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ORIGINAL ARTICLE

Assessment of iodine nutritional status and gestational thyroid function reference ranges during the first trimester of pregnancy in Taiwan

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Abstract

Background: Iodine nutrition is critical for fetal neurodevelopment in the first trimester of pregnancy, a period associated with dramatic changes in thyroid function. The aim of this study was to evaluate iodine nutritional status and thyroid function reference ranges in the first trimester in Taiwan.

Methods: Pregnant women aged 20 years and above in the first trimester were recruited in Taipei Veterans General Hospital, Taiwan from March 2019 to July 2022. Each participant provided a spot urine sample for measurement of urinary iodine concentration (UIC) and a blood sample for checkup of thyroid function and thyroid autoantibodies. A simple food frequency questionnaire was also completed.

Results: A total of 209 women with a mean age of 32.9±4.4 years were enrolled. The median UIC was 160.9 μg/L (interquartile range [IQR]: 105.0-246.2 μg/L), indicating overall iodine sufficiency. The gestational thyroid function reference ranges were: thyroid stimulating hormone (TSH) (median: 0.93 [0.007-2.9] μIU/mL), free T4 (1.3 [0.93-2.2] ng/dL), free T3 (3.0 [2.3-5.0] ng/dL), total T4 (9.9 [6.4-16.9] ng/dL), and total T3 (135 [88-231] ng/dL). If the nonpregnant reference range of serum TSH was used, eight women (4.8%) would be misclassified as having subclinical hyperthyroidism, and two women (1.2%) with subclinical hypothyroidism would be missed. In multivariate analysis, nulliparous (adjusted odds ratio [OR] from model 1-3: 2.02, 2.05, 2.02; 95% CI, 1.08-3.77, 1.10-3.81, 1.11-3.66; p = 0.027, 0.023, 0.022, respectively) and multivitamin nonusers (adjusted OR from model 1-3: 1.86, 1.85, 1.78; 95% CI, 1.04-3.34, 1.03-3.32, 1.004-3.71; p = 0.038, 0.039, 0.049, respectively) had increased odds of having lower UIC levels <150 μg/L.

Conclusion: The iodine nutritional status in the first trimester is adequate in Taiwan; however, certain subgroups such as nulliparous and multivitamin nonusers are still at risk for iodine deficiency. Gestational thyroid function reference ranges are needed for correct diagnosis of thyroid dysfunction in pregnancy.

Keywords: Gestation; Iodine; Pregnancy; Taiwan; Thyroid

1. INTRODUCTION

Iodine is an essential micronutrient and the major component of thyroid hormones; it is vital in pregnancy to promote normal fetal growth and neurodevelopment.[1–3] Profound hypothyroidism, brain damage, congenital hypothyroidism, and low intelligence quotient may result from severe iodine deficiency in pregnancy, and these intellectual deficits can be reversed by iodine supplementation.[1–5] Although the benefits of iodine supplementation in mild to moderate iodine deficiencies have not been universally demonstrated, studies have shown associations between increased pregnancy complications, mild thyroid alterations and worse intellectual development in children born to mothers with mild to moderate iodine deficiencies.[1,2,5–9] The fetal thyroid does not mature until the beginning of the second trimester, making fetuses entirely dependent on maternal thyroid hormone during early pregnancy. The contribution of maternal thyroid hormones to the fetus continues until birth because of the relatively low fetal thyroid reserve even after the initiation of thyroid hormone production.[2,3] The recommended daily iodine

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intake to meet the maternal and fetal thyroid hormone demand during pregnancy is 250 μg/d, which is 100 μg more than the usual recommended amount.[10] Due to increased glomerular filtration rate and iodine loss from urine during pregnancy, the criterion to define iodine sufficiency in pregnancy is a population median urinary iodine concentration (UIC) of 150 to 249 μg/L, in contrast to the median UIC of 100 to 299 μg/L for the general population.[11]

According to the result of the Nutrition and Health Survey in Taiwan 2017 to 2020, the population median UIC was 104 μg/L for adults over 19 years old, indicating overall iodine sufficiency[12]; however, the population median UIC for pregnant women was 148 μg/L according to a national survey in 2017 to 2019, suggesting mild iodine deficiency in pregnancy.[13] The process of thyroid hormone neurodevelopment includes two stages. The first stage of neuronal proliferation and migration starts in the first trimester and continues into the early part of the second trimester, whereas the second stage of neurogenesis, neuron migration, and myelination occurs later in pregnancy.[14] It is important to maintain adequate iodine nutrition throughout gestation; however, pregnancy often remains unnoticed until 2 months after conception, and the nutritional awareness is generally low in early pregnancy. Most women recruited in previous surveys were in late pregnancy, and there was little information regarding iodine nutritional status in the initial critical period of neurodevelopment.[15] A survey of pregnant women residing around metropolitan Taipei, where the population median UIC was 225.3 μg/L, included only 16 women in the first trimester out of a total of 257 pregnant women.[16] Obstetricians in Taiwan have started to recommend routine nutritional supplement only after 12 weeks of gestation, which may result in different iodine statuses between early and late pregnancy.

In response to elevation of placental human chorionic gonadotropin, a maternal free T4 surge occurs that suppresses maternal thyroid stimulating hormone (TSH) at the end of the first trimester.[15,17] This guarantees that maternal fT4 is sufficiently supplied to the fetus, but also causes misinterpretation of thyroid function tests if gestational thyroid function reference ranges are not used.[15,17] The increased production of thyroxine-binding globulin during pregnancy also leads to elevated concentrations of total T4 and T3, necessitating a gestational thyroid function reference range for each thyroid hormone.[15,17,18] The American Thyroid Association (ATA) has proposed that the upper limit of serum TSH in the first trimester should be 0.5 mIU/L lower than the usual upper limit for the nonpregnant population.[18] However, there is wide variation in thyroid hormone values among different ethnicities and iodine statuses,[18–42] and the ATA has also suggested the establishment of local regional gestational thyroid function reference ranges for each region[18]; these data are currently lacking in Taiwan. The present study aimed to evaluate the iodine nutritional status and thyroid function reference ranges in early pregnancy in Taiwan.

2. METHODS

2.1. Study design and data collection

This study enrolled pregnant women who received prenatal checkups at Taipei Veterans General Hospital, Taiwan from March 2019 to July 2022. Eligible participants were women 8 to 13+6 weeks pregnant who were aged 20 years or older. Women currently taking antithyroid drugs or levothyroxine, with previous history of thyroid surgery or head and neck irradiation, and those scheduled for abortion, were excluded. Each participant provided a random spot urine sample for measurement of UIC and a blood sample for measurement of TSH, free T4, total T4, free T3, T3, antithyroglobulin antibodies (aTG), antithyroid peroxidase antibodies (aTPO), TSH receptor antibody (TR-Ab), and thyroglobulin. A food frequency questionnaire was completed on the day of sample collection. The study was approved by the local Institutional Review Board (IRB No. 2016-03-013A). Informed consent was obtained from each participant before enrollment.

2.2. Iodine and thyroid function measurements

Urine samples were stored in a –20°C environment before analysis. An Agilent 7700 Series inductively coupled plasma mass-spectrometry system (Agilent, Santa Clara, CA) was used for measuring UIC.[43] Serum TSH, free T4, total T4, free T3, total T3, aTPO, and aTG were measured by an electrochemiluminescence immunoassay (cobase 801; Roche Diagnostics GmbH, Mannheim, Germany). TR-Ab was determined by a radioreceptor assay (E5010 Cobra Quantum gamma counter; Packard BioScience, Meriden, CT).

Hypothyroidism was defined as a TSH level above the upper limit and an fT4 below the lower limit, whereas subclinical hypothyroidism was defined as a TSH level above the upper limit with an fT4 level within the reference interval. The definition of hyperthyroidism was a TSH level below the lower limit with an elevated fT4 level, whereas subclinical hyperthyroidism was defined as a TSH level below the lower limit with an fT4 level within the reference interval.

2.3. Food frequency questionnaire

The food frequency questionnaire was similar to previously described versions.[16] The first part of the questionnaire asked about the frequency of consumption of iodine-containing foods, including seaweed, fish, seafood other than fish, dairy products, and multivitamins, with response options of 1, 3, 5, 7 d/wk, or never. The second part of the questionnaire was designed to assess the types of salt (iodized or noniodized) used in the participants' households.

2.4. Gestational thyroid function reference ranges

The gestational thyroid function reference ranges were determined based on the 2.5th and 97.5th percentiles of those studied women who tested negative on all thyroid autoantibodies (including aTG, aTPO, TR-Ab) and who had no known thyroid disease.[18] Furthermore, due to a modification in the thyroid function test kit at Taipei Veterans General Hospital in October 2022, data from the first six women, whose thyroid function tests were conducted using different kits, were excluded from the analysis. Finally, 165 pregnant women were analyzed for gestational thyroid function references.

The percentage of women with thyroid dysfunction including overt dysfunction or the subclinical forms was calculated based on the thyroid function reference ranges derived from this study and compared to the nonpregnant reference ranges provided by the manufacturer.

2.5. Statistical analysis

Iodine status was determined by median UIC according to the recommendation from the United Nations International Children's Emergency Fund.[11] UIC and intake frequencies were not normally distributed and were therefore presented as medians with interquartile range, while the other continuous variables were expressed as mean ± SD. The Mann-Whitney *U* test and Kruskal-Wallis test was used for comparison between continuous variables. Categorical variables were presented as numbers with percentages and assessed by Pearson's Chi-square test. Variables with a p value ≤0.1 in univariate analysis were included in multivariable logistic regression models to determine the independent risk factors associated with lower UIC.

All data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM, Armonk, NY). A two-tailed p value of <0.05 was considered as statistically significant.

3. RESULTS

3.1. Characteristics of the study population

A total of 209 women with a mean age of 32.9 ± 4.4 years were enrolled. The characteristics of the study population are presented in Table 1. The median UIC was 160.9 μg/L (IQR: 105.0-246.2 μg/L), indicating overall iodine sufficiency. The positivity rates for aTG and aTPO were 8.7% (n = 18) and 8.2% (n = 17), respectively. Four women had positive TR-Ab and two were incidentally diagnosed with mild Graves' disease.

3.2. Food frequency questionnaire

The results of the food frequency questionnaire analysis are shown in Table 2. The most commonly ingested iodine-containing food type was dairy products, with 90.9% of participants ingesting a helping at least once per week and 71.8% of participants consuming them on at least 3 d/wk. Seaweed, seafood, and fish were consumed at least once per week by more than 60% of participants. The consumption of multivitamin was variable, with 34.0% of participants taking multivitamin every day, but 58.4% of participants never doing so.

3.3. Variables associated with UIC

Univariate analysis of factors associated with median UIC and its distribution are summarized in Table 3. Nulliparous women were associated with lower median UIC (146.2 vs 186.6 μg/L, p = 0.031) and higher likelihood for UIC <150 μg/L (51.6% vs 35.6%, p = 0.022). Compared to those with multivitamin intake, the median UIC was significantly lower in those who never consumed multivitamin (191.2 vs 146.4 μg/L, p = 0.010) and the percentage of women with UIC <150 μg/L was also significantly higher in those who did not ingest multivitamin (36.8% vs 50.8%, p = 0.044). The other demographic or dietary variables were not significantly associated with median UIC level or its distribution (Table 3).

In multivariate analysis, nulliparous (adjusted OR: 2.02, 2.05, 2.02; 95% CI, 1.08-3.77, 1.10-3.81, 1.11-3.66; p = 0.027, 0.023, 0.022, respectively) and multivitamin nonusers (adjusted OR: 1.86, 1.85, 1.78; 95% CI: 1.04-3.34, 1.03-3.32, 1.004-3.71; p = 0.038, 0.039, 0.049, respectively) had increased odds of having UIC level <150 μg/L in all models (Table 4).

Table 1

Baseline demography of the studied population

Variables	Mean ± SD or n (%)
Age, y	32.9 ± 4.4
Height, cm	160.6 ± 5.4
Weight, kg	59.6 ± 11.3
BMI, kg/m^2	23.1 ± 4.0
Education (bachelor or above)	196 (93.8)
Region (metropolis)	192 (91.9)
Smoking	4 (1.9)
Parity ≥2	87 (41.6)
Positive miscarriage history	69 (33.0)
Positive aTG	18 (8.7)
Positive aTPO	17 (8.2)
Positive TR-Ab	4 (1.9)
TSH, mIU/L	1.09 ± 1.05
Free T4, ng/dL	1.3 ± 0.3
Total T4, μg/dL	10.1 ± 2.5
Total T3, ng/dL	141.0 ± 33.6
Free T3, pg/mL	3.5 ± 7.0
UIC[a], μg/L	160.9 (105.0-246.2)

aTG = thyroglobulin antibody; aTPO = thyroid peroxidase antibodies; BMI = body mass index; n = number; TR-Ab = thyroid stimulating hormone receptor antibody; UIC = urinary iodine concentration.
[a]Presented by median and interquartile range.

3.4. Gestational thyroid function reference ranges

The gestational reference ranges for thyroid function tests are presented in Table 5. The upper limit of serum TSH was 1.3 mIU/L lower in the first trimester than the upper limit provided by the manufacturer (pregnant vs nonpregnant range: 0.007-2.9 vs 0.27-4.2 mIU/L). The upper limits of free T4 and free T3 were higher than the respective nonpregnant values (pregnant vs nonpregnant free T4 range 0.93-2.2 vs 0.93-1.7 ng/dL; pregnant vs nonpregnant free T3 range: 2.3-5.0 vs 2.0-4.4 pg/mL). The ranges of T4 and T3 in the first trimester were also higher than the nonpregnant ranges (pregnant vs nonpregnant T4 range: 6.4-16.9 vs 5.1-14.1 μg/dL; pregnant vs nonpregnant T3 range: 88-231 vs 80-200 ng/dL).

If the nonpregnant reference range of serum TSH was used, eight women (4.8%) would be misclassified as having subclinical hyperthyroidism, and two women (1.2%) with subclinical hypothyroidism would be missed. There was only one women (0.6%) whose TSH was above 4.2 mIU/L (nonpregnancy reference upper limit) and would be diagnosed with subclinical hypothyroidism by both references; whereas four women (2.4%) whose TSH was below 0.007 mIU/L would be diagnosed with subclinical hyperthyroidism by both references (Fig. 1).

4. DISCUSSION

To the best of our knowledge, this is the first study to describe the iodine nutritional status and gestational thyroid function reference ranges in the first trimester of pregnancy in Taiwan. The overall median UIC of 160.9 μg/L indicated overall sufficient iodine status; however, certain subgroups such as nulliparous and multivitamin nonusers may still be at risk for iodine deficiency. The gestational thyroid function reference ranges significantly differed from the manufacturer's reference range, and utilizing the nonpregnant reference range for diagnosing thyroid dysfunction in pregnancy may result in misclassifications that may impair proper patient care.

The result of the multivariate analysis revealed that nulliparous women and those who did not consume multivitamins were at higher risk for low UIC. A study conducted by Adalsteinsdottir et al[44] also demonstrated that nulliparous women had lower UIC compared to those who have given birth. In 1971, Taiwan previously instituted a mandatory salt iodization strategy and eliminated endemic goiter[45]; however, the change of policy from mandatory to voluntary salt iodization has resulted in reoccurrence of iodine deficiency in 2013.[46] Despite efforts to increase public awareness, increase the iodine content in fortified salts, and mandate labeling of iodine content of table salts, certain vulnerable populations such as pregnant women still remained at risk for iodine deficiency even after the iodine status has become borderline adequate for the general population.[47] Most salt in Taiwan is noniodized, and it appears that Taiwanese people lack a stable source of iodine nutrition from foods. This has made iodine supplementation an important factor that influences iodine status, especially during pregnancy and lactation.[13,48] Routine iodine supplementation in pregnancy has been suggested in

Table 2

Food frequency questionnaire: intake frequency (days/week)

Food, n (%)	0 d	1 d	3 d	5 d	7 d	Median (IQR)
Seaweed	71 (34.0)	103 (49.3)	33 (15.8)	1 (0.5)	1 (0.5)	1 (0-1)
Fish	50 (23.9)	85 (40.7)	64 (30.6)	6 (2.9)	4 (1.9)	1 (1-3)
Seafood	78 (37.3)	77 (36.8)	50 (23.9)	3 (1.5)	1 (0.5)	1 (0-2)
Dairy products	19 (9.1)	40 (19.1)	67 (32.0)	26 (12.5)	57 (27.3)	3 (1-7)
Multivitamin	122 (58.4)	3 (1.4)	9 (5.3)	4 (1.9)	71 (34.0)	0 (0-7)

IQR = interquartile.

Table 3

Urinary iodine concentration and its distributions

		Urinary iodine concentration, μg/L				
Characteristics	**Number, %**	**Median (IQR)**	***p***	**UIC <150**	**150 ≥ UIC**	***p***
Total	209	160.9 (105.0-246.2)		94	105	
Age, y			0.673			0.745
20-29	51 (24.4)	155.5 (108.4-221.0)		24 (47.1)	27 (52.9)	
30-34	90 (43.1)	156.3 (115.3-233.4)		42 (46.7)	48 (53.3)	
35 or above	68 (32.5)	188.7 (98.2-288.8)		28 (41.2)	40 (58.8)	
Body mass index, kg/m^2			0.492			0.880
≥27	32 (15.3)	181.1 (130.7-254.5)		14 (43.7)	18 (56.3)	
<27	177 (84.7)	160.0 (100.2-244.5)		80 (45.2)	97 (54.8)	
Education			0.067			0.101
Bachelor or above	196 (93.8)	159.3 (101.9-244.8)		91 (46.4)	105 (53.6)	
High school or below	13 (6.2)	215.7 (149.2-274.1)		3 (23.1)	10 (76.9)	
Residing area			0.763			0.857
Metropolis	192 (91.9)	161.4 (104.4-248.5)		86 (44.8)	106 (55.2)	
Suburb	17 (8.1)	160.0 (104.8-203.8)		8 (47.1)	9 (52.9)	
Parity			0.031			0.022
≥2	87 (41.6)	186.6 (119.3-255.4)		31 (35.6)	56 (64.4)	
1	122 (58.4)	146.2 (99.8-220.4)		63 (51.6)	59 (48.4)	
Positive miscarriage history			0.376			0.233
Yes (≥1)	69 (33.0)	177.2 (121.9-263.8)		27 (39.1)	42 (60.9)	
No (=0)	140 (67.0)	158.4 (99.7-239.3)		67 (47.9)	73 (52.1)	
Salt intake			0.178			0.433
Noniodized	85 (40.7)	152.6 (101.1-218.0)		41 (48.2)	44 (51.8)	
Iodized	124 (59.3)	171.1 (107.3-286.6)		53 (42.7)	71 (57.3)	
Seaweed			0.358			0.137
Yes (≥1)	138 (66.0)	176.8 (31.0-1284.8)		57 (41.3)	81 (58.7)	
No (=0)	71 (34.0)	144.2 (25.6-1075.1)		37 (52.1)	34 (47.9)	
Fish			0.799			0.628
Yes (≥1)	159 (76.1)	160.0 (27.6-1052.9)		73 (45.9)	86 (54.1)	
No (=0)	50 (23.9)	173.0 (34.7-1430.0)		21 (42.0)	29 (58.0)	
Seafood (except fish)			0.291			0.241
Yes (≥1)	131 (62.7)	155.5 (24.5-1130.7)		63 (48.1)	68 (51.9)	
No (=0)	78 (37.3)	185.9 (56.0-975.7)		31 (39.7)	47 (60.3)	
Dairy product			0.911			0.792
Yes (≥1)	190 (90.9)	160.5 (31.2-1041.4)		86 (45.3)	104 (54.7)	
No (=0)	19 (9.1)	184.9 (27.6-1583.9)		8 (42.1)	11 (57.9)	
Multivitamin intake			0.010			0.044
Yes (≥1)	87 (41.6)	191.2 (121.1-289.8)		32 (36.8)	55 (63.2)	
No (=0)	122 (58.4)	146.4 (94.0-222.7)		62 (50.8)	60 (49.2)	

IQR = interquartile range; UIC = urinary iodine concentration.

some countries including the United States and Canada, where a daily 100 μg of additional iodine was recommended.[18] In the present study, the median UIC for women without multivitamin intake was 146.4 μg/L, which indicates iodine deficiency. In contrast to the 79.4% of women mostly in the late trimester taking multivitamin in a previous study in 2018, only 41.6% of participants did so in the present study.[16] This result is in line with obstetricians' recommendation of starting supplementation after 12 weeks of gestation. However, this suggestion may need to be modified according to the result of the current study. In addition to the differences in multivitamin intake, the percentage of women ingesting seaweed, seafood, and fish were also higher in 2018 (seaweed: 79.4% vs 66.0%; seafood: 86.8% vs 62.7%; fish: 90.7% vs 76.1%).

Table 4

Multivariable analysis of the risk factors for UIC <150 μg/L

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, y	1.02 (0.95-1.09)	0.595	1.02 (0.95-1.09)	0.617	1.02 (0.96-1.10)	0.509
Body mass index, kg/m^2	0.99 (0.92-1.06)	0.712				
Education (ref: high school or below)	3.41 (0.86-13.48)	0.080	3.39 (0.86-13.34)	0.081		
Parity (ref: ≥2)	2.02 (1.08-3.77)	0.027	2.05 (1.10-3.80)	0.023	2.01 (1.11-3.66)	0.022
Salt intake (ref: user)	1.01 (0.56-1.83)	0.978	1.01 (0.56-1.82)	0.979		
Seaweed (ref: user)	1.55 (0.85-2.88)	0.158	1.53 (0.84-2.80)	0.164		
Multivitamin intake (ref: user)	1.86 (1.04-3.34)	0.038	1.85 (1.03-3.32)	0.039	1.78 (1.00-3.17)	0.049

OR = odds ratio.

Table 5

Reference ranges for thyroid function tests

	First trimester	Manufacture
TSH, mIU/L	0.93 (0.007-2.9)	0.27-4.2
Free T4, ng/dL	1.3 (0.93-2.2)	0.93-1.7
Total T4, μg/dL	9.9 (6.4-16.9)	5.1-14.1
Free T3, pg/mL	3.0 (2.3-5.0)	2.0-4.4
Total T3, ng/dL	135 (88-231)	80-200

TSH = thyroid stimulating hormone.

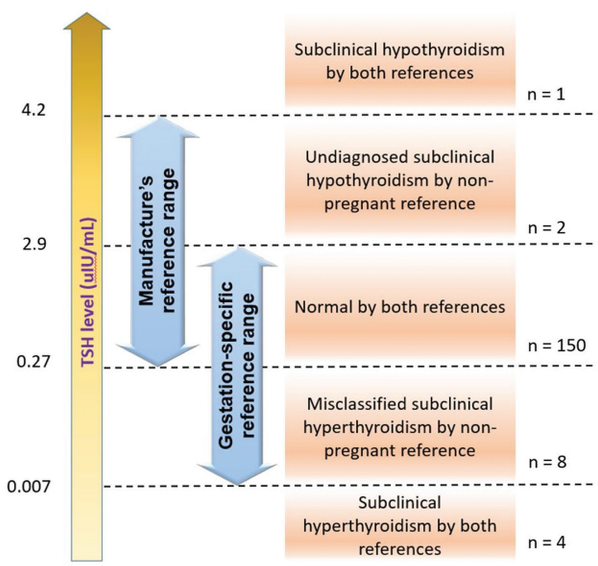

Fig. 1 Diagnosis of thyroid dysfunction by the gestational and manufacture's TSH reference range. TSH = thyroid stimulating hormone.

These dietary differences suggest that women in their second and trimesters received better nutritional support, and that iodine nutritional status in the first trimester can be improved by dietary adjustment.

The upper limit of serum TSH for pregnant women has been considered much lower than that for nonpregnant individuals, with reference intervals of 0.1 to 2.5 mIU/L in the first trimester and 0.2 to 3.0 mIU/L in the second and third trimesters suggested by the ATA in 2011.[49,50] However, recent research in Chinese pregnant women revealed that the upper limit of serum TSH during weeks 7 to 12 of gestation was only slightly lower than that for weeks 4 to 6 (4.34 vs 5.31 mIU/L, respectively).[19] As a result, the ATA adjusted their recommendation regarding upper limit of TSH in the first trimester to only 0.5 mIU/L below the nonpregnancy value in 2017.[18] Our finding for the first trimester TSH upper limit (0.007-2.9 mIU/L) was closer to those reported in Japan (0.04-3.39 mIU/L) and the United States (0.16-2.82 mIU/L), but lower than the values reported in China (0.56-5.31 mIU/L), Korea (0.03-4.24 mIU/L), India (0.25-4.97 mIU/L), and Spain (0.12-5.76).[19,24,28,30–42] These values may be affected by several factors, such as ethnicity, interindividual or intraindividual variation, body mass index, aTPO status, iodine deficiency, and iron deficiency.[22,27,30,32–35,51–59] The exact cause for discrepancies could not be determined because not all factors were evaluated in each study. The utilization of different test kits in different laboratories also prevented a direct comparison between local regional gestational thyroid function references ranges.

While TSH remains a crucial indicator for identifying thyroid disease in various scenarios, it is important to note that the influence of human chorionic gonadotropin on TSH levels can obscure subclinical hypothyroidism and potentially lead to overdiagnosis of subclinical hyperthyroidism (Fig. 1).[18] Therefore, a whole panel of thyroid function tests including free T4, total T4, total T3 in addition to TSH is of particular importance in pregnancy. In cases where the TSH level is close to the upper border, a first-trimester fT4 level at the lower border may warrant special attention. An accurate reference range for free and total T4 may then point to maternal thyroid hormone deficiency, a condition that may not be detected if the degree of TSH elevation is not obvious. Because the fetus relies solely on the mother for the supply of thyroid hormone in the first trimester,[15] the finding that the upper limits of free T4 and free T3 were higher in the first trimester compared to the nonpregnant reference range is reasonable.

Overall, this study provides data for the establishment of gestational thyroid function reference ranges which enables healthcare providers to appropriately diagnose, treat, and monitor thyroid disorders during pregnancy, thereby ensuring maternal and fetal health. However, the study was subject to certain limitations. First, the findings obtained in a medical center could not be generalized to the whole Taiwanese population, and the gestational thyroid function reference ranges we derived in this study apply only to gestational 8 to 13+6 weeks and are not applicable to before gestational 8 weeks or late trimesters. Second, we compared the serum TSH levels of the cohort with nonpregnant reference ranges provided by the assay manufacturer, but a potentially more relevant control group such as nonpregnant women tested with the same kit within the same medical facility would be more informative. Third, the lack of information on serving size in the food frequency questionnaire, and the absence of comprehensive data on iodine content in foods and supplements in Taiwan, make estimation of actual iodine intake very

difficult. Further large, multicenter studies involving pregnant women from various regions of Taiwan are needed to provide more precise thyroid function ranges for specific gestational periods within the first trimester and also potentially allow for more generalizable findings.

In conclusion, the iodine nutritional status of pregnant women in early pregnancy in Taiwan is adequate; however, certain subgroups including nulliparous women and those without multivitamin intake may still be at risk for iodine deficiency. The upper limit of serum TSH in the first trimester was lowered by approximately 1.3 mIU/L from the manufacturer's upper limit. Utilizing gestational thyroid function ranges is important for accurate diagnosis of thyroid dysfunction in pregnancy.

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