was 1.13 mU/liter and higher than those in the groups less than 150 and 150–249 μg/liter of UIC (1.00 and 0.95 mU/liter, respectively). There were no significant differences in FT_4 values among the five groups.

Relationship between maternal UI excretion and neonatal TSH

TSH concentration in 711 neonatal infants ranged from less than 0.05 to 11.3 mU/liter. The recall rate was 0.68%, and no infant was diagnosed as being congenitally hypothyroid. The mean and median TSH values were 2.37 mU/liter (95% CI, 2.24–2.50) and 2.52 mU/liter (IQR, 1.70–3.78), respectively. No significant linear correlation was found between the natural log of neonatal TSH and the natural log of maternal UIC or UI/Cr in each of the trimesters, gestational months, or postpartum period (data not shown).

Discussion

WHO/UNICEF/ICCIDD-recommended criteria have been used to classify a population's severity of IDD based on school-aged children, and the median UIC of 100–199 μg/liter indicates adequate iodine nutrition (14). For pregnant and lactating women, median UIC of 150–249 μg/liter and at least 100 μg/liter indicate adequate iodine intake, respectively, and a median UIC over 500 μg/liter in pregnant women is regarded as excessive, although the term "excessive" means in excess of the amount needed to prevent and control iodine deficiency (14). We have previously reported that the median UIC of school children in Tokyo and Hokkaido were 282 and 288 μg/liter, respectively, and the iodine status is regarded as "more than adequate" (15, 16). In the present study, the overall median UIC values in pregnant and lactating women in Yokohama were 219.0 and 135.0 μg/liter, respectively, and the trimester-specific values were from 193.0 to 221.0 μg/liter, suggesting that iodine intake in Japanese pregnant and postpartum women was adequate and not excessive. The median UIC in pregnancy was lower than that of school-aged children, and this finding was consistent with previous reports from the areas of more than adequate iodine intake, the United States (17) and China (18), or of

TABLE 4. Gestational change of UI and Cr excretion

Gestational period (wk)	≤8	9–12	13–16	17–20	21–24	25–28	29–32	33–36	≥37	Postpartum
n	131	95	71	73	77	247	176	327	53	533
Age (yr)*	30.6 (4.5)	31.6 (4.4)	31.0 (4.3)	30.9 (4.1)	30.0 (4.3)	30.8 (3.9)	31.4 (3.9)	31.2 (4.2)	30.8 (4.2)	30.9 (4.2)
Gestational weeks*	7.9 (0.7)	10.4 (1.1)	15.0 (1.1)	18.8 (1.2)	23.1 (1.1)	27.7 (1.1)	30.2 (1.1)	35.7 (0.8)	38.5 (1.2)	34.0 (3.4)**
UIC (μg/liter)										
Median	231.0[a]	207.0[a]	266.0[a]	239.0[a]	199.0[a]	206.0[a]	195.0[a]	193.0[a]	207.0[a]	135.0
IQR	143.0–434.0	135.0–436.0	136.0–436.0	107.0–422.0	115.5–465.0	95.0–383.0	125.3–359.8	101.0–371.0	116.5–710.0	78.0–262.0
Range	27.0–16,300	19.0–6,000	48.0–5,500	17.0–10,000	19.0–8,700	19.0–3,360	18.0–6,976	7.0–10,800	43.0–7,400	6.0–12,200
Geometric mean	281.5[a]	269.1[a]	277.3[a]	244.7	260.5[a]	212.0	223.6[a]	215.3[a]	297.3[a]	157.0
95% CI	230.8, 343.7	212.9, 340.1	210.3, 365.4	184.8, 324.1	196.5–345.3	186.8, 240.6	191.7, 260.9	190.8, 242.9	210.7, 419.5	143.3, 172.0
Cr (mg/dl)										
Mean (SD)	137.4 (75.5)	128.9 (68.2)	120.4 (73.8)	91.0 (54.5)[b,c]	88.9 (52.3)[b,c,d]	85.7 (55.2)[b,c,d]	94.8 (54.0)[b,c]	93.7 (58.1)[b,c,d]	91.8 (43.4)[b,c]	88.8 (54.0)[b,c,d]
UI/Cr (μg/g Cr)										
Median	184.0	202.8	219.9	296.3[a]	255.2[a]	259.9[a]	227.6[a]	229.2[a]	312.5[a]	173.8
IQR	113.0–392.6	110.9–334.4	126.1–442.8	179.4–565.4	163.6–637.2	150.2–598.7	146.6–484.0	143.6–533.1	148.8–717.0	104.9–406.0
Range	33.1–9,166	56.3–6,980	44.4–8,814	68.4–16,472	49.1–8,510	59.6–7,037	57.0–5,895	48.4–11,711	36.0–4,466	27.0–19,636
Geometric mean	245.4	252.6	284.2	346.6[a]	358.4[a]	317[a]	289.9[a]	288.5[a]	372.8[a]	217.2
95% CI	202.0, 298.1	198.7, 321.1	212.5, 379.9	276.3, 434.8	279.4, 459.8	281.1, 357.4	251.8, 333.8	258.5, 322	267.6, 519.3	198.8, 237.3

IQR, 25–75th percentiles.

* Values are expressed as means (SD).

** Postpartum days; 1 μg/liter = 0.0079 μmol/liter.

[a] Different from postpartum ($P < 0.001$).

[b] Different from ≥8 wk ($P < 0.05$).

[c] Different from 9–12 wk ($P < 0.05$).

[d] Different from 13–16 wk ($P < 0.05$).

insufficient iodine intake, *i.e.* Tasmania (11). In contrast, a recent study from Switzerland demonstrated that the median UIC values in the second and third trimesters were higher than that in school-aged children (162 *vs.* 120 μg/liter) partially due to the higher use of iodine-containing supplements by pregnant women (5).

Recently, the median UIC and UI/Cr in Japanese women living in Kobe (n = 514) were reported to be 328 μg/liter and 259.5 μg/g Cr, respectively, in early pregnancy (13). These values are more than 40% higher than those observed in our study population (n = 243; UIC, 221 μg/liter; UI/Cr, 185.4 μg/g Cr). Two studies were performed in the same period of 2005–2007 using the same method for UI measurement, and the age and gestational age of the subjects were nearly identical (30.9 *vs.* 30.9 yr; 10.5 *vs.* 9.3 wk gestation). This difference in UI excretion between the two studies might be related to the higher iodine intake of the women residing in Kobe because the median UIC in the female students of Kobe University (n = 1624; age, 18–22 yr) is reported to be 225 μg/liter (19), and approximately 30% higher than that of the women (mean age, 45.7 yr) used for control in our study (175.0 μg/liter). However, both Yokohama and Kobe are located in coastal regions, and the exact reason for this observation is not clear.

The present study showed that both UIC and UI/Cr were higher in an older age group. It has been reported that a median UI/Cr increases steadily with age in both men and nonpregnant women, whereas UIC shows no age-related change (20, 21). This observation for the UI/Cr is consistent with our results. The higher UI/Cr in older individuals could be accounted for by a decreased Cr excretion with age presumably due to an age-related reduction in muscle mass. However, in our study, factors other than Cr excretion might affect UI/Cr because there were no significant differences in the mean urinary Cr values except in postpartum women and the body weight between two age groups.

Several studies on the changes in UI excretion throughout gestation have been reported either in the iodine-sufficient areas from Sweden (22), Switzerland (5, 23), Spain (24), Iran (25) and Sri Lanka (26) or in the mildly iodine-deficient areas from Ireland (27, 28), France (29), Sudan (22), and Tasmania (11); however, no detailed study on the gestational pattern of UI excretion has been carried out in iodine-sufficient areas. We found that there was a trend for iodine excretion to decrease with advancing gestation in accordance with previous reports from Switzerland (23), Iran (25), Sri Lanka (26), Ireland (27, 28, 30), and Tasmania (11). This decrease might represent the fraction of iodine pool transferred from mother to fetus. However, some other studies show conflicting changes of UI excretion. Mean UIC did not change with progression of pregnancy in France (29), Sweden and Sudan (22), whereas data from the United Kingdom (28), Spain (24), and Hong Kong (31) indicated an increasing level of UIC with advancing gestational age, although the median UIC of pregnant women in these studies except Sri Lanka (26) and Sudan (32) was higher than that in the nonpregnant female control.

There are a few data on trimester-specific change of UI/Cr during pregnancy (23, 27). In the present study, the UI/Cr increased through pregnancy and was highest in the second trimester. Urinary Cr excretion increased by about 30% in early pregnancy (<17 wk) in parallel with the increase in UIC and then remained stable during the remainder of the pregnancy and after delivery. Therefore, the UI/Cr was higher only in the latter half of gestation than in postpartum. However, a steady decrease in the UI/Cr has been shown by others in Switzerland (23) and Ireland (27). The different observations on the gestational pattern of UI excretion could be explained by initial thyroidal iodine store, ethnic variation of dietary iodine intake, degree of overall iodine deficiency, difference in study design and/or sample size, and the existence of threshold to control iodine metabolism, which is set high in the areas with high iodine intake (28, 31).

In this study, the percentage in the postpartum women with UIC below 100 μg/liter increased, and that with UIC above 500 μg/liter decreased compared with those in the pregnant women. This change of prevalence is consistent with previous reports in Ireland (30), Iran (25), and Tasmania (11), indicating a normalization of thyroid hormone production, renal function for UI excretion, and in part iodine loss into breast milk in lactating women.

Some epidemiological studies in certain areas with adequate or high iodine intake suggest that the incidence of subclinical hypothyroidism and autoimmune thyroiditis increases (33), but this phenomenon is still under controversy (34), probably due to genetic, racial, or environmental differences (35). In the present study, a high UIC of more than 500 μg/liter was observed in 22.2% of the pregnant women, and 13.5% excreted a large amount of iodine greater than 1000 μg/liter; however, there were no differences in the prevalence of positive ThAb between the women with high iodine intake and those with normal intake, nor were there any differences in the mean and median UIC or UI/Cr between ThAb-positive and -negative women. It has been reported that there was no correlation between the amount of iodine excretion and prevalence of positive ThAb among Japanese adults residing in four different regions, suggesting that a high dietary iodine intake does not affect ThAb positivity (34). Our results in pregnant women are consistent with their observation in nonpregnant Japanese adults.

During pregnancy, thyroid antibody titers including TgAb, TPOAb, and TSH receptor antibody decline due to the immunosuppressive effect of pregnancy and increase in the postpartum period (28). The prevalence of positive ThAb in Japanese women less than 40 yr old is reported to be 35.2% for TgAb and 15.2% for TPOAb (36). In the present study, TgAb and TPOAb were detected in 11.7 and 6.8% of pregnant women, respectively, suggesting this immunosuppressive effect.

A positive relationship between UI/Cr and TSH has been reported in the adult nonpregnant population in the United States (20). A recent study in Japan reported that serum UIC correlate positively with serum TSH concentrations and negatively with serum thyroid hormone concentrations (FT_4 and free T_3) in early pregnancy (13). In our study, there was no direct correlation between UIC and serum TSH or FT_4 concentrations during pregnancy; however, the highest iodine excretion group (UIC >1 mg/liter) has a higher TSH level than those in lower iodine excretion groups. This observation is in part consistent with the Japanese study (13) and other (20) results, although the difference of TSH is minimal (0.17 μU/ml), and TSH values fluctuate within a physiological range without significant change in serum FT_4. The precise cause of this finding is unclear, and further studies are necessary.

Little is known about the effect of maternal dietary iodine intake on fetal and neonatal thyroid function in a population that is chronically exposed to large doses of iodine mainly from dietary sources. A transient elevation of TSH was observed in some neonates born to Japanese mothers who were supposed to consume iodine-rich food during pregnancy or in lactation (37). In the present study, there was no direct relationship between maternal iodine intake assessed by UI and neonatal TSH on the fourth postnatal day, and this observation was consistent with the findings of others (13, 38), suggesting that neonatal TSH was not influenced by an increase of iodine intake within the range observed in this study population.

Here we reported UIC both in terms of concentration (micrograms per liter) and ratio to Cr (UI/Cr in micrograms per gram Cr). UI/Cr minimize variations caused by differences in urine volume and dilution among subjects in a well-nourished population (39) and are of value to describe a population's iodine status (40). In this study, UIC was strongly correlated with the UI/Cr, and the UIC results were generally comparable to those of the UI/Cr, suggesting that the UI/Cr might be useful to assess iodine status in pregnancy and postpartum by taking account of the gestational pattern of Cr excretion.

In conclusion, this study shows for the first time the gestational pattern of iodine secretion and iodine status of pregnant women living in a long-term iodine-sufficient country. Although the data are local, our results provide additional information on the reference range for UIC throughout gestation.

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