Clin. Lab. 2021;67:XXX-XXX

ORIGINAL ARTICLE

Thyroid Function Tests in the First Trimester of Pregnancy According to Maternal Age in Asia

You La Jeon, Sang Gon Lee, Eun Hee Lee, Chang-Wook Kim, Sung-Ho Kim

Department of Laboratory Medicine, Green Cross Laboratories, Yongin, Gyeonggido, Republic of Korea

SUMMARY

Background: **The American Thyroid Association suggested selective performance of the thyroid function test (TFT) in pregnant women with risk factors such as age over 30 years. We evaluated the limited indication of TFT based on age by analyzing our institution's retrospective data about TFT in pregnant women.**
Methods: **We retrospectively analyzed the results of thyroid stimulating hormone (TSH) and free thyroxine (FT4) with the anti-thyroid autoantibody test using the Cobas 8000 e801 module (Roche Diagnostics, Mannheim, Germany) performed during the first trimester of pregnancy. Data were analyzed and compared between subjects younger or older than 30 years.**
Results: **The mean values of TSH and FT4 did not show any significant differences according to age. Also, the two groups had similar prevalence of overt/subclinical hypothyroidism. It was analyzed that over 20% of overt hypothyroidism could be missed by applying age-based screening.**
Conclusions: **Selective screening according to age (> 30 years) can miss a considerable number of pregnant women with hypothyroidism. Considering the value of appropriate screening and treatment in pregnant women with hypothyroidism, universal screening is necessary rather than selective screening considering the age of pregnant women.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200460)

Correspondence:
Sang Gon Lee, MD
Department of Laboratory Medicine
Green Cross Laboratories
Ihyeonro 30 beon-gil 107
Giheng-gu
Yongin-Si
Gyeonggi-do
Republic of Korea
Phone: +82 31 260 9209
Fax: +82 31 260 9656
Email: sglee@gclabs.co.kr

Manuscript accepted June 8, 2020

KEY WORDS

thyroid function test, thyroid stimulating hormone, free thyroxine, pregnancy, hypothyroidism

INTRODUCTION

Thyroid disorders in pregnancies are common and can adversely affect maternal and fetal health [1-4]. However, clinical diagnosis of thyroid disease in pregnant women is complex and challenging because the physiological changes of pregnancy are similar to symptoms of hypothyroidism [5,6]. Therefore, the data of thyroid function involving thyroid stimulating hormone (TSH) provide important information to clinicians.
However, the 2017 American Thyroid Association (ATA) guidelines recommend selective screening tests for thyroid function only in pregnant women who have a risk factor for thyroid dysfunction [7]. This differs from the suggestion of the European Thyroid Associa-

tion (ETA), which states that screening should be performed on all pregnant women and women of childbearing potential [8]. One of the risk factors suggested by the ATA guidelines is a pregnant woman older than 30 years of age; if screening is performed considering the risk factors related to this age, 30% to 80% of hypothyroidism in early pregnancy may be missed [9].

Race as it affects iodine nutritional status may affect thyroid function tests, but studies in Asia comprise only recent Chinese reports [10]. Therefore, we analyzed the results of the thyroid function test (TFT) conducted on pregnant women in Korea to evaluate the differences according to age and to analyze the prevalence of thyroid dysfunction, especially hypothyroidism, according to age.

MATERIALS AND METHODS

From January 2017 to December 2018, we retrospectively analyzed the results of TSH, free thyroxine (FT4), anti-microsome antibody (anti-thyroid peroxidase antibody), and anti-thyroglobulin antibody during the first trimester of pregnancy. The tests were performed through the electrochemiluminescence method using the Cobas 8000 e801 module (Roche Diagnostics, Mannheim, Germany). Data were analyzed and compared between subjects younger or older than 30 years. The reference range of TSH was 0.01 - 4.0 mU/L (ATA guidelines) and that of FT4 was 0.94 - 1.52 ng/dL (manufacturer's instructions). Anti-microsome antibody (thyroid peroxidase antibody, TPOAb) was interpreted as negative when the value was 34 IU/mL or less and positive when the value was higher than 34 IU/mL. Anti-thyroglobulin antibody was interpreted as negative when the value was 115 IU/mL or less and positive when the value was higher than 115 IU/mL. Student's *t*-test test was used for continuous variables and Pearson's chi-squared test for categorical variables. p-values < 0.05 were considered significant. This study was approved by the Institutional Review Board of Green Cross Laboratories (IRB number: GCL-2020-1018-01).

RESULTS

We performed TSH measurements in the first trimester of 15,638 pregnancies (< 2.5 mU/L; 12,941 (82.2%), 2.5 - 4.0 mU/L; 1,896 (12.1%), > 4.0 mU/L; 801 (5.1%)) and FT4 measurements in 7,366 pregnancies. The mean patient age was 32.8 ± 3.9 years.

Comparing the mean of TSH and FT4 by age of 30 years showed no significant difference. Also, the distributions according to TSH (< 2.5, 2.5 - 4.0, > 4.0) (mU/L) were similar between below and above 30 years (> 30 years; 82.4%, 12.4%, 5.2%, ≤ 30 years; 83.8%, 11.2%, 4.9%, respectively, p = 0.092). When the thyroid function state of pregnant women was classified based on TSH and FT4, there was no difference in prevalence according to age (Table 1). The positive rate of anti-microsome antibody and anti-thyroglobulin antibody also did not show differences between the groups (anti-microsome antibody: 36/274 (13.1%) and 99/767 (12.9%), respectively; anti-thyroglobulin antibody: 5/202 (17.3%) and 97/528 (18.4%), respectively). Anti-microsome antibody or anti-thyroglobulin antibody test was performed in 1,041 and 730 pregnant women, respectively. For both autoantibodies, the average value of TSH or FT4 showed significant differences depending on the presence or absence of the antibody. Pregnant women positive for anti-microsome antibody or anti-thyroglobulin antibody showed significantly higher TSH and lower FT4 than autoantibody-negative pregnant women (Table 2 and Figure 1). The prevalence of hypothyroidism was statistically higher in the autoantibody-positive group, whereas the prevalence of hyperthyroidism did not differ according to autoantibody results.

DISCUSSION

Thyroid hormone during pregnancy plays a very important role, affecting the growth and development of the fetal brain [11-13]. In particular, since thyroid development of the fetus in the first trimester is not complete, the mother's dependence on thyroid hormone is high [4, 14]. Therefore, thyroid hormone should be maintained at an appropriate level in early pregnancy.

Thyroid disease in pregnant women is relatively common, at a prevalence of 15% [4]. Thyroid disease has relatively clear clinical symptoms depending on hormone secretion status. However, due to physiological changes of pregnancy, it is difficult to distinguish the presence or absence of the disease by symptoms alone. Therefore, laboratory tests of thyroid function in pregnancy can provide crucial evidence.

The ATA guidelines recommend clinical observations related to thyroid function status in pregnant women, and laboratory tests should be performed when pregnant women have specific risk factors [7]. One of the risk factors is age greater than 30. In the general population, there is a tendency for TSH to increase and FT4 to decrease in the elderly, so it can be predicted that the risk of thyroid disease is higher in elderly women over 30 years of age [15-17].

However, in this study, when analyzing TSH and FT4 in pregnant women under and over 30 years of age, there was no difference. In addition, the prevalence of hypothyroidism was not statistically significant at age over 30 years. In previous studies involving pregnant women with various iodine nutritional statuses and mean maternal ages, the risk of thyroid disease in pregnant women over 30 years of age was not higher than that in those under 30 years of age [9,18-20]. Moreover, as the average age of pregnant women is increasing, screening tests for those over 30 years of age do not significantly reduce the number of subjects compared to

Table 1. The profiles of TSH and FT4 values and thyroid function state according to age of pregnant women in the first trimester.

	≤ 30 years of age	> 30 years of age	p-value
TSH profile			
Number (total = 15,638)	4,063 (26.0%)	11,575 (74%)	
Age (years) (median, range)	29, 19 - 30	34, 31 - 48	< 0.001
TSH (mU/L) (mean ± SD)	1.47 ± 1.60	1.54 ± 2.34	1.000
FT4 profile			
Number (total = 7,366)	1,960 (26.6%)	5,406 (73.4%)	
Age (years) (median, range)	28, 19 - 30	34, 31 - 48	< 0.001
FT4 (ng/dL) (mean ± SD)	1.35 ± 0.35	1.32 ± 0.31	0.509
Thyroid function state *			
Number (total = 7,382)	1,965	5,417	
Normal function	1,516 (77.2%)	4,204 (77.6%)	0.147
Overt hypothyroidism	19 (1.0%)	63 (1.2%)	
Subclinical hypothyroidism	93 (4.7%)	299 (5.5%)	
Isolated hypothyroxinemia	14 (0.7%)	65 (1.2%)	
Hyperthyroxinemia	85 (4.3%)	224 (4.1%)	
Subclinical hyperthyroidism	11 (0.6%)	27 (0.5%)	
Isolated hyperthyroxinemia	224 (11.4%)	530 (9.8%)	
Inconclusive cases	3 (0.2%)	5 (0.1%)	

* - Thyroid function state includes TSH and FT4 measurements of 7,366 pregnant women. The other 16 were classified as overt hypothyroidism with TSH results higher than 10 mU/L.

Table 2. The profiles of TSH and FT4 values and thyroid function state according to thyroid autoantibody.

	Anti-microsome antibody		p-value	Anti-thyroglobulin antibody		p-value
	positive	negative		positive	negative	
TSH profile						
Number	135/1,041 (13.0%)	906/1,041 (87.0%)		132/730 (18.1%)	598/730 (81.9%)	
Age (years) (median, range)	33, 24 - 42	33, 20 - 44		33, 23 - 41	33, 20 - 44	
TSH (mU/L) (mean ± SD)	4.59 ± 6.61	2.58 ± 3.06	0.001	5.04 ± 10.27	2.64 ± 3.46	0.009
FT4 profile						
Number	132/1,010 (13.1%)	878/1,010 (86.9%)		130/710 (18.3%)	580/710 (81.7%)	
Age (years) (median, range)	33, 24 - 42	33, 20 - 44		33, 23 - 41	33, 20 - 44	
FT4 (ng/dL) (mean ± SD)	1.18 ± 0.27	1.28 ± 0.27	< 0.001	1.16 ± 0.23	1.27 ± 0.25	< 0.001
Thyroid function state						
Hypothyroidism *	53/132 (40.2%)	109/878 (12.4%)	< 0.001	45/130 (34.6%)	71/580 (12.2%)	< 0.001
Hyperthyroidism	7/132 (5.3%)	44/878 (5.0%)	0.887	3/130 (2.3%)	31/580 (5.3%)	0.175

* - Overt hypothyroidism and subclinical hypothyroidism were included in hypothyroidism.

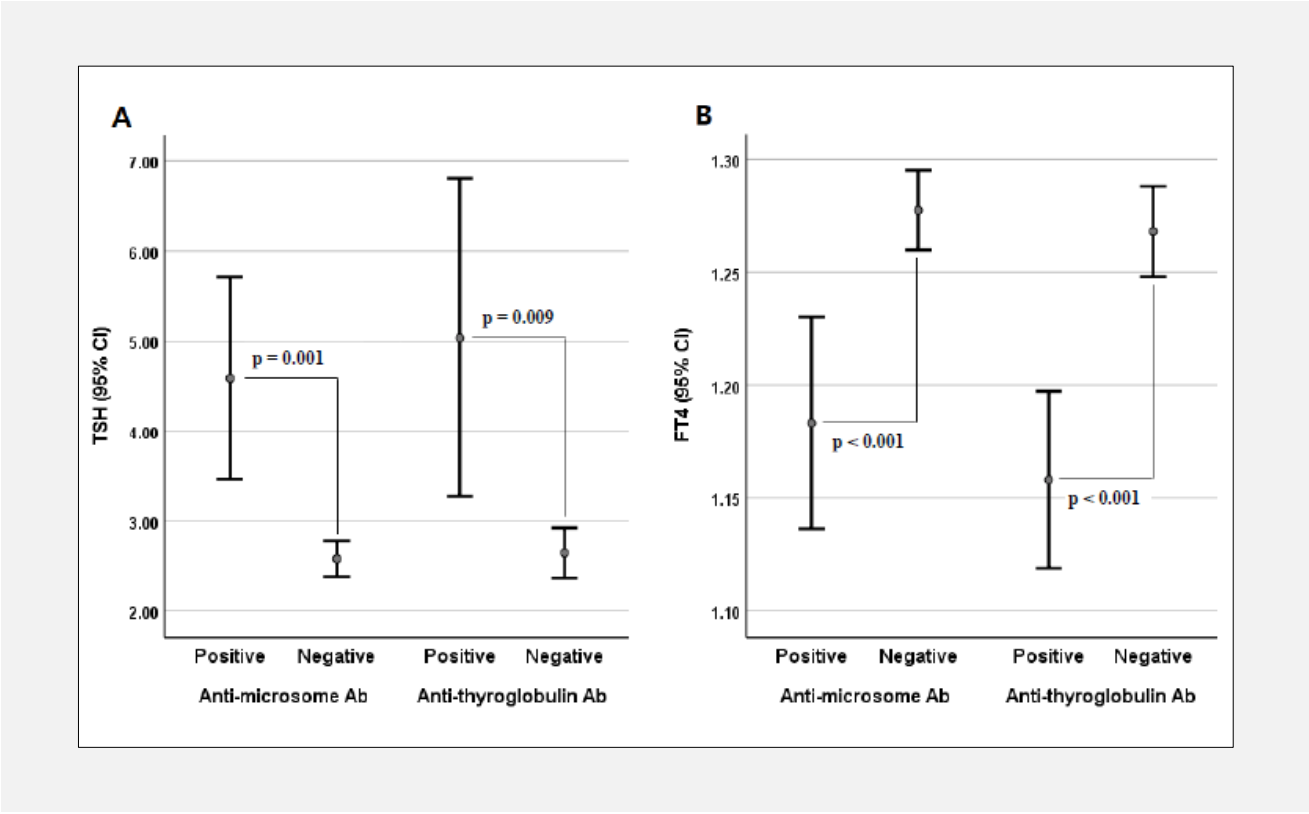

Figure 1. The results of TSH and FT4 showed significant differences depending on presence or absence of autoantibodies.

Abbreviations: Ab - antibody.

universal screening. In this study, 3/4 of all pregnant women were older than 30 years of age. Even in studies where the average age of pregnant women was less than 30 years, 30% to 80% of pregnant women with overt/subclinical hypothyroidism may be missed if only pregnant women over 30 years of age are screened [9,20]. In addition, universal screening is more cost-effective than selective screening when considering the benefits and effects of early screening and treatment of hypothyroidism in pregnant women [21]. The authors drew this conclusion by comparing the cost-effectiveness of strategy with universal screening, risk-based screening, and no screening for analyzing many randomized controlled trials with respect to several variables such as costs for TFT, test utilities, treatment, and adverse outcome [21]. The positive rates of anti-microsome antibody and anti-thyroglobulin antibody were 13% and 18%, respectively. Autoantibody against thyroid such as anti-microsome antibody or anti-thyroglobulin antibody is a risk factor of maternal thyroid abnormality [7]. These autoantibodies affect maternal thyroid functional status in the postpartum as well as pregnancy period and increase the incidence of delivery complication such as miscarriage [7,22]. In this study, analysis of autoantibody and TFT results in early pregnancy revealed a prevalence of hypothyroidism about 40% higher in groups with positive autoantibodies. However, the prevalence of hyperthyroidism was not correlated with positive rate of autoantibodies.

ATA recommends levothyroxine therapy for overt hypothyroidism found in pregnancy. They also guide pregnant women with TSH levels above 2.5 to treat with levothyroxine based on the results of anti-microsome antibody. These recommendations appear to apply to general pregnancies as well as high risk pregnancies, which include those over the age of 30 [7].

The limitation of this study was that it was conducted as a cross-sectional study, and the effect of TFT on the overall pregnancy was not evaluated. In addition, there is a lack of clinical information on management according to the TFT. Nevertheless, it can be said to be significant as a large-scale retrospective study in Asia.

Because overt/subclinical hypothyroidism, which occurs in early pregnancy, lowers the quality of pregnancy and threatens the well-being of the fetus, universal screening is necessary rather than a selective screening plan based on age of pregnant women.

Declaration of Interest:
We declare no conflicts of interest.

References:

1. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;105:239-45 (PMID: 15684146).

2. Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000;7:127-30 (PMID: 11126160).

3. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55 (PMID: 10451459).

4. Saki F, Dabbaghmanesh MH, Ghaemi SZ, et al. Thyroid function in pregnancy and its influences on maternal and fetal outcomes. Int J Endocrinol Metab 2014;12:e19378 (PMID: 25745488).

5. Hales C, Taylor PN, Channon S, et al. Controlled Antenatal Thyroid Screening II: Effect of Treating Maternal Suboptimal Thyroid Function on Child Cognition. J Clin Endocrinol Metab 2018; 103:1583-91 (PMID: 29346569).

6. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F. Subclinical hypothyroidism in pregnancy: intellectual development of offspring. Thyroid 2011;21:1143-7 (PMID: 2194 3136).

7. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017;27:315-89 (PMID: 28056690).

8. Lazarus J, Brown RS, Daumerie C, et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014;3: 76-94 (PMID: 25114871).

9. Yang H, Shao M, Chen L, et al. Screening strategies for thyroid disorders in the first and second trimester of pregnancy in China. PLoS One 2014;9:e99611 (PMID: 24925135).

10. Zimmermann MB, Andersson M. Update on iodine status worldwide. Curr Opin Endocrinol Diabetes Obes 2012;19:382-7 (PMID: 22892867).

11. Hollowell JG Jr, Garbe PL, Miller DT. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:2016-7 (PMID: 10617 396).

12. Pop VJ, Brouwers EP, Vader HL, et al. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59:282-8 (PMID: 12919150).

13. Männistö T, Vääräsmäki M, Pouta A, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 2010;95:1084-94 (PMID: 20080846).

14. Korevaar TI, Muetzel R, Medici M, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:35-43 (PMID: 26497402).

15. Vadiveloo T, Donnan PT, Murphy MJ, Leese GP. Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS). J Clin Endocrinol Metab 2013;98:1147-1153 (PMID: 23345094).

16. Tekle HA, Bobe TM, Tufa EG, Solomon FB. Age-sex disparities and sub-clinical hypothyroidism among patients in Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia. J Health Popul Nutr 2018;37:18 (PMID: 30029689).

17. Andersen SL, Olsen J, Laurberg P. Maternal thyroid disease in the Danish National Birth Cohort: prevalence and risk factors. Eur J Endocrinol 2016;174:203-12 (PMID: 26582484).

18. Potlukova E, Potluka O, Jiskra J, et al. Is age a risk factor for hypothyroidism in pregnancy? An analysis of 5223 pregnant women. J Clin Endocrinol Metab 2012;97:1945-52 (PMID: 22438 224).

19. Diéguez M, Herrero A, Avello N, Suárez P, Delgado E, Menéndez E. Prevalence of thyroid dysfunction in women in early pregnancy: does it increase with maternal age? Clin Endocrinol (Oxf) 2016;84:121-6 (PMID: 25488673).

20. Vaidya B, Anthony S, Bilous M, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 2007;92:203-7 (PMID: 17032713).

21. Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. J Clin Endocrinol Metab 2012;97:1536-46 (PMID: 22399510).

22. Bhattacharyya R, Mukherjee K, Das A, Biswas MR, Basunia SR, Mukherjee A. Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life. J Nat Sci Biol Med 2015;6:402-5 (PMID: 26283839).