Thyroid structure, function and iodine status by pregnancy trimester in Harbin, China

doi: 10.6133/apjcn.202010/PP.0003
Published online: October 2020

Running title: Thyroid diseases and iodine during pregnancy

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ABSTRACT

Background and Objectives: Thyroid disease in pregnancy can have devastating effect on the fetus. In Harbin, China, there is insufficient knowledge about the incidence of and contributing factors to thyroid disease in pregnancy. This study investigates whether urine iodine concentration (UIC), as a proxy for iodine intake, affects the thyroid structure and/or function during each trimester. **Methods and Study Design:** Data of 24000 pre-pregnant women were collected from January 2017 to August 2019. Serum thyroid hormone levels were measured, and thyroid ultrasonography was performed. If thyroid ultrasonography and thyroid function findings were normal before pregnancy and were abnormal after pregnancy, the current gestational age was recorded and the UIC was measured. Finally, a total of 500 participants were included in the study. **Results:** There were significant differences in the incidence of abnormal thyroid structure and function between trimester groups (p<0.05). Thyroid nodular lesions were the most common abnormal ultrasound finding, and positive thyroid peroxide antibodies (TPOAb) were the most common abnormal thyroid function test results. There were significant differences in the median UIC between trimester groups (p<0.001); the median UIC decreased with increasing gestational age. The incidence of abnormal thyroid structure or function was not significantly different across UIC groups (p>0.05). **Conclusions:** In women from Harbin, thyroid structural or functional abnormalities commonly occur in the second and third trimesters of pregnancy. Thyroid nodular lesions and positive TPOAb are the commonest thyroid abnormalities. The median UIC significantly declines with increasing gestational age. Pregnant women in Harbin have iodine-deficient states.

Key Words: pregnancy, thyroid, structure, function, urine iodine concentration

INTRODUCTION

Thyroid disease in pregnancy is a hot topic because of potential fetal consequences.[1-3] Iodine is essential for normal thyroid structure and function. Insufficient iodine during pregnancy can lead to thyroid diseases such as hypothyroidism and hypothyroxinemia,which increases the risk of miscarriage, premature birth, growth,and mental impairment.[4-7] In 1996, the Chinese government implemented a policy of Universal Salt Iodization (USI) to prevent iodine deficiency disorders (IDD), though excess iodine may cause thyroid disease.[8,9] A study of Zhejiang and Fujian provinces' found that the iodine levels in pregnant women were adequate after salt iodization, but some rural areas and the third pregnancy trimester were still

iodine deficient.[10] Harbin locates in Heilongjiang Province, China. It was reported that the prevalence of thyroid disease of 56.0% in Heilongjiang Province was higher than that of adjoining Jilin Province at 32.6%.[11] However, there is limited information on the incidence rate and influencing factors of thyroid disease in pregnancy, in Harbin. This study investigates whether there is a correlation between pregnancy trimester, Urine Iodine Concentration (UIC), and effect on thyroid structure and function, to accurately guide clinical iodine supplementation and prevention of thyroid disease.

MATERIALS AND METHODS

Study participants and methods

Participants

24,000 pre-pregnant women were collected in the ultrasound department of the Harbin Medical University Affiliated Fourth Hospital, China, from January 2017 to August 2019. Serum thyroid hormone concentrations and thyroid-related antibodies were measured and thyroid ultrasonography was performed. If the thyroid ultrasound examination and thyroid function were normal before pregnancy and they were abnormal after pregnancy, the current gestational age were recorded and the UIC were measured. Finally, a total of 500 participants were included in the study. They were divided into three groups: first trimester (T1), second trimester (T2), and third trimester (T3). The exclusion criteria included participants with pre-pregnancy thyroid function or structural abnormalities or auto-immune disease, hypertension, diabetes, and on treatment for thyroid disease. The investigation was approved by the ethics committee of Harbin Medical University, and informed consent was obtained from the participants.

Methods

Thyroid ultrasonography was performed by an experienced examiner using a linear array, high-frequency (6–15 MHz) transducer (Logiq E9, USA). A venous sample (5mL) was collected from the antecubital fossa. Serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free tetraiodothyronine (FT4), and thyroid peroxidase antibody (TPOAb) were measured using an ADVIA Centaur XP Automated Chemiluminescence System. A morning urine sample (10 mL) was collected from each participant. UIC was measured by the arsenic bismuth catalytic spectrophotometric method.

Diagnostic criteria for abnormal thyroid structure

Thyroid structural abnormalities were divided into three categories: nodular lesions (normal thyroid volume with nodules >1 mm in diameter), diffuse lesions (diffusely increased left and right lobes without nodules on ultrasound) and diffuse with nodular lesions (diffusely increased left and right lobes with nodules on ultrasound).

Diagnostic criteria for abnormal thyroid function

Disorder of thyroid function was divided into six categories according to the American Thyroid Association, 2009:[12] clinical hypothyroidism (TSH >4.2 mIU/L, FT4 <11.5 pmol/L or FT3 <3.1 pmol/L), subclinical hypothyroidism (TSH >4.2 mIU/L, FT4 within the normal range), clinical hyperthyroidism (TSH <0.27 mIU/L, FT4 >22.7 pmol/L or FT3 >6.8 pmol/L), subclinical hyperthyroidism (TSH <0.27 mIU/L, FT3 and FT4 within the normal range), hypothyroxinemia (FT4 <11.5 pmol/L, TSH within the normal range), positive TPOAb test (TPOAb >60 IU/mL). The normal ranges were FT3 (3.1–6.8 pmol/L), FT4 (11.5–22.7 pmol/L), TSH (0.27–4.2 mIU/L), TPOAb (0–60 IU/mL).

Diagnostic criteria for UIC

The reference range for UIC was based on the WHO standard.13 UIC was divided into three groups: insufficient iodine group (UIC <150 μg/L), normal iodine group (150≤UIC≤500 μg/L), and excess iodine group (UIC >500 μg/L).

Statistical Analysis

UIC Median and interquartile ranges were used. Analysis of variance was used for quantitative data, and ratios were compared using the χ^2 test. A difference of $p<0.05$ was considered statistically significant. SPSS version 22.0 software (SPSS Inc, Chicago, IL) was used for all analyses.

RESULTS

The incidence of thyroid structural abnormalities in each trimester

The incidence of thyroid structural abnormalities was significantly different between the T1, T2, and T3 groups ($\chi^2=65.3$, $p<0.001$). Pairwise intergroup comparison showed that the differences were statistically significant ($p<0.05$). The incidence of thyroid structural abnormalities in the T2 and T3 groups was 84.9% and 82.9% respectively, which was higher

than in the T1 group at 76.4%. The incidence of thyroid nodular lesions was higher than that of diffuse lesions, and diffuse with nodular lesions, in each group (Table 1 and Figure 1).

The incidence of thyroid functional abnormalities in each trimester

The incidence of abnormal thyroid function tests was significantly different between the T1, T2 and T3 groups (χ^2=18.8, p<0.05). Pairwise intergroup comparison showed that the difference between T2 and T3 groups was not significant (p>0.05), although the difference between T1 and T2 groups, and T1 and T3 groups, was significant (p<0.05). The incidence of abnormal thyroid function in the T2 and T3 groups was higher than in the T1 group. The commonest thyroid function test abnormality was a positive TPOAb test, more common than other causes, in each group (Table 2).

UIC in each trimester

The median UIC declined with increasing gestational age (Table 3) and was significantly different between the T1, T2 and T3 groups (F=1.84, p<0.001). Pairwise intergroup comparison showed that the difference between the T2 and T3 groups was not statistically significant (p>0.05), while the difference between the T1 and T2 groups, and between the T1 and T3 groups, was significant (p<0.05).

Correlation of abnormal thyroid structure with UIC

The incidence of abnormal thyroid structure in the UIC ranges of <150 μg/L, 150–500 μg/L, and >500 μg/L was 87.6%, 71.7% and 85.7%, respectively. This was not statistically significant (χ^2=7.03, p>0.05). The incidence of thyroid nodular lesions was higher than both that of diffuse lesions, and diffuse with nodular lesions, in UIC groups (Table 4).

Correlation of abnormal thyroid function tests with UIC

The incidence of abnormal thyroid function in the UIC groups, <150 μg/L, 150–500 μg/L, >500 μg/L, was 73.2%, 65.9%, and 85.7%, respectively. This was not statistically significant (χ^2=11.5, p>0.05). A positive TPOAb test was the most common thyroid functional abnormality in UIC groups (Table 5).

DISCUSSION

In pregnancy, disorders of thyroid structure and function may be explained by an increased production of both estrogen and HCG and an increased requirement for iodine.[14,15] Since more 80% of dietary iodine is excreted by glomerular filtration. UIC can be used to evaluate iodine intake.[16] Ultrasonography has been recognized as the preferred method for observing the thyroid structure because of its non-invasive nature and avoidance of radiation.[17] Thyroid function tests are an easy method for diagnosing functional thyroid disease.

Our results showed for pregnant women in Harbin, the incidence of abnormal thyroid structure in the T2 and T3 groups of 84.9% and 82.9% was higher than in the T1 group at 76.4%, and the incidence of abnormal thyroid function in the T2 and T3groups, of 84.2% and 68.8%, was higher than that in the T1group, at 58.8 %. One possible explanation is that estrogen, whose level increases with increasing gestational age, reaches a peak in the third trimesterr, binds to thyroid receptors, and produces TSH.[18,19] Another reason is that the placenta secretes HCG, peaking at 10-12 weeks, which inhibits TSH production.[20] TSH enhances thyroid cell proliferation and causes structural changes to the thyroid.[21] In addition, the consumption of thyroid hormones increases as gestational age and basal metabolic rate increase.[22]

We found that the incidence of thyroid nodular lesions (67.2%) was higher than that of diffuse lesions (10.4%) and diffuse with nodular lesions (3.8%). According to the literature, thyroid nodules are found in more than 10% of the world population.[23]

This study found that the commonest thyroid function test abnormality in pregnancy was a positive TPOAb test (23.2%), higher than clinical hypothyroidism (7.0%), subclinical hypothyroidism (11.4%), clinical hyperthyroidism (9.2%), subclinical hyperthyroidism (15.0%) and hypothyroxinemia (4.8%). The literature supports that FT3 and FT4 levels in pregnant women are significantly lower than those in non-pregnant women.[24] The fetal thyroid hormone is mainly provided from the mother, and it participates in the generation of nerve myelin sheath, and neurotransmitter regulation, in fetal brain development. Therefore, abnormal thyroid function in pregnancy could adversely affect fetal development.[25]

In this study, the median UIC of overall the participants was 120 μg/L, and the median UIC of the participants in the T1, T2 and T3 groups were 154 μg/L, 121 μg/L, 114 μg/L, respectively. The proportion of pregnant women with insufficient iodine (59.8%) was higher than that with normal iodine (38.8%) and excess iodine (1.4%). This indicates that pregnant women in Harbin are in an iodine deficient state. de Escobar believed that insufficient iodine was a common cause of abnormal thyroid function in pregnancy, which could lead to fetal

neurological dysplasi; he proposed supplement of iodine in the first trimester.[26] The American Thyroid Association have recommended that daily iodine intake is 150-250 μg in pregnant women and lactating women.[12]

There are several possible causes for iodine deficiency. First, as basal metabolic rate increases in pregnancy, so does the requirement for thyroid hormones, hence depleting body iodine. Second, an increased glomerular filtration rate enhances iodine clearance. Third, iodine requirements during pregnancy increase due to increasing fetal demand.[22,27]

This study shows that the incidence of abnormal thyroid structure in the insufficient iodine group (87.6%) and excess iodine group (85.7%) was higher than that in the normal iodine group (71.7%), and the incidence of abnormal thyroid function in the insufficient iodine group (73.2%) and excess iodine group (85.7%) was higher than in the normal iodine group (65.9%). However, the incidence of thyroid structural or functional abnormalities was no different between UIC groups. This indicates that insufficient or excess iodine could result in abnormal thyroid structure and function in pregnant women, but is not the main reason.[28-30] Thyroid structural abnormalities may be related to age, hormonal changes in pregnant women, and an increased detection of thyroid diseases using ultrasonography.[31,32] Other factors include altered maternal immune status during pregnancy and genetic susceptibility to thyroid disease.[33] When iodine intake is relatively insufficient or excessive, the body will activate the autoregulatory and protective systems to maintain thyroid function in a relatively stable state. In addition, the body will autoregulate iodine levels as explained by the Wolff–Chaikoff effect and the escape phenomenon. When there is insufficient or excess iodine, the iodine transportation mechanism will be impaired and synthesis of thyroid hormones will be inhibited, affecting thyroid structure and function.[34-36] The relationship between UIC and the incidence of thyroid diseases is a “U” curve, which is consistent with findings in a previous study.[37] Therefore, more attention must be given to insufficient or excess iodine during pregnancy.[38]

Pregnant women in Harbin should take appropriate iodine supplementation and monitor urine iodine. Thyroid ultrasonography and thyroid function tests can provide individual guidance in pregnant women with UIC <150 μg/L and >500 μg /L.

This study has certain limitations. Firstly, UIC, thyroid function and structure assessment, are not routinely done in pregnant women, thus limiting their application as a screening tool for thyroid disease. Secondly, the number of cases included in the study was small hence affecting result reliability.

Conclusion

Abnormal thyroid structure and function commonly occur in the second and third trimester of pregnancy, in Harbin. Thyroid nodular lesions and a positive TPOAb test were the commonest thyroid abnormalities identified, and insufficient or excess iodine can lead to thyroid disease in pregnant women. UIC gradually decreases with increasing gestational age. It is essential to strengthen the screening for thyroid disease in pregnancy in areas of structure and function and establish urine iodine deficiency, to reduce the impact on mother and fetus.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors have no conflicts of interest to declare. This work was supported by the Natural Science Foundation of Heilongjiang Province (Grant No. ZD2017016).

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Table 1. The incidence of thyroid structural abnormalities in each trimester (n, %)

Group	N	Nodular lesions	Diffuse lesions	Diffuse with nodular lesions	Total	χ^2	*p*-value
T1	165	112 (67.9)	2 (1.2)	12 (7.3)	126 (76.4)	42.5[a]	<0.001
T2	165	95 (57.6)	42 (25.5)	3 (1.8)	140 (84.9)	28.4[b]	<0.001
T3	170	129 (75.9)	8 (4.7)	4 (2.4)	141 (82.9)	7.98[c]	0.018
Total	500	336 (67.2)	52 (10.4)	19 (3.8)	407 (81.4)	65.3[d]	<0.001

T1: The first trimester; T2: The second trimester; T3: The third trimester.
[a] The difference between the T1 and T2 was significant (p<0.001).
[b] The difference between the T2 and T3 was significant (p<0.001).
[c] The difference between the T1 and T3 was significant (p=0.018).
[d] The differences in the T1, T2, and T3 were significant (p<0.001).

Table 2. The incidence of thyroid functional abnormalities in each trimester (n, %)

Group	N	Clinical hypothyroidism	Subclinical hypothyroidism	Clinical hyperthyroidism	Subclinical hyperthyroidism	Hypothyroxinemia	Positive TPOAb level	Total	χ^2	*p*-value
T1	165	3 (1.8)	21 (12.7)	8 (4.9)	22 (13.3)	5 (3.0)	38 (23.0)	97 (58.8)	13.7[a]	0.017
T2	165	18 (10.9)	16 (9.7)	22 (13.3)	33 (20.0)	7 (4.2)	43 (26.1)	139 (84.2)	5.36[b]	0.373
T3	170	14 (8.2)	20 (11.8)	16 (9.4)	20 (11.8)	12 (7.1)	35 (20.6)	117 (68.8)	11.1[c]	0.049
Total	500	35 (7.0)	57 (11.4)	46 (9.2)	75 (15.0)	24 (4.8)	116 (23.2)	353 (70.6)	18.8[d]	0.043

T1: The first trimester; T2: The second trimester; T3: The third trimester.
[a] The difference between the T1 and T2 was significant (p=0.017).
[b] The difference between the T2 and T3 was not significant (p=0.373).
[c] The difference between the T1 and T3 was significant (p=0.049).
[d] The differences in the T1, T2, and T3 were significant (p=0.043).

Table 3. Urinary iodine concentration in each trimester

Group	N	UIC ranges (n, %)			UIC	*F*	*p*-value
		0 ~	150 ~	500 ~	M (P25, P75)		
T1	165	75 (45.5)	87 (52.7)	3 (1.8)	154 (118, 211)	1.61[a]	0.010
T2	165	96 (58.2)	65 (39.4)	4 (2.4)	121 (84.9, 208)	1.17[b]	0.156
T3	170	128 (75.3)	42 (24.7)	0 (0)	114 (67.2, 147)	1.83[c]	<0.001
Total	500	299 (59.8)	194 (38.8)	7 (1.4)	120 (95.2, 176)	1.84[d]	<0.001

T1: The first trimester; T2: The second trimester; T3: The third trimester.
[a] The difference between the T1 and T2 was significant (p=0.010).
[b] The difference between the T2 and T3 was not significant (p=0.156).
[c] The difference between the T1 and T3 was significant (p<0.001).
[d] The differences in the T1, T2, and T3 were significant (p<0.001).

Table 4. The incidence of thyroid structural abnormalities in UIC groups (n, %)

Group	N	Nodular lesions	Diffuse lesions	Diffuse with nodular lesions	Total	χ^2	*p* -value
Insufficient iodine	299	212 (70.9)	40 (13.4)	10 (3.3)	262 (87.6)		
Normal iodine	194	120 (61.9)	11 (5.7)	8 (4.1)	139 (71.7)	7.03	>0.05
Excess iodine	7	4 (57.1)	1 (14.3)	1 (14.3)	6 (85.7)		
Total	500	336 (67.2)	52 (10.4)	19 (3.8)	407 (81.4)		

T1: The first trimester; T2: The second trimester; T3: The third trimester.
[a] The difference between the T1 and T2 was significant (p=0.010).
[b] The difference between the T2 and T3 was not significant (p=0.156).

Table 5. Knowledge of coeliac disease and gluten free food preparation amongst chefs/cooks and culinary students

Group	N	Clinical hypothyroidism	Subclinical hypothyroidism	Clinical hyperthyroidism	Subclinical hyperthyroidism	Hypothyroxinemia	Positive TPOAb level	Total	χ^2	*p*-value
Insufficient iodine	299	24 (8.0)	42 (14.0)	26 (8.7)	38 (12.7)	17 (5.7)	72 (24.1)	219 (73.2)		
Normal iodine	194	10 (5.2)	15 (7.7)	19 (9.8)	36 (18.6)	7 (3.6)	41 (21.1)	128 (65.9)	11.5	>0.05
Excess iodine	7	1 (14.3)	0 (0)	1 (14.3)	1 (14.3)	0 (0)	3 (42.9)	6 (85.7)		
Total	500	35 (7.0)	57 (11.4)	46 (9.2)	75 (15.0)	24 (4.8)	116 (23.2)	353 (70.6)		

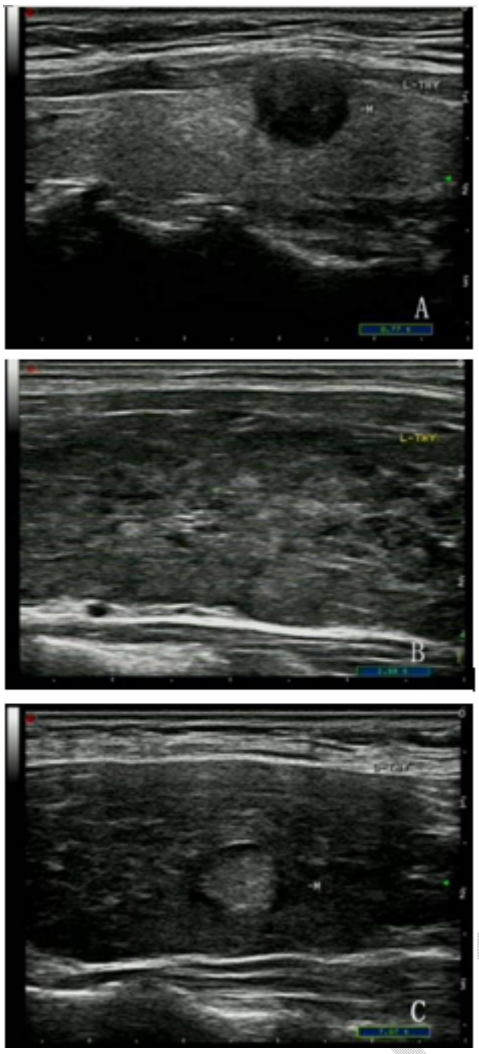

Figure 1. (A) Thyroid nodular lesion; (B) Thyroid diffuse lesion; (C) Thyroid diffuse with nodular lesion.