

# Iodine status in healthy pregnant women in Korea: a first report

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## Abstract

**Purpose** Proper iodine intake is important during pregnancy for both fetal neurodevelopment and maternal thyroid function. Korea is known as a high iodine intake area. However, there are no data regarding iodine status in pregnant Korean women. Therefore, we evaluated the iodine status of pregnant women in Korea by measuring urine iodine concentration.

**Methods** This study had an observational, prospective design. We enrolled 344 healthy pregnant women who visited Samsung Medical Center in Korea for a routine

antenatal checkup between April 2012 and September 2013. We measured iodine and creatinine concentration (Cr) in spot urine samples and TSH level in serum at the time of enrollment.

**Results** The median urinary iodine concentration (UIC) and UIC adjusted by Cr were 427.3  $\mu\text{g/L}$  and 447.9  $\mu\text{g/gCr}$ , respectively. There was no difference in median UIC according to trimester of pregnancy ( $P$  value = 0.953). Serum TSH level was not different according to UIC level when subjects were grouped according to WHO iodine recommendations ( $P$  value = 0.401).

**Conclusions** The median UIC of healthy pregnant women in Korea was 427.3  $\mu\text{g/L}$  and 447.9  $\mu\text{g/gCr}$ , which are more than adequate according to WHO criteria. Considering the wide range of UIC, we recommend active education about adequate iodine intake during pregnancy in areas where iodine intake is more than adequate according to WHO criteria.

Yoon Young Cho and Hye Jeong Kim have equally contributed to this study as the first authors.

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## Introduction

Iodine is an essential component of thyroid hormones. Intake of an appropriate level of iodine during pregnancy is important for fetal brain development and maternal thyroid function. It is well established that iodine deficiency during pregnancy is linked to maternal goiter and fetal intellectual dysfunction [1–3].

During pregnancy, iodine requirement increases due to change in maternal thyroid hormone metabolism and renal clearance. The main physiologic changes in thyroid hormone level are caused by an increase in serum thyroxine-binding globulin (TBG) and stimulation of the

thyrotropin receptor by human chorionic gonadotropin (hCG). Transfer of iodine from the mother to the fetus also increases the need for maternal iodine. Moreover, renal iodine excretion increases because glomerular filtration rate (GFR) is enhanced by up to 50 % in normal pregnant women [4–7].

In 2007, the World Health Organization (WHO) proposed epidemiologic criteria for assessing iodine nutrition based on the median urinary iodine concentration (UIC) in pregnant women [8]. A median UIC of 150–249  $\mu\text{g/L}$  is considered as an adequate intake of iodine. A UIC between 250 and 499  $\mu\text{g/L}$  is more than adequate, and 500  $\mu\text{g/L}$  or more is defined as excessive iodine intake.

Regarding the safe upper limit of iodine intake during pregnancy, data are limited and current guidelines suggest variable cutoffs of tolerable daily iodine intake. According to the guidelines recently published by the Endocrine Society [9] and the European Thyroid Association [10], iodine intake of pregnant women should not exceed 500  $\mu\text{g/day}$ , which is twice the daily recommended iodine intake during pregnancy (250  $\mu\text{g/day}$ ), whereas the American Thyroid Association guidelines recommend <500–1100  $\mu\text{g/day}$  of sustained iodine intake during pregnancy [11].

Korea is known as a high iodine intake area. A previous study reported that the average iodine intake of healthy adults in Korea was 479  $\mu\text{g/day}$  according to a food questionnaire, and that the average UIC was 674  $\mu\text{g/g}$  creatinine (Cr) [12]. Recently, Lee et al. [13] reported excessive iodine status in Korean preschool children (2–7 years of age), reporting a median UIC of 438.8  $\mu\text{g/L}$ . However, the iodine status of pregnant women in Korea, who are also exposed to iodine-rich diet environment, has not yet been reported.

In 2010, the total population of Korea was 48.6 million, with approximately 44 % in Seoul, the capital city, and its suburbs, which is the present study was conducted [14].

Therefore, our aim in this study was to report for the first time the iodine status of pregnant Korean women in Seoul and its suburbs. In addition, we investigated whether iodine status affected thyroid function in healthy pregnant women in Korea.

## Methods

### Subjects

We consecutively and prospectively enrolled 344 healthy pregnant women who visited the Obstetrics Department at Samsung Medical Center for a routine antenatal checkup. We used an observational, prospective design, and the

study period was between April 2012 and September 2013. Samsung Medical Center is located in the southern part of Seoul, and most pregnant women visiting its Obstetrics Department live in Seoul or its surrounding suburbs. According to a census report performed every 5 years by the Korean Statistical Information Service (KOSIS), Korea had a population of 48.6 million in 2010, and 44 % of Koreans resided in metropolitan Seoul (9.8 million) or its suburbs (11.4 million), where this study was performed [14].

All trimesters were represented in our sample (78 in the first trimester, 133 in the second trimester, and 133 in the third trimester). Exclusion criteria were a visible or palpable diffuse or nodular goiter, a history of thyroid disease or medication usage, multi-fetal gestation, high-risk pregnancy, pregnancy by any artificial reproductive technology, and pregnancy-related complications of any type. Informed consent was obtained from all participants. The research protocol was approved by the institutional review board of Samsung Medical Center.

### Laboratory methods

Urine and blood samples were obtained from all subjects during obstetrical visits. We simultaneously measured urinary iodine and creatinine (Cr) from single-voided spot urine at the time of enrollment. UIC is presented in two ways in this study: simple iodine concentration ( $\mu\text{g/L}$ ) and iodine concentration relative to Cr ( $\mu\text{g/gCr}$ ). Creatinine concentration adjusts for the adequacy of urine sample collection. The iodine to Cr ratio in a random single-voided urine sample of a well-nourished person may be a more reliable measure than simple iodine concentration because of the large day-to-day variability in iodine intake and hydration status of each individual [4]. Urinary iodine was measured by inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7500 series instrument (Agilent Technologies, Inc., Tokyo, Japan) as described in a previous study [15]. Urine Cr was measured using a Cobas Integra 800 instrument (Roche Diagnostics, Basel, Switzerland). Blood samples were obtained in order to determine serum TSH, which was measured using an immunoradiometric assay kit (Immunotech, Marseille, France). Serum titer of anti-TPO antibody was determined using a radioimmunoassay kit (BRAHMS AG, Hennigsdorf, Germany). Serum anti-Tg antibody level was measured using an anti-Tg RIA kit (BRAHMS AG, Hennigsdorf, Germany). Values of anti-TPO antibody and anti-Tg antibody less than 60 U/mL were considered negative. We used trimester-specific reference ranges for serum TSH of 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and

0.3–3.0 mIU/L in the third trimester based on the current guidelines of the Endocrine Society and American Thyroid Association [9, 11].

Statistical analysis

Statistical analyses were performed using SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean, SD, median, interquartile ranges) were tabulated for baseline characteristics and UIC. Clinical variables that did not show a normal distribution, including UIC and serum TSH, were analyzed using nonparametric statistics, such as the Kruskal–Wallis test and Mann–Whitney test, as appropriate. For variables with a normal distribution, values are presented as mean ± SD. Independent *t* test was used for comparison among patients in the three trimesters.

Results

Baseline characteristics

The mean (±SD) age of 344 participants was 33 (±4) years. About 63 % of women (*n* = 217) were primiparous, and 68 % (*n* = 234) lived in Seoul, with the remaining residing in its suburbs. Approximately 5 % of subjects were positive for anti-TPO antibody (14/312), and 2 % showed positive results for anti-Tg antibody (7/312). The baseline characteristics of study participants are described in Table 1.

Urinary iodine concentration

The median of simple UIC and adjusted by Cr were 427.3 µg/L and 447.9 µg/gCr, respectively. The median

**Table 2** Concentrations of urinary iodine according to trimester of pregnancy

Variables	Trimesters			Total ( <i>n</i> = 344)
	First ( <i>n</i> = 78)	Second ( <i>n</i> = 133)	Third ( <i>n</i> = 133)	
UIC (µg/L)				
Median	449.0	392.6	446.5	427.3
IQR	175.9–834.4	179.4–1017.8	175.4–1027.8	177.3–1022.6
Range	20.0–5020.5	29.0–13,390.0	19.0–7100.0	19.0–13,390.0
UIC (µg/gCr)				
Median	414.9	415.2	583.0	447.9
IQR	204.0–1226.9	244.9–1198.4	333.1–1628.3	251.5–1348.1
Range	77.7–12,192.2	87.2–28,124.4	96.4–20,898.6	77.7–28,124.4

Range means the upper and lower limits of urinary iodine concentrations in each trimester  
UIC urine iodine concentration, IQR interquartile range

**Table 1** Baseline characteristics

Variables	Trimesters			Total ( <i>n</i> = 344)
	First ( <i>n</i> = 78)	Second ( <i>n</i> = 133)	Third ( <i>n</i> = 133)	
Age (years)	33 ± 3	33 ± 4	34 ± 3	33 ± 4
Weight (kg)*	55 ± 7	60 ± 7	64 ± 8	61 ± 8
Height (cm)	163 ± 5	162 ± 5	162 ± 5	162 ± 5
BMI (kg/m <sup>2</sup> )*	21.3 ± 3.7	23.2 ± 3.8	24.5 ± 2.7	23.3 ± 3.6
Smoking, <i>n</i> (%)				
Yes	–	1 (1 %)	1 (1 %)	2 (1 %)
No	78 (100 %)	132 (99 %)	132 (99 %)	342 (99 %)
Parity, <i>n</i> (%)				
Primipara	45 (58 %)	80 (60 %)	92 (69 %)	217 (63 %)
Multi-para	33 (42 %)	53 (40 %)	41 (31 %)	127 (37 %)
Region of residence				
Metropolis	57 (73 %)	89 (67 %)	88 (66 %)	234 (68 %)
Suburb	21 (27 %)	43 (32 %)	44 (33 %)	108 (31 %)
Thyroid auto-antibodies				
Anti-TPO antibody	2 (3 %)	4 (3 %)	8 (6 %)	14/312 (5 %)
Anti-Tg antibody	2 (3 %)	3 (2 %)	2 (2 %)	7/312 (2 %)

Variable with a normal distribution, such as age, weight, height, and BMI, is presented as mean ± SD  
Parity is the number of pregnancies beyond 20 weeks, including live births and stillbirths  
Information regarding living area was not available in two women

\* *P* value <0.001

**Table 3** Concentrations of urinary iodine according to region of residence

Variables	Region of residence ( <i>n</i> = 342)	
	Metropolis ( <i>n</i> = 234)	Suburb ( <i>n</i> = 108)
UIC ( $\mu\text{g/L}$ )		
Median	434.1	409.7
IQR	176.4–1023.2	178.9–1024.0
Range	20.0–13,390.0	19.0–8660.0
UIC ( $\mu\text{g/gCr}$ )		
Median	442.3	501.5
IQR	245.0–1181.7	257.5–1494.5
Range	77.7–28,124.4	91.5–20,898.6

Information regarding living area was not available in two women

UICs according to trimester were 449.0  $\mu\text{g/L}$  in the first trimester, 392.6  $\mu\text{g/L}$  in the second trimester, and 446.5  $\mu\text{g/L}$  in the third trimester, and there was no difference in UIC among the three trimesters ( $P$  value = 0.953). Median, interquartile ranges and minimum and maximum values of UIC ( $\mu\text{g/L}$  and  $\mu\text{g/g Cr}$ ) according to pregnancy trimester are detailed in Table 2. When we compared UIC according to region of residence, we found no difference between Seoul and its suburbs (Table 3).

#### Distribution of urinary iodine concentrations

When we divided all subjects by UIC level according to WHO criteria [8], only 13 % (46/344) were in the adequate range (i.e., UIC between 150 and 249  $\mu\text{g/L}$ ). Approximately two-thirds of the patients (224/344, 65 %) showed a UIC 250  $\mu\text{g/L}$  or greater. On the contrary, 21 % (73/344) of participants had a UIC <150  $\mu\text{g/L}$  (Table 4). However, interpretation and extrapolation of these UIC results to individual patients should be performed with caution because dietary iodine intake and UIC are highly variable from day to day. Thus, even in populations with high iodine intake, there are always individuals with a low UIC on the day of the survey; however, this does not necessarily imply iodine deficiency.

#### Maternal thyroid function according to urinary iodine concentration

Median serum TSH was 1.18, 1.50, and 1.63 mIU/L in the first, second, and third trimesters, respectively. Maternal serum TSH was not statistically different according to UIC group determined by WHO criteria (serum TSH 1.52 mIU/L in UIC  $\leq$ 150  $\mu\text{g/L}$ , 1.44 mIU/L in UIC 150–249  $\mu\text{g/L}$ , and 1.48 mIU/L in UIC 250–499  $\mu\text{g/L}$ ) (Table 4).

**Table 4** Distribution of urinary iodine concentrations in pregnant women according to WHO criteria and thyroid function

	Urinary iodine concentration ( $\mu\text{g/L}$ )			
	<150	150–249	250–499	$\geq$ 500
Trimesters, <i>n</i>				
First	18	6	19	35
Second	25	25	27	56
Third	30	15	28	60
Total, <i>n</i> (%)	73 (21)	47 (14)	74 (21)	150 (44)
Serum TSH (mIU/L), median*	1.52	1.44	1.48	1.56
Serum TSH (mIU/L) >3.0, <i>n</i> (%)**	5 (7)	5 (11)	6 (8)	22 (15)

\* Serum TSH was not different among groups with different UICs ( $P$  value = 0.401)

\*\* TSH values of the trimester-specific pregnancy reference ranges according to the American Thyroid Association (first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; and third trimester, 0.3–3.0 mIU/L) [11]. The proportions of serum TSH >3.0 mIU/L were not different among groups with different UIC values ( $P$  value = 0.266)

## Discussion

Here, we report the iodine status of 344 healthy pregnant women in Korea, and found that the median UIC was 427.3  $\mu\text{g/L}$  and 447.9  $\mu\text{g/gCr}$ . There was no association between thyroid function and UIC in these study subjects. To the best of our knowledge, this is a first report of iodine status in pregnant women in Korea, where iodine intake is considered high.

Korea is an iodine-sufficient country. Kim et al. [12] reported that the mean iodine intake of healthy adults in Korea was 479  $\mu\text{g/day}$  according to a food questionnaire, and that the mean UIC was 674  $\mu\text{g/gCr}$ . A recent study of 540 healthy adults living in an urban area in Korea found that the median UIC was 268  $\mu\text{g/L}$  [16]. Another study for healthy preschool children aged between 2 and 7 years reported that the median UIC was 439  $\mu\text{g/L}$ , and that two-thirds of the children had excessive iodine intake. As the dietary habits of children are determined by those of parents, this result suggests that the Korean population as a whole consumes iodine-rich foods [13]. In the present study, the median UIC was comparable to the figure reported for preschool children, which indicates that iodine intake in Korea is excessive according to WHO criteria.

The median UIC of pregnant women in Korea in this study was higher than that reported in previous studies in populations with high iodine intake in adjacent regions in Asia. Fuse et al. [17] reported a sufficient iodine status in 934 pregnant Japanese women, with a median UIC of

219.0  $\mu\text{g/L}$ . Another Japanese group reported a median UIC of 328  $\mu\text{g/L}$  in 514 women in early pregnancy [18]. Iodine status is highly variable according to province in China [19]; a recent study of pregnant Chinese women reported a median UIC of 1240  $\mu\text{g/L}$  in subjects from areas where tap water is supplemented with iodine [20].

In the present study, the median UIC was consistently high across all trimesters. Fuse et al. [17] reported that the median UIC in Japan tended to decrease in late pregnancy (221  $\mu\text{g/L}$  in the first trimester, 193  $\mu\text{g/L}$  in the third trimester), although the difference was not significant. A similar tendency has been observed in several previous studies conducted in iodine-deficient areas such as Australia, Ireland, Iran, and Switzerland [21–24]. Iodine transfer from mother to fetus in late pregnancy might cause decreased maternal renal excretion of iodine [25], although an insufficient UIC does not always indicate real depletion of the iodine pool. However, the passage of iodine from mother to fetus does not seem to cause much change in UIC during late pregnancy in areas where iodine intake is excessive.

UIC value determined as micrograms per liter and adjusted according to Cr from spot urine was used in this study. All iodine is obtained by oral intake; because more than 90 % of dietary iodine is excreted through urine [4, 26], UIC is considered the best indicator of iodine status in epidemiologic studies. There are several methods to assess iodine status, and measuring spot urine is preferred to 24-h urine sampling in epidemiologic studies due to the simplicity and practicality of spot urine sampling [4, 27]. As UIC in each individual can vary widely according to diet, time of measurement, and urine volume, individual-level iodine status should not be determined from the value of UIC in single spot urine sample. However, this variation tends to be negligible when analyzing population-level data [8]; therefore, spot urine iodine concentration is accepted as an international criterion for assessing and monitoring the iodine status of population. During pregnancy, GFR begins to rise within 4 weeks after conception and increases through the end of the first trimester [7, 28]. As renal hyperfiltration leads to an increase in urinary iodine excretion, several studies have suggested that UIC calculated as  $\mu\text{g/gCr}$  may be a more reliable tool for measurement of iodine status in pregnant women than simple UIC expressed as  $\mu\text{g/L}$  [4, 17, 29]. However, due to the additional expense of measuring Cr, a single measurement of UIC is recommended by various health organizations as an useful indicator of iodine status in a large number of pregnant women [8]. In our study, simple urine iodine concentration ( $\mu\text{g/L}$ ) and urine iodine to creatinine ratio ( $\mu\text{g/gCr}$ ) did not differ significantly across the trimester.

We did not find an association between UIC and maternal serum TSH in this study population. Consistent with our results, no significant correlation was observed between

UIC and serum TSH in a Japanese study [17]. However, several studies have reported a positive correlation between UIC and serum TSH. Orito et al. [18] reported a positive relationship between UIC and serum TSH ( $r = 0.1326$ ;  $P < 0.005$ ) in early pregnant women, although the correlation was weak. Sang et al. [20] also suggested that excessive iodine intake during the late period of pregnancy may cause mild thyroid dysfunction in mothers, which mainly presents as subclinical hypothyroidism. Teng et al. [30] demonstrated that excessive iodine intake may trigger autoimmunity of thyroid glands, which leads to either subclinical or overt hypothyroidism in non-pregnant adults. Possible explanation for the lack of a relationship between UIC and serum TSH in our study population was that we enrolled only healthy pregnant women without goiter or history of thyroid disease. The prevalence of thyroid autoantibody was  $<5\%$  in our study group, which is far less than that reported in the normal population [31, 32]. In addition, subjects with low UIC might not actually have iodine deficiency because day-to-day variation in UIC can be quite high in individuals.

There are some limitations to this study. First, this study was conducted at a tertiary referral hospital and not in a primary hospital setting, and it was not a cohort-based study. However, the Obstetrics Department of Samsung Medical Center functions not only as a tertiary referral hospital, but also as a primary care center for pregnant women. This is because the hospital is located in a populated area containing few delivery hospitals due to poor reimbursement for childbirth from the national health insurance system. Thus, we are confident that the participants in this study reflect normal pregnancy in Korea because we excluded all high-risk pregnancies and all conditions that could affect thyroid functional status. Furthermore, there were no differences in UIC according to habitation region. Secondly, information about iodine intake was not collected during this study. Calculation of iodine intake and iodine contents in food is quite difficult because of the complexity of Korean foods. The major sources of dietary iodine in Korean healthy adults are seaweeds and dairy products [12]. However, a positive strong relationship between iodine intake and UIC was demonstrated in a previous study of Korean adults [12]. Finally, we did not evaluate the relationship between maternal UIC and neonatal outcome, especially neonatal thyroid function, because it was beyond the scope of the study. In most adults, thyroid homeostasis is maintained in spite of chronic excessive iodine status [33, 34]. However, avoidance of the acute Wolff–Chaikoff effect, which is one of processes by which thyroid hormone production recovers, may not occur in fetuses younger than 36-week gestation [35, 36]. Thus, in the setting of iodine excess, the fetus may be susceptible to hypothyroidism [35, 36]. However, the few studies that have studied iodine intake and fetal

outcomes in iodine-excessive areas have reported favorable outcomes even in iodine-excessive areas [17, 18], although the longest duration for observation was 1 year after birth [18]. Further investigations are warranted to clarify the long-term, neurodevelopmental outcomes of children born to mothers with high iodine intake, and to determine the safe upper limits of UIC in pregnant women.

In conclusion, this is a first report of iodine status in normal pregnant women in Korea. The median UIC and UIC adjusted by Cr were 427.3  $\mu\text{g/L}$  and 447.9  $\mu\text{g/gCr}$ , respectively, which were more than adequate according to WHO criteria. Considering the wide range of UIC, we recommend active education about adequate iodine intake for pregnant women even in areas where the UIC is more than adequate according to WHO criteria. Further investigations about the effect of iodine status in pregnancy on fetal outcome are warranted.

**Conflict of interest** The authors have nothing to declare about this study.

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