IS IRON DEFICIENCY A RISK FACTOR FOR THE DEVELOPMENT OF THYROID AUTOANTIBODIES IN EUTHYROID WOMEN WITH REPRODUCTIVE AGES?

N. Okuroglu¹, A. Ozturk¹, A. Özdemir^{1,*}

¹University of Health Sciences, “Fatih Sultan Mehmet” Training and Research Hospital, Istanbul, Turkey

Abstract

Context. The first trimester of pregnancy is the most sensitive period in terms of thyroid hypofunction. Iron deficiency has been associated with both thyroid function and thyroid autoimmunity.

Objective. We aimed to investigate whether iron deficiency is a risk factor for thyroid autoimmunity in non-pregnant women at childbearing age.

Design. This cross-sectional study was conducted in non-pregnant women who presented to the Internal Medicine Polyclinic between January 2018 and December 2018 in the University of Health Sciences “Fatih Sultan Mehmet” Training and Research Hospital.

Methods. Three hundred fifty-eight non-pregnant women of reproductive ages (203 iron deficient-ID, 155 control) participated in this study. Women with known thyroid disease, currently undergoing treatment for thyroid disease or whose thyroid function tests were outside the reference range were excluded from the study. Blood sample was taken after at least 8-10 hours of fasting for measurement of serum iron (Fe), total iron binding capacity (TIBC), serum ferritin (SF), whole blood count, thyroid function tests (fT4, TSH), anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibody (TgAb). The patients with SF levels ≤ 15 ng/dL were accepted as iron deficiency.

Results. The group with ID had higher TSH and lower T4 values that did not reach statistical significance compared to the control group ($p=0.101$ and $p=0.098$, respectively). Antibody positivity was more frequent in the ID group than in the control group (35.96% vs. 20.65%, $p=0.002$).

Conclusions. Iron deficiency is associated with thyroid autoimmunity and it should be considered as a risk factor for screening thyroid antibody, particularly in pregnancy planning women.

Key words: iron deficiency, thyroid autoimmunity, reproductive age.

INTRODUCTION

Anemia affects one-quarter of the world's population and is concentrated in preschool-aged children and women (1). Iron deficiency (ID) with or without anemia has been associated with thyroid dysfunction and shown to cause hypothyroidism through several mechanisms (2-4). Studies in rats have suggested that ID reduces plasma thyroid hormone concentrations by decreasing hepatic thyroxine deiodinase activity, disrupting peripheral conversion of T4 to T3, and decreasing TSH response to TRH (5). Presumably, ID affects thyroid hormone feedback by disturbing the pituitary threshold leading to TSH secretion. Additionally, ID may also lead to decreased TPO activity, which impairs the metabolism of iodine in the thyroid (6). Few studies have shown a relationship between thyroid autoimmunity (TAI) and ID (7, 8).

In this study, thyroid antibodies as well as thyroid function were examined in women of reproductive ages with ID and compared with age-match controls without ID.

MATERIALS AND METHODS

This cross-sectional study was conducted in 358 women between the ages of 18 and 45 who presented to the Internal Medicine Polyclinic between January 2018 and December 2018 in the University of Health Sciences “Fatih Sultan Mehmet” Training and Research Hospital. The women who did not have chronic disease history, did not use any medication that would affect their thyroid function, and who were not pregnant were included the study. Women with known thyroid disease such as thyroidectomy and radioactive iodine therapy or with a positive history of autoimmune thyroid disease, who already use thyroid hormone replacement and have a thyroid function test result outside the normal reference ranges (free T3, free T4,

*Correspondence to: Ali Özdemir PhD, “Fatih Sultan Mehmet” Training and Educational Hospital, Department of Internal Medicine, E-5 yolu üzeri Bostanci, Istanbul, 34750, Turkey, E-mail: alemoz2004@yahoo.com

TSH) were not included in the study. Likewise, patients with high C-reactive protein levels were excluded from the study. The study protocol was approved by the Local Ethics Committee and an informed consent form was taken from each of the participants.

Blood sample was taken after at least 8-10 hours of fasting for measurement of serum iron (Fe), total iron binding capacity (TIBC), serum ferritin (SF), whole blood count, C-reactive protein, anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibody (TgAb). Serum Fe levels and TIBC were measured by Abbott Architect C8000 Clinical Chemistry Analyzer. SF levels were measured by chemiluminescent microparticle immunoassay (CMIA) method (Architect i2000, Abbott Laboratories). Serum transferring saturation (TSAT) was calculated using formula serum Fe/TIBC x 100. The patients with SF levels ≤ 15 ng/dL were included in the iron deficiency group and women with SF levels above these values were control subjects. TSH, free T4, free T3, TPOAb and TgAb were measured by the CMIA method (Architect i2000, Abbott Laboratories). The range of 0.35-4.2 mIU/L for TSH, 0.58-1.64 ng/dL for free T4 and 1.71-3.71 pg/mL for free T3 were accepted as normal values. Values above 5.6 IU/mL for TPOAb and 10 IU/mL for TgAb were considered as positive.

Statistical analysis was conducted by using Statistical Package for Social Sciences (IBM SPSS, Armonk, NY USA) for Windows 22 programs. Results were expressed as means $\pm$ standard deviation. Distribution of parameters was tested by Kolmogorov Smirnov test. Comparisons between ID and the control groups were made using student t test for parameters

with normal distribution and Mann Whitney U test for parameters with non-normal distribution. Comparison of frequency distribution was performed by means of the Chi-Square test. Results were analyzed with 95% confidence interval and probability levels less than 0.05 were considered significant.

RESULTS

Of the 358 women, 203 were in the ID group and 155 were in the control group. There was no statistically significant difference between groups in terms of age ($p=0.736$). As expected, the ID group had lower hemoglobin (Hb) ($p < 0.001$), Fe ($p < 0.001$), the TSAT ($p < 0.001$), SF levels ($p < 0.001$) and higher TIBC ($p < 0.001$) (Table 1). The group with ID had higher TSH and lower T4 values that did not reach statistical significance compared to the control group ($p=0.101$ and $p=0.098$, respectively). Antibody positivity was significantly higher in the ID group than in the control group (35.96% vs. 20.65%, $p = 0.002$). There was no significant difference in TPO Ab and TgAb positivity between the groups ($p>0.05$), but TPOAb plus TgAb positivity was significantly more common in the iron deficiency group ($p=0.031$) (Table 2). Of the women with positive antibodies, 50.48% were at or under the median age of 32, 49.52% were above the median age.

DISCUSSION

Thyroid auto-antibodies are present in 2% to 17% of unselected pregnant women (9). On the other hand, iron deficiency has been associated with both

Table 1. Iron parameters and demographic characteristics among the groups

	Iron deficiency group (n=203)	The control group (n=155)	P value
Age (years)	31.63 $\pm$ 8.19	31.33 $\pm$ 8.61	0.736
BMI (kg/m ²)	27.04 $\pm$ 4.55	26.70 $\pm$ 5.63	0.538
Hb (g/dL)	11.57 $\pm$ 1.36	12.88 $\pm$ 0.97	<0.001
Iron (μ g/dL)	48.34 $\pm$ 29.47	78.68 $\pm$ 31.80	<0.001
TSAT (%)	13.07 $\pm$ 8.80	25.52 $\pm$ 11.64	<0.001
ferritin(ng/dL)	7.46 $\pm$ 3.59	37.80 $\pm$ 33.04	<0.001

The data is expressed as mean $\pm$ SD. P value was calculated at 95 % confidence interval.

Table 2. Thyroid functions and antibodies among the groups

	Iron deficiency group (n=203)	The control group (n=155)	P value
TSH (mIU/L)	1.90 $\pm$ 0.97	1.74 $\pm$ 0.91	0.101
Free T4 (ng/dL)	0.96 $\pm$ 0.11	0.97 $\pm$ 0.11	0.098
Free T3 (pg/mL)	2.77 $\pm$ 0.42	2.81 $\pm$ 0.60	0.481
Total antibody positivity (%)	35.96	20.65	0.002
TPOAb (%)	8.37	3.87	0.085
TgAb (%)	9.85	7.10	0.358
TPOAb + TgAb (%)	17.73	9.68	0.031

The data is expressed as mean $\pm$ SD for TSH, free T4 and T3 and as percentage for Auto-antibodies. P value was calculated at 95 % confidence interval.

thyroid autoimmunity and thyroid function (2-4). In a previous cross-sectional study, Zimmermann *et al.* reported that the anemia of iron deficiency reduced the conversion of T4 to T3 in the periphery and increased TSH levels while reducing plasma T3 and T4 levels (2). Li *et al.* reported that TPO positivity was more frequent, TSH levels were higher and T4 levels were lower in Chinese women with iron deficiency in early gestation (8). In another study, Veltri *et al.* reported that women with ID in their first trimester of pregnancy had higher prevalence of thyroid autoimmunity, higher serum TSH, and lower FT4 levels (7). On the other hand, thyroid autoimmunity has been associated with adverse obstetric or child outcomes such as miscarriage, recurrent spontaneous pregnancy loss, premature delivery, perinatal death, increased risk for placental abruption, postpartum depression and neonatal respiratory distress syndrome (10-16). In women with thyroid autoimmunity, overt or sub-clinical hypothyroidism may occur during the pregnancy because the ability of the thyroid to augment hormone production is compromised (17). The first trimester of pregnancy is the most sensitive period to the adverse effects of overt or sub-clinical hypothyroidism.

It is a continuing debate about whether all pregnant women or only those with risk factors should be screened for thyroid function. Only by risk-based screening, it has been reported that TPO positivity missed in 33% of pregnant women (18). Many patients with autoimmune thyroiditis are clinically and hormonally euthyroid. Our results support that ID is associated with thyroid autoimmunity. Although it does not reach statistical significance, the change in TSH and T4 is also consistent with the literature. Considering the relation between thyroid autoimmunity and thyroid dysfunction and the sensitivity of early gestation to thyroid dysfunction, pre-pregnancy recognition of thyroid autoimmunity may be important. Our results and some others suggest that iron deficiency is a risk factor for thyroid autoimmunity. In particular, if a risk-based screening is to be carried out, ID should be considered as a risk factor in pregnant or pregnancy planning women and they should be screened not only for thyroid hormones but also for thyroid autoimmunity. It can also be said that women with autoimmune thyroiditis tend to develop iron deficiency anemia. Even so, it does not eliminate the need for women with iron deficiency to be evaluated for thyroid autoimmunity.

The most important limitation of this study is that the study population is living in the mild iodine deficient region. Previously, it has been reported that

dietary iodine intake may be associated with thyroid antibody positivity. The iodine status was not assessed in our study. Since the iron-deficient group and the control group live in the same region, the effect of iodine status can be neglected. However, there may be individual differences in iodine uptake.

In conclusion, the results of this study support the association of iron deficiency with thyroid autoimmunity. In cases where the outcome of clinical or sub-clinical thyroid dysfunction is substantial such as pregnancy and/ or pregnancy planning, we recommend that iron deficiency should be considered as a risk factor for screening thyroid antibody.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- McLean EI, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nut.* 2009; 12(4):444-454.
- Zimmermann MB, Burgi H, Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. *J Clin Endocrinol Metab.* 2007; 92(9):3436-3440.
- Zhang HY, Teng XC, Shan ZY, Wang ZJ, Li CY, Yu XH, Mao JY, Wang WW, Xie XC, Teng WP. Association between iron deficiency and prevalence of thyroid autoimmunity in pregnant and non-pregnant women of childbearing age: a cross-sectional study. *Chin Med J (Engl).* 2019;132(18):2143-2149.
- Rayman MP. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. *Proc Nutr Soc.* 2019;78(1):34-44.
- Brigham DE, Beard JL. Effect of thyroid hormone replacement in iron-deficient rats. *Am J Physiol.* 1995; 269(5 Pt 2):R1140-1147.
- Hess SY, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. *J Nut.* 2002;132(7):1951-1955.
- Veltri F, Decaillet S, Kleynen P, Grabeczan L, Belhomme J, Rozenberg S, Pepersack T, Poppe K. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? *Eur J Endocrinol.* 2016; 175(3):191-199.
- Li S, Gao X, Wei Y, Zhu G, Yang C. The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy. *J Nutr Sci Vitaminol (Tokyo).* 2016; 62(6):397-401.
- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid.* 2017; 27(3):315-389.
- Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA.* 1990;19(264(11):1422-1425.

11. Iravani AT, Saeedi MM, Pakraves J, Hamidi S, Abbasi M. Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. *Endocr Pract.* 2008;14(4):458-464.
12. Glinoe D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, Kinthaert J, Robijn C, Grun JP, de Nayer P. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab.* 1991; 73(2):421-427.
13. Männistö T, Väärasmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab.* 2009; 94(3):772-779.
14. Haddow JE, Cleary-Goldman J, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, Porter TF, Nyberg DA, Bernstein PS, D'Alton ME. First- and Second-Trimester Risk of Aneuploidy (FaSTER) Research Consortium. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. *Obstet Gynecol.* 2010;116(1):58-62.
15. Groer MW, Vaughan JH. Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. *J Obstet Gynecol Neonatal Nurs.* 2013; 42(1):E26-32.
16. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. *J Clin Endocrinol Metab.* 2011; 96(6):E920-924.
17. Glinoe D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab.* 1994; 79(1):197-204.
18. Aghajanian P, Spencer CA, Wilson ML, Lee RH, Goodwin TM, Mestman JH. Evaluation of risk-factorbased screening for thyroid peroxidase antibody positivity in pregnancy. *Clin Endocrinol (Oxf).* 2016; 84(3):417-422.