ORIGINAL ARTICLE

Thyroid volume and nodular and diffuse thyroid diseases by ultrasonography in pregnant women: A case–control study

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Background: Currently, it is shown that pregnancy may have an impact on the thyroid that can be leading to pregnancy complications such as abortion, preeclampsia, and preterm delivery. The objective was to compare the thyroid volume, number and characteristics of thyroid nodules, and prevalence of diffuse thyroid diseases in a sample of Iranian pregnant women in the first trimester to nonpregnant women. **Materials and Methods:** This case–control study was conducted on 298 pregnant and 290 nonpregnant women. Thyroid volume, maximum diameter of thyroid nodules and prevalence of moderate to highly suspicious thyroid nodules, Hashimoto's appearance and goiter were assessed using thyroid ultrasonography. Antithyroperoxidase (TPO) antibodies were measured if the sonographic features were highly suggested for Hashimoto's thyroiditis. **Results:** The mean of total thyroid volume in pregnant and nonpregnant women was 6 and 6.5 ml, respectively (P = 0.053), and the median (interquartile range) was 6.2 and 5.5, respectively. Nodules were observed in 16.4% of pregnant and 16.6% of nonpregnant women (P = 0.845). Hashimoto's thyroiditis was detected in 6.7% of pregnant and 12.4% of nonpregnant women (P = 0.013). Anti-TPO antibodies were detected in 5% of pregnant and 9.3% of nonpregnant women (P = 0.034). **Conclusion:** The thyroid volume and nodule characteristics in the first trimester of pregnancy were similar to nonpregnant women. Hashimoto's thyroiditis and anti-TPO antibodies in pregnant women were significantly lower than in nonpregnant women.

Key words: Anti-thyroperoxidase antibody, Hashimoto's disease, pregnancy, thyroid, thyroid diseases, thyroid nodule, thyroid volume, ultrasonography

How to cite this article: Shokri S, Hekmatnia A, Farghadani M, Aminorroaya A, Amini M, Kianpour M, *et al*. Thyroid volume and nodular and diffuse thyroid diseases by ultrasonography in pregnant women: A case–control study. J Res Med Sci 2020;25:13.

INTRODUCTION

Gender, age, thyrotropin (TSH), iodine supply, genetic factors, anthropometric parameters, parity, and smoking are among the factors that influence the size of the thyroid gland.[1] Pregnancy can have a profound impact on the thyroid gland and its functions.[2] In the first trimester of pregnancy, the serum levels of TSH decrease due to thyrotrophic activity of human chorionic gonadotropin but increase proportionally during the second and third trimesters, however still remain lower than nonpregnant status.[1,3,4] In addition, it is reported that with the progression of pregnancy, the levels of serum free thyroxine and free triiodothyronine will decrease considerably.[5] These modifications could result in alterations of thyroid function and volume.

During pregnancy, in areas with iodine deficiency, an increase of thyroid volume is reported up to 50%.[6] In

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_42_18

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Submitted: 18-Mar-2018; **Revised:** 17-Jul-2018; **Accepted:** 11-Oct-2019; **Published:** 20-Feb-2020

geographic areas with iodine sufficiency, some studies reported an increase in thyroid volume, and in some other studies, no increase in thyroid size had been reported.[7,8]

The state of thyroid nodules during pregnancy has been assessed in the literature; however, the conclusion has been different regarding the impact of pregnancy on thyroid nodules, and therefore, controversial issues are encountered.[9-11] In areas with iodine deficiency, thyroid nodules may be present in up to 45% of pregnant women, and in these areas, higher gravidity was related with a higher prevalence of thyroid nodules.[12,13] On the other hand, in general population, in women, and in those with iodine deficiency, thyroid nodules are more common.[14]

The current data suggest that pregnancy may have an impact on the thyroid volume and alter the size, volume, and number of nodules. However, the data on the thyroid volume and nodule characteristics in pregnant women in comparison to nonpregnant women are limited. Therefore, the purpose of this study was to evaluate the differences in the thyroid volume, characterization of thyroid nodules, and diffuse thyroid disease (specifically, Hashimoto's thyroiditis) in a sample of Iranian pregnant women in the first trimester in comparison to nonpregnant women.

MATERIALS AND METHODS

Study design and participants

This case–control study was conducted on 298 pregnant and 290 nonpregnant women in reproductive age that referred to Isfahan Endocrine and Metabolism Research Center and also health-care centers in Isfahan, Iran, for routine care. The sample size was calculated using two independent proportion formulas, considering $\beta = 0.2$ and Type 1 error = 0.05. The prevalence of nodular thyroid disease was estimated in a pilot study including ten pregnant and ten nonpregnant women.

Women who presented to Isfahan Endocrine and Metabolism Research Center and also health-care centers with confirmed eligibility criteria were selected by an obstetrician and referred to the Imaging Department of Kashani Hospital and scheduled for thyroid sonography. First-trimester pregnancy was considered as inclusion criteria for case-patients, and exclusion criteria were presence of any history of thyroid diseases, taking thyroid medications, multifetal pregnancy, or pregnancy-related complications. Nonpregnant participants without any history of thyroid medications or disease which were age and parity status matched were included in the study.

Study variables

The collected data included thyroid volume, nodule characteristics (including number of nodules and number of moderate and highly suspicious nodules), features of Hashimoto's thyroiditis, and goiter measured by a sonographer and also laboratory checked antithyroperoxidase (TPO) antibody. Thyroid ultrasonography of all participants was performed by the same radiologist using a 4–12-MHz linear array probe of a Philips affinity 70 ultrasound machine. Participants were examined in the supine position with the neck hyperextended. The volume (ml) of each thyroid lobe was calculated based on ellipsoid formula with a correction factor (length × width × thickness × 0.529). The total thyroid volume was obtained by the sum of volumes of both lobes. For risk stratification of thyroid nodules, we used the 2017 ACR TI-RADS classification system, according to which nodules with TI-RADS Grades 4 and 5 were regarded moderate and highly suspicious, respectively. Hashimoto's thyroiditis was detected based on clinical and preclinical findings and the standard sonographic features described in diagnostic ultrasound which were considered as gold standard for the diagnosis in this study.[15] Blood levels of anti-TPO antibodies were measured in the cases of highly suggestive sonographic appearance for Hashimoto's thyroiditis. The positivity of anti-TPO was considered as values ≥60 IU/ml.

Statistical analysis

Statistical analyses were done using SPSS software (SPSS Inc., Chicago, IL, USA, version 23). Descriptive data are reported as mean ± standard deviation and median (interquartile range [IQR]) as appropriate.

Independent-samples *t*-test, Chi-square test (with Fisher's exact test), and Mann–Whitney U-test were used to compare outcomes between pregnant and nonpregnant women, as depicted in Table 1. The sensitivity, specificity, and accuracy were calculated by a two-by-two contingency table. The level of significance is considered to be <0.05.

RESULTS

To select the study sample, 436 pregnant and 444 nonpregnant women were evaluated for eligibility. Eighteen pregnant women were excluded: 16 pregnant women because of levothyroxine consumption and two others due to twin pregnancy. In the nonpregnant group, six women were excluded due to levothyroxine consumption. Eventually, 418 eligible pregnant and 438 eligible nonpregnant women were invited for thyroid sonographic evaluation, but 120 pregnant and 148 nonpregnant women did not participate. Eventually, 298 pregnant and 290 nonpregnant women participated and undergone thyroid sonography, and the obtained data were analyzed ultimately.

Table 1 shows a comparison of studied variables between pregnant and nonpregnant women. The mean of total thyroid volume in pregnant and nonpregnant women was 6 and 6.5 ml, respectively ($P = 0.053$), which was not statistically

Table 1: Demographic and clinical characteristics of studied population for comparison based on thyroid volume and nodular and diffuse thyroid diseases

Characteristics	Groups				*P*
	Pregnant (*n*=298)		Nonpregnant (*n*=290)		
Age (year)	29.4±4.8		29.5±5.0		0.805*
Total thyroid volume (ml)	6.2 (4.7-7.8)	6.2#	5.5 (5.1-8.0)	5.5#	0.053††
Prevalence of nodules	49 (16.4)		48 (16.6)		0.845**
Number of nodules	1.6±1.2		1.5±1.1		0.904*
Maximum diameter of the largest nodules (mm)	6.2 (3.4-11.5)		6.5 (4.0-9.0)		0.965††
Moderate and highly suspicious nodules	0.63±0.78		0.47±0.58		0.247*
Sonographic features of Hashimoto's thyroiditis	20 (6.7)		36 (12.4)		0.013†
Positive anti-TPO antibodies	15 (5)		27 (9.3)		0.034
Goiter	57 (19.2)		67 (23.1)		0.247†

The data are presented as mean±SD, #Median (IQR), *P* values calculated using *Independent-samples *t*-test, †Chi-square test, ††Mann-Whitney U-test, **Fisher's exact test. TPO=Thyroperoxidase; SD=Standard deviation; IQR=Interquartile range

significant, and the median (IQR) was 6.2 and 5.5, respectively. Nodules were observed in 16.4% of pregnant and 16.6% of nonpregnant women ($P = 0.845$). Other nodule characteristics including number of nodules and prevalence of moderate and highly suspicious nodules in each patient were similar between pregnant and nonpregnant women without statistical significance. Hashimoto's appearance in pregnant women was significantly less than nonpregnant women (6.7% vs. 12.4%, respectively, $P = 0.013$). In addition, the presence of anti-TPO antibodies in pregnant women with consistent sonographic features was significantly less than nonpregnant counterparts (5% vs. 9.3%, respectively; $P = 0.034$). On the other hand, the presence of anti-TPO antibodies was detected in 42 women of all pregnant and nonpregnant participants with suggestive sonographic findings (7.1%). The sensitivity of anti-TPO antibodies in the detection of Hashimoto was 100% (91.51%–100%), and also, the specificity rate was 97.44% (95.73%–98.59%) as presumed. The prevalence of goiter was 19.2% and 23.1% in pregnant and nonpregnant women, respectively, with no statistical significance.

DISCUSSION

This study aimed to evaluate thyroid volume and nodular and diffuse thyroid disease between pregnant and nonpregnant women. Our findings show that thyroid volume and nodule characteristics and prevalence of goiter in studied pregnant women in the first trimester were similar to nonpregnant women. Hashimoto's appearance and anti-TPO antibodies in pregnant women were significantly less than nonpregnant women.

Rezvanian *et al*. study did not reveal any increase in thyroid size during pregnancy, which is congruent with our findings.[16] However, several studies have shown that thyroid volume increases during pregnancy, thyroid volume in studied pregnant women in De Zoysa *et al*. study in the first trimester was 5.16 ml, in Fister *et al*. study was 8.7 ml, and in Vannucchi *et al*. study was 8.9 ml.[7,17,18] These results are similar to our findings in pregnant women in the first trimester. Although those studies show that thyroid volume was significantly increased in the second and third trimesters of pregnancy. No significant differences in thyroid volume between pregnant and nonpregnant women in our study could be explained by the fact that pregnant women in the present study were evaluated in the first trimester of pregnancy.

In the present study, we showed that thyroid nodules were present in 16.4% of pregnant women in the first trimester. This was similar to the three studies which were performed in areas with mild-to-moderate iodine deficiency and reported the prevalence of thyroid nodules to be up to 21%.[10,11,19] In contrast, in Sahin *et al*. study, thyroid nodules were present in 30.1% of studied pregnant women, which was nearly twice as high as of our findings. The difference between our study and Sahin *et al*. study may be explained by the difference in the iodine status of pregnant women and the iodine status in the studied areas. It is presumably due to severe iodine deficiency in most of the studied pregnant women in Sahin *et al*. study.[9]

In the present study, we did not find any difference in the thyroid volume and nodule characteristics between studied pregnant women in the first trimester and nonpregnant women.

Selection of pregnant subjects in the first trimester of pregnancy can be considered as the main limitation of the present study. We were expecting to observe major thyroid changes in this period, because it has been illustrated that thyroid function tests are affected by changes in BHCG level; while on the other hand, BHCG level varies significantly in the first trimester of pregnancy. The Lack of data about patients' geographical area in the city and their socioeconomic status that may be influential on their diet shall be counted as another limitation of the present study. Hence, further studies are necessary to evaluate the thyroid volume, parenchymal and nodule characteristics,

and their alterations during all trimesters of pregnancy by matching geographic area in the city and socioeconomic status of the subjects.

We found anti-TPO antibodies as an accurate test for the detection of Hashimoto's thyroiditis with a sensitivity of 100%, a specificity of 97.44%, a positive predictive value of 75%, and overall accuracy of 97.62%. This was similar to other two studies. Premawardhana *et al*. reported that cases with positive anti-TPO antibodies eventually developed postpartum thyroiditis among almost half of the studied women. They show that anti-TPO antibodies screening in early pregnancy had a sensitivity of 100%, with a specificity of 41% and a positive predictive value of 48%.[20] Another study by Yadav and Yadav revealed that anti-TPO antibody test had a sensitivity of 88%, with a specificity of 89%, a positive predictive value of 48%, and overall accuracy of 88.5% to detect Hashimoto's thyroiditis.[21] The current study supports the findings of these previous studies and shows the advantage of anti-TPO antibody test in the detection of Hashimoto's disease. These results show the application of anti-TPO antibodies in the detection of thyroiditis, and further studies are needed to be done to assess the combination of anti-TPO antibodies with another test to find a way for differential diagnosis between Hashimoto's thyroiditis and postpartum thyroiditis.

Among the previously performed studies, two upcoming studies are of precise value for comparison because they were performed in the exact same geographical area as the current study (Isfahan, Iran). In Rezvanian *et al*. study, the mean thyroid volume in pregnant and nonpregnant women was 7.8 ± 3.2 and 7.8 ± 2.8 mL, and in Adibi *et al*. study, the overall thyroid volume in females was 7.71 ± 2.63 ml, which in comparison, the current study revealed lower overall thyroid volumes of 6 (4.7–7.8) and 6.5 (5.1–8.0) ml in pregnant and nonpregnant women, respectively.[16,22]

In Adibi *et al*. study, thyroid volume ≥8.37 ml was considered goiter in female population, based on which the prevalence of goiter in our study was 19.2% in pregnant and 23.1% in nonpregnant women and nonsignificant statistically. In Rezvanian *et al*. study, thyroid volume of ≥9.5 ml was considered goiter, and the prevalence of goiter was reported 29% and 21% in pregnant and nonpregnant women, respectively. In our study, the prevalence of goiter shows a decrease in comparison with Rezvanian *et al*. study, either using 9.5 ml (based on which, the prevalence of goiter would be 11.7% and 15.2% in pregnant and nonpregnant groups, respectively). The above findings suggest the efficacy of iodine replacement therapy in the recent years in Isfahan.

CONCLUSION

The findings of the present study reveal that thyroid volume and nodule characteristics in normal pregnant women in the first trimester are similar to other nonpregnant women in the reproductive age. However, sonographic features of Hashimoto's thyroiditis and the presence of anti-TPO antibodies in pregnant women were significantly higher than nonpregnant women.

Furthermore, the presence of anti-TPO antibodies can be used as an appropriate test for the detection of Hashimoto's thyroiditis. This study additionally suggests the efficacy of iodine replacement therapy by demonstration of decrease in thyroid volume and prevalence of goiter in comparison to the recent studies in Isfahan which is a strength point of this study. It also emphasizes on the determination of regional reference values for thyroid volume and goiter definition.

Acknowledgment

This study was financially supported by Isfahan University of Medical Sciences, Isfahan, Central Iran (Project number 396355).

Financial support and sponsorship

This study was financially supported by Isfahan University of Medical Sciences, Isfahan, Iran.

Conflicts of interest

There are no conflicts of interest.

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