Thyroid Dysfunction during Late Gestation Is Associated with Excessive Iodine Intake in Pregnant Women

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Context: Adequate iodine intake during pregnancy is essential for both the synthesis of maternal thyroid hormones and the maintenance of normal fetal brain development. Scant evidence is available on the effects of excessive iodine intake during pregnancy.

Objective: The study assesses the relationship between iodine nutritional status and thyroid function of pregnant women with excessive iodine intake during late gestation.

Design and Participants: A cross-sectional study of 384 pregnant women was carried out in Tianjin and Haixing from April to October in 2010.

Main Outcome Measures: Morning urine samples and blood samples were obtained from all subjects. Serum levels of free T_3, free T_4, and sensitive TSH and urinary iodine concentration were measured.

Results: The median urinary iodine concentration of pregnant women with excessive iodine intake was significantly higher than those with adequate iodine intake ($P < 0.001$). The prevalence of thyroid disease, especially subclinical hypothyroidism, in pregnant women with excessive iodine intake was significantly higher than in those with adequate iodine intake ($P < 0.05$). Subclinical hypothyroidism was the most frequent pattern of thyroid disease for pregnant women and those with positive or negative thyroid autoantibodies. Living with high water iodine content and having urinary iodine concentration higher than 250 μg/liter are associated risk factors for subclinical hypothyroidism in pregnant women ($OR_1 = 41.822$, $OR_2 = 6.202$; $P < 0.05$, where OR_1 is the odds ratio for living with high water iodine content and hypothyroidism and OR_2 is the odds ratio for urinary iodine concentration >250 μg/liter and hypothyroidism).

Conclusions: Excessive iodine intake during late pregnancy may lead to maternal thyroid dysfunction, particularly subclinical hypothyroidism. The appropriate measurements should be performed to monitor the onset of hypothyroidism in pregnant women with excessive iodine intake. **(*J Clin Endocrinol Metab* 97: E1363–E1369, 2012)**

Iodine is required for the synthesis of thyroid hormones. Optimal iodine intake during pregnancy is essential for maintaining proper thyroid function in the mother, as well as for the development of a healthy fetal brain and psychomotor skills. Various studies have shown that low iodine intake during pregnancy may result in hypothyroidism and brain damage (1, 2).

Iodine intake is recommended during pregnancy for a number of health reasons (3). High T_4 levels maintain whole-body metabolism while pregnant, and the transfer

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Abbreviations: CV, Coefficient of variation; FT_3, free T_3; FT_4, free T_4; sTSH, sensitive TSH; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

of T_4 and iodide from the mother is needed for a healthy fetus. In addition, increased iodine intake is needed to help offset its loss due to increased renal clearance by the kidneys during pregnancy (4). The recommended daily iodine intake established by the World Health Organization was 200 μg in 1996 (5) and 250 μg in 2007 (6). A median urinary iodine of 150 to 249 μg/liter is adequate, whereas 250–499 μg/liter is considered above the requirement (6).

Recent studies have linked excess iodine intake with adverse effects such as iodine excess disorders (7, 8). However, few data are known about the adverse effects of excessive iodine intake in pregnant women. In this study, the effects of excessive iodine intake during pregnancy are explored to provide preventive measures necessary to prevent thyroid diseases in pregnant women and their offspring.

Subjects and Methods

Subjects

A cross-sectional study was performed in two cities of Haixing, where residents had excessive iodine intake owing to the high iodine content in the local drinking water (9), and in Tianjin, where the residents had sufficient iodine levels based on previous investigation of iodine deficiency diseases (10). The study was performed from April to October 2010. Iodine supplementation, intake, and other demographic factors during pregnancy were recorded. Women using iodine supplementation during pregnancy or who had lived in their local area for less than 5 yr were excluded. A total of 384 healthy pregnant women (210 in Haixing and 174 in Tianjin) with no previous history of thyroid disease or medications were recruited to the study. The demographics of the study are presented in Table 1. There were no statistically significant differences between women in Haixing and Tianjin, except for the water iodine contents.

Research protocols were approved by the medical ethics committee of Tianjin Medical University. Informed consent was obtained from all of the participants.

Laboratory methods

Morning urine and blood samples were obtained during the third trimester of pregnancy in all subjects. Serum was prepared and stored with morning urine samples at −80 C and 4 C, respectively, for further assay within 2 wk.

Serum free T_3 (FT_3), free T_4 (FT_4), and sensitive TSH (sTSH) were measured in all subjects by a chemiluminescence immunoassay, using diagnostic kits (Bayer Healthcare, Siemens, Berlin, Germany). The normal reference ranges of FT_3, FT_4, and sTSH during the third trimester were 3.52–5.20 pmol/liter, 9.2–16.7 pmol/liter, and 0.47–4.54 mIU/liter, respectively (11). The intra- and interassay coefficients of variation (CV; n = 20) in our laboratory were, respectively, 2.4 and 4.2% for FT_3, 3.2 and 5.5% for FT_4, and 2.7 and 4.7% for sTSH. The sensitivity for each assay was 0.3 pmol/liter (FT_3), 1.3 pmol/liter (FT_4), and 0.01 mIU/liter (sTSH). Accuracy was assessed by analysis of three levels of certified reference material of FT_3, FT_4, and sTSH with each batch. It gave means ± SD for FT_3 of 3.63 ± 0.227 (CV, 6.3%), 9.63 ± 0.473 (CV, 4.9%), and 14.35 ± 0.592 (CV, 4.1%) pmol/liter; for FT_4 of 14.35 ± 0.592 (CV, 7.8%), 21.81 ± 0.569 (CV, 2.6%), and 52.64 ± 1.125 (CV, 2.1%) pmol/liter; and for sTSH of 0.574 ± 0.0294 (CV, 5.1%), 6.22 ± 0.612 (CV, 9.8%), and 42.59 ± 1.126 (CV, 2.7%) mIU/liter, which were all located in the normal range.

Serum thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) were detected by RIA (China Institute of Atomic Energy). The normal negative ranges for TPOAb and TgAb were 20 and 30%, respectively. The intra- and interassay CV (n = 10) in our laboratory were, respectively, 7.6 and 13.2% for TPOAb and 8.5 and 14.3% for TgAb.

Urinary iodine excretion was determined in all subjects by national standard methods (ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction) (12) with quality control. Two levels of certified reference material, lyophilized human urine (lot no.GBW09108 h, GBW09110k; National Reference Laboratory, Beijing), with the mean certified iodine concentrations of 88 μg/liter (95% central interval: 79, 97 μg/liter) and 212 μg/liter (95% central interval: 202, 222 μg/liter) were run with each batch of samples. The intra- and interassay CV (n = 6) in our laboratory were 1.5–3.9 and 2.8–5.5%. The accuracy of the method was 92.6–107.0%.

Diagnostic criteria

Hypothyroidism was diagnosed when serum sTSH was greater than 4.54 mIU/liter and serum FT_4 was less than 9.2 pmol/liter. Subclinical hypothyroidism was diagnosed when serum TSH was greater than 4.54 mIU/liter and serum FT_4 was within normal range. Hyperthyroidism was diagnosed when serum TSH was less than 0.47 mIU/liter and serum FT_4 was greater

TABLE 1. Basic characteristics of pregnant women

	Haixing (excessive iodine intake)	Tianjin (adequate iodine intake)
n	210	174
Age (yr)	27.69 ± 4.73 (range, 20–44)	28.07 ± 4.87 (range, 19–2)
Height (cm)	163.73 ± 4.88	163.40 ± 4.59
Weight (kg)	73.78 ± 11.16	76.59 ± 11.18
Median water iodine content (μg/liter)	617.80	8.23
Smoking	None	None
Gestational length (wk)	39.91 ± 1.05	38.56 ± 1.84
Mode of delivery, n (%)		
Cesarean section	154 (73.3%)	127 (73.0%)
Vaginal delivery	56 (26.7%)	47 (27.0%)

Data are expressed as mean ± SD, unless otherwise specified.

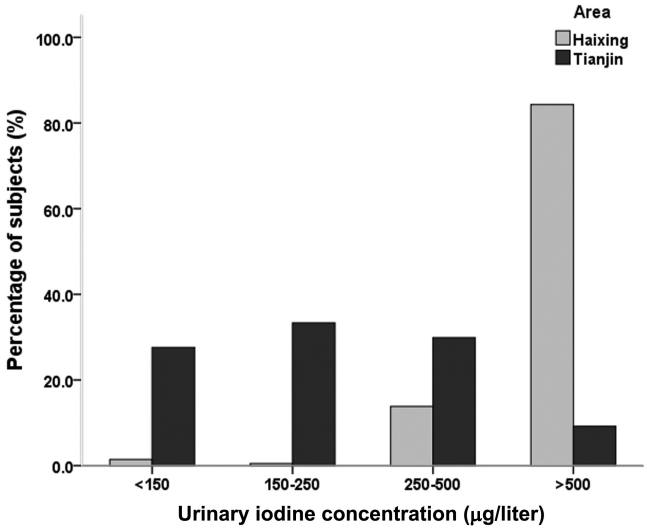

FIG. 1. Urinary iodine concentration distribution of pregnant women with excessive and adequate iodine intake in two areas. The distribution of urinary iodine concentrations of pregnant women with excessive and adequate iodine intake was significantly different ($\chi^2 = 176.315$; $P = 0.000$).

than 16.7 pmol/liter, and/or FT_3 was greater than 5.2 pmol/liter. Subclinical hyperthyroidism was diagnosed when serum TSH was less than 0.47 mIU/liter and serum FT_4 and FT_3 were within normal ranges. Thyroid autoantibodies were positive when TPOAb was greater than 20% and/or TgAb was greater than 30%.

Statistical analysis

Statistical analysis was performed with SPSS version 13.0 (SPSS Inc., Chicago, IL). Normally distributed data (serum FT_3 and FT_4 concentrations and some demographic factors of pregnant women) are presented as mean and SD values, and skewed data (urinary iodine and serum sTSH concentrations) are presented as median and interquartile range (25th-75th percentiles). Wilcoxon rank sum tests were performed to compare the water iodine, urinary iodine, and serum sTSH concentrations in different areas. Two independent-sample *t* tests were used to compare serum FT_3 and FT_4 concentrations and some demographic factors of pregnant women in different areas. Differences in frequencies were analyzed by χ^2 tests, including percentage of mode of delivery, positive rate of thyroid autoantibodies, and prevalence of thyroid diseases. Pearson bivariate correlation was assessed to test the relevance between the logarithm of urinary iodine concentration and serum FT_3 concentration, whereas Spearman rank bivariate correlation was assessed to test the correlation between urinary iodine concentration and serum FT_4 and sTSH concentration of pregnant women. Single factor analysis and logistic regression were used to analyze the risk factors of subclinical hypothyroidism. Two-tailed cutoffs were used, and a value of $P < 0.05$ was considered statistically significant.

Results

Study population

The study demographics of the two areas are summarized in Table 1. No significant differences were detected between the two areas except for water iodine content.

Urinary iodine concentration

The median urinary iodine concentrations of pregnant women in Haixing and Tianjin were 1240.70 (672.20–1964.87) and 217.06 (145.93–332.86) μg/liter, respectively ($Z = 12.196$; $P = 0.000$). In Haixing, 84.3% of pregnant women exhibited excessive iodine nutritional status. In Tianjin, 9.2% of pregnant women had urinary iodine concentration of more than 500 μg/liter. In Haixing and Tianjin, 0.5 and 33.3% of pregnant women had adequate iodine intake, respectively, whereas 13.8 and 29.9% had iodine intake that was above the requirement, respectively. However, 27.6% of pregnant women in Tianjin and 1.4% in Haixing were iodine deficient, with urinary iodine concentration of less than 150 μg/liter (Fig. 1).

Thyroid hormones and autoantibodies

In Haixing, pregnant women had higher serum concentrations of sTSH (2.89 *vs.* 2.19 mIU/liter; $Z = 3.283$; $P = 0.001$) and FT_3 (4.03 *vs.* 3.78 pmol/liter; $t = 3.572$; $P < 0.001$), and lower concentrations of FT_4 (13.35 *vs.* 13.77 pmol/liter; $t = -2.048$; $P = 0.041$) than pregnant women from Tianjin (Table 2). There were no significant differences in the positive rates of TPOAb and TgAb in pregnant women between Haixing and Tianjin (16.2 *vs.* 24.1% for TPOAb and 7.1 *vs.* 3.4% for TgAb; $P > 0.05$; Table 2).

TABLE 2. Thyroid parameters of pregnant women with different iodine intake

	Haixing (excessive iodine intake)	Tianjin (adequate iodine intake)	P^a
n	210	174	
FT_3 (pmol/liter), mean ± SD	4.03 ± 0.59	3.78 ± 0.38	<0.001
FT_4 (pmol/liter), mean ± SD	13.35 ± 1.59	13.77 ± 1.61	0.041
sTSH (mIU/liter), median (interquartile range)	2.89 (1.85–4.31)	2.19 (1.54–3.26)	0.001
TPOAb positive, n (%)	34 (16.2%)	42 (24.1%)	n.s.
TgAb positive, n (%)	15 (7.1%)	6 (3.4%)	n.s.

n.s., Not significant.

[a] Comparisons between Haixing and Tianjin, made by two independent-samples *t* test for serum FT_3 and FT_4 concentrations, Wilcoxon rank sum test for serum sTSH concentration, and χ^2 test for positive rate of TPOAb and TgAb.

TABLE 3. Thyroid diseases of pregnant women with different iodine intake

	Haixing (excessive iodine intake)	Tianjin (adequate iodine intake)	P^a
n	210	174	
Hyperthyroidism	1 (0.5%)	0 (0.0%)	[b]
Subclinical hyperthyroidism	4 (1.9%)	0 (0.0%)	n.s.
Hypothyroidism	1 (0.5%)	0 (0.0%)	[b]
Subclinical hypothyroidism	42 (20.0%)	4 (2.3%)	<0.001
Total	48 (22.9%)	4 (2.3%)	<0.001

Data are expressed as number (percentage). n.s., Not significant.

[a] Comparisons between Haixing and Tianjin, made by χ^2 test.

[b] Some analysis cannot be carried out because of crosstabs that have minimum expected count less than 1.0.

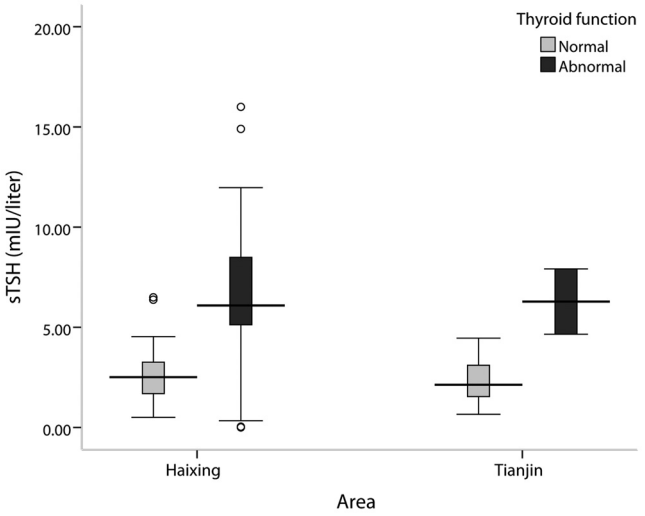

FIG. 2. Serum sTSH concentration (mIU/liter) of pregnant women with normal or abnormal thyroid function in two areas. There was no significant difference in serum sTSH concentration of pregnant women with normal or abnormal thyroid function in Haixing and Tianjin ($P > 0.05$).

Thyroid diseases

A total of 48 pregnant women (22.9%) were diagnosed with thyroid dysfunction in Haixing— one (0.5%) with hyperthyroidism, four (1.9%) with subclinical hyperthyroidism, one (0.5%) with hypothyroidism, and 42 (20.0%) with subclinical hypothyroidism. However, only four pregnant women (2.3%) were diagnosed with subclinical hypothyroidism in Tianjin. The total prevalence of thyroid disease was 10-fold greater in Haixing than in Tianjin (22.9 *vs.* 2.3%; $P < 0.001$; Table 3). The prevalence of subclinical hypothyroidism was significantly higher in Haixing than in Tianjin (20.0 *vs.* 2.3%; $P < 0.001$; Table 3).

Thyroid function and serum sTSH concentration

Pregnant women demonstrated no significant differences in serum sTSH concentration with (6.09 *vs.* 6.28 mIU/liter; $P > 0.05$) or without (2.50 *vs.* 2.13 mIU/liter; $P > 0.05$; Fig. 2) thyroid disease between Haixing and Tianjin.

Thyroid function and iodine intake of pregnant women with positive or negative thyroid autoantibodies

Pregnant women with excessive iodine intake and the same thyroid autoimmunity status were more likely to develop thyroid disease, namely subclinical hypothyroidism, than those with normal iodine intake ($P < 0.05$; Table 4). In the same area, the prevalence of thyroid diseases seemed no different in pregnant women with positive or negative thyroid autoantibodies ($P > 0.05$; Table 4). Hyperthyroidism (2.8%), subclinical hyperthyroidism (2.8%), hypothyroidism (2.8%), and subclinical hypothyroidism (25.0%) were typically observed in pregnant women with excessive iodine intake and positive thyroid autoantibodies. However, pregnant women with adequate iodine intake presented only with subclinical hypothyroidism (4.5%). For pregnant women with negative thyroid autoantibodies, subclinical hyperthyroidism (1.7%) and subclinical hypothyroidism (19.0%) were more frequent with excessive iodine intake, whereas subclinical hypothyroidism (1.5%) was associated with adequate iodine intake.

The relationship between urinary iodine concentration and thyroid hormone in pregnant women

The logarithm of urinary iodine concentration of pregnant women positively correlated with serum FT_3 concentration ($r = 0.217$; $P < 0.001$). There were no significant relationships between urinary iodine concentration or serum FT_4 and sTSH concentration in pregnant women ($P > 0.05$).

Analysis of risk factors for subclinical hypothyroidism

Single factor analysis showed that the prevalence of subclinical hypothyroidism was significantly different in pregnant women based on factors such as living in areas with different water iodine content and urinary iodine concentration (higher or lower than 250 μg/liter). Logistic regression showed that risk factors for subclinical hypothyroidism in pregnant women were living with high water iodine content (odds ratio = 41.822; 95% confidence interval = 6.633 to 263.689; $P < 0.001$) and high (>250 μg/liter) urinary iodine concentration (odds ratio = 6.202; 95% confidence interval = 1.097 to 35.073; $P = 0.039$).

TABLE 4. Thyroid hormones and thyroid diseases of pregnant women with the same thyroid autoimmunity and different iodine intake

	Haixing (excessive iodine intake)	Tianjin (adequate iodine intake)	P^a
n	210	174	
Group A (TPOAb positive and/or TgAb positive)			
n	36	44	
Hyperthyroidism	1 (2.8%)	0 (0.0%)	[b]
Subclinical hyperthyroidism	1 (2.8%)	0 (0.0%)	[b]
Hypothyroidism	1 (2.8%)	0 (0.0%)	[b]
Subclinical hypothyroidism	9 (25.0%)	2 (4.5%)	0.021
Total	12 (33.3%)	2 (4.5%)	0.001
Group B (both TPOAb and TgAb negative)			
n	174	130	
Hyperthyroidism[b,c]	0 (0.0%)	0 (0.0%)	[b]
Subclinical hyperthyroidism[b,c]	3 (1.7%)	0 (0.0%)	n.s.
Hypothyroidism[b,c]	0 (0.0%)	0 (0.0%)	[b]
Subclinical hypothyroidism[c]	33 (19.0%)	2 (1.5%)	<0.001
Total[c]	36 (20.7%)	2 (1.5%)	<0.001

Data are expressed as number (percentage). n.s., Not significant.

[a] Comparison between Haixing and Tianjin of pregnant women in group A and group B, made by χ^2 test.

[b] Some analysis cannot be carried out because of crosstabs that have minimum expected count less than 1.0.

[c] Comparision between group A and group B of pregnant women in the same area, made by χ^2 test.

Discussion

Iodine intake during pregnancy needs to compensate for increases in maternal blood volume and urinary iodine excretion. However, a proper balance of iodine intake is needed during pregnancy for the mother and the developing fetus. Studies have demonstrated that iodine deficiency during pregnancy may lead to maternal hypothyroidism (13) and impaired physical and intellectual development (14). Thus, many countries and institutions such as the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) have established that the recommended nutrient intake of iodine for pregnant women should be at least 250 μg/d (6, 15). However, excessive iodine intake may be detrimental to pregnant women and may increase their risk for developing hypothyroidism and autoimmune thyroiditis, as shown in the nonpregnant population (8). Few studies have explored the effects of excessive iodine intake in pregnant women. Therefore, we performed a population study of pregnant women in areas of different iodine intake.

Data from one cross-sectional study of 1844 pregnant women demonstrated that the intake of iodine supplements while pregnant may lead to thyroid dysfunction (16). In our study, we found that serum sTSH concentration of pregnant women with excessive iodine intake was higher than those in an area of adequate iodine intake, whereas serum FT_4 concentration was lower. The elevated sTSH of pregnant women in areas of high iodine intake may have a number of causes. The association may be the result of the Wolff-Chaikoff effect (17). This involves decreased formation and release of the thyroid hormone at high iodide levels, which induces a feedback loop to increase sTSH levels. Consequently, hypothyroidism or subclinical hypothyroidism might develop (17, 18). On the other hand, excessive iodine intake could directly increase TSH levels by the action of the pituitary gland and hypothalamus (18).

In our population study, the incidence of subclinical hypothyroidism in pregnant women was higher in areas of high iodine intake than in those with adequate intake. Abortion, stillbirth, and intrauterine growth retardation have been linked to hypothyroidism or subclinical hypothyroidism (19, 20). The prevalence of subclinical hypothyroidism in pregnant women in our study was higher than reported in some international epidemiological surveys (21, 22). However, the positive correlation between urinary iodine concentration and serum FT_3 concentration in pregnant women has previously been noted (23). In our study, living in an area of high water iodine content and urinary iodine concentration (>250 μg/liter) led to greater risk of having subclinical hypothyroidism. Therefore, the amount of iodine consumed in pregnancy should be monitored.

No significant differences were observed in TPOAb and TgAb levels between pregnant women of Haixing and Tianjin. The positive rates of thyroid autoantibodies in pregnant women in our study were higher than those reported in general female populations (23–25). These autoantibodies can appear after iodine supplementation, as

reported in a population that was formerly iodine-deficient (25, 26). The fact that we found a higher positive rate of TPOAb in pregnant women living in the iodine-adequate area of Tianjin may be related to changes in the nutritional status of iodine in Tianjin, where iodine deficiency once existed.

Positive thyroid autoantibodies may interact with excessive iodine exposure and increase the prevalence of hypothyroidism in a population with excessive iodine intake (27). Our study showed that the prevalence of subclinical hypothyroidism and total thyroid disease in pregnant women with positive and negative thyroid autoantibodies was higher in excessive than in adequate iodine-intake areas. This suggests that pregnant women living in excessive water iodine content areas should monitor their thyroid function even if their thyroid autoantibodies are negative. However, it is debatable whether thyroid autoimmunity is a risk factor for hypothyroidism or subclinical hypothyroidism (28–30). We did not observe a significant difference in the occurrence of thyroid disease in pregnant women positive or negative for thyroid autoantibodies in our study. However, careful monitoring of thyroid function in pregnant women with thyroid autoantibodies is still warranted.

Management of thyroid disease is important because there are changes in thyroid function during pregnancy that may be adverse to both the mother and fetus. The American Association of Clinical Endocrinologists, the Latin American Thyroid Society, the Asia and Oceania Thyroid Society, the American Thyroid Association, and the European Thyroid Association have published guidelines for thyroid disease management (31) that include regular screening, proper diagnosis, and timely treatment. However, we did not do the follow-up study of the pregnant women and their neonates because of the limited funding. Therefore, we do not have any information about the follow-up of these subjects at the present time. Further studies are necessary to investigate the outcome of these subjects.

In China, guidelines have been established to ensure an appropriate intake of adequate iodine in pregnant women. These include stopping the supply of iodized salt and changing the drinking water in areas with excessive iodine in drinking water. Moreover, the concentration of iodine in iodized salt measures should be adjusted to local conditions. Monitoring of urinary iodine concentration, thyroid function, and thyroid autoantibodies in pregnant women have been recommended, especially in those with excessive iodine intake. Implementation of these Chinese guidelines, which are in line with those of The Endocrine Society Clinical Practice Guidelines (31), will be an invaluable step in protecting the health of women and the population as a whole. However, due to the increased iodine requirement during pregnancy, we still recommend increased iodine intake in adequate and deficient iodine areas in China and elsewhere in the world.

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