

Evaluation of ovarian reserve in women with overt or subclinical hypothyroidism

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Abstract

Introduction: Thyroid dysfunction is among the most common autoimmune disorders in women of reproductive age. Previous studies have shown the association between autoimmune thyroid disease (AITD) and infertility. Anti-Müllerian hormone (AMH) is secreted by granulosa cells and is a useful marker for assessment of ovarian reserve. In the present study, we sought to evaluate the ovarian reserves of women with autoimmune thyroid disorder by measurement of AMH values.

Material and methods: This prospective study included women with newly diagnosed AITD aged between 20 and 40 years. Patients were divided into three groups: subclinical hypothyroidism (SCH, $n = 21$), overt hypothyroidism (OH, $n = 21$) and controls (CG, $n = 32$). Study parameters included serum free T4, free T3, thyroid-stimulating hormone, anti-thyroglobulin, anti-thyroid peroxidase antibodies, follicle-stimulating hormone, luteinizing hormone, estradiol and AMH concentrations measured in the early follicular phase. Antral follicle count (AFC) was assessed with ultrasound. Body mass index (BMI) and waist circumference of the patients were noted.

Results: No significant difference was found among SCH, OH and CG in regard to ovarian reserves measured by AMH values ($p = 0.19$) and AFC ($p = 0.80$). A significant negative correlation was found between AMH and BMI ($r = -0.382$, $p = 0.001$). Anti-Müllerian hormone and waist circumference ($r = -0.330$, $p = 0.004$) were also negatively correlated.

Conclusions: Although AMH values were not significantly different among groups, AMH values were lower in OH and SCH patients, indicating a possible need for close monitoring of these patients.

Key words: anti-Müllerian hormone, autoimmune thyroid disease, fertile women.

Introduction

Thyroid diseases are the most common autoimmune diseases among women during reproductive age. Prevalence of subclinical and overt hypothyroidism is 4–10% and 0.1–2% respectively in this population [1–3]. Presence of thyroid hormone receptors on oocytes suggests that thyroid hormones may influence ovarian functions [4]. It is well known that disturbances of the menstrual cycle are increased as much as 3-fold in Hashimoto thyroiditis [4]. In addition, the majority of data suggest that

ovarian function is disturbed and frequency of miscarriages and infertility are increased in patients with autoimmune thyroid diseases [5, 6].

Antral follicle count (AFC), ovarian volume, serum follicle-stimulating hormone (FSH), and estradiol (E2) concentrations at the early follicular phase of the menstrual cycle are also used to evaluate ovarian reserve [7–9]. Besides these, serum anti-Müllerian hormone (AMH) and inhibin-B concentrations are also used [10, 11]. Anti-Müllerian hormone is secreted from growing granulosa cells. An *in vitro* fertilization trial demonstrated that AMH concentrations show a significant correlation with oocyte count after superovulation, and can be used as a good marker [12]. Concentration of AMH tends to decrease with age [13].

Previous studies have shown the association between autoimmune thyroid disease (AITD) and infertility [14–16].

In this study, we aimed to determine ovarian reserve measured by AMH concentration in women with Hashimoto disease related subclinical or overt hypothyroidism.

Material and methods

This prospective study was performed in the Department of Endocrinology, Obstetrics and Gynecology of Corum Hitit University Training and Research Hospital between June 2014 and June 2015. The study was conducted in accordance with the Declaration of Helsinki 2013 Brazil version, and was approved by the local ethics research committee. All subjects provided written informed consent prior to participation in the study.

A total of 74 women aged between 20 to 40 years were included in this study. Newly diagnosed patients with subclinical hypothyroidism (SCH, $n = 21$) or overt hypothyroidism (OH, $n = 21$) due to Hashimoto thyroiditis formed the two patient groups, whereas 32 healthy women served as controls (CG). Subclinical or overt hypothyroid patients were diagnosed as having Hashimoto disease when they had high levels of anti-thyroid peroxidase (TPOAb) or anti-thyroglobulin antibodies (TgAb) together with parenchymal heterogeneity on thyroid ultrasonography. Presence of increased thyroid-stimulating hormone (TSH > 10 $\mu\text{U/ml}$) together with low free T4 (fT4 < 0.8 ng/dl) was regarded as overt hypothyroidism, while a mildly increased TSH (4.2–10 $\mu\text{U/ml}$) in the presence of normal free T3 (fT3) and fT4 values was regarded as subclinical hypothyroidism.

Hashimoto thyroiditis patients were enrolled in the endocrinology department. The control group consisted of the routinely gynecological examined women without any complaints associated with thyroid disease (euthyroid and negative for TPOAb and TgAb); almost all patients in this group were

women visiting the gynecology department for a yearly smear screening test.

Patients with a history of any of the following were excluded: thyroidectomy, radioactive iodine ablation, radiotherapy to neck region, oophorectomy, tobacco or alcohol consumption, any malignancy or gynecologic disorder, chronic renal or hepatic disease of any kind, infertility, polycystic ovary syndrome (PCOS). Pregnant women, patients in the postpartum period or currently on levothyroxine, methimazole or propylthiouracil were also excluded.

Venous blood samples were taken from the antecubital regions of all patients between 08:00 am and 09:00 am after an overnight fast, in the early follicular phase (days 2–4) of the menstrual cycle. Serum fT4, fT3, TSH, TgAb, TPOAb, FSH, luteinizing hormone (LH), and estradiol (E2) concentrations were measured by the chemiluminescence microparticle immunoassay method (Cobas E6000, Roche Diagnostic, Germany). Three milliliters of serum sample was stored at -80°C and assayed for AMH. Anti-Müllerian hormone was assayed by the electrochemiluminescence method (Cobas C601, Roche Diagnostic, Germany).

On the same morning of the blood tests, pelvic ultrasound examination was performed. Pelvic ultrasound examination was carried out by the same gynecologist, blinded to all patient data, using a Toshiba Xario 100 (Toshiba Medical Systems Corporation, Nasu, Japan) with a 7.5-MHz vaginal transducer. On the 3rd day of the cycle, antral follicles measuring 2–10 mm in diameter were counted. The total numbers of follicles in ovaries were added for total AFC. Thyroid ultrasonography examinations of the patients were performed in the endocrinology department by an endocrinologist, using the Aplio 500 (Toshiba America Medical Systems, California, USA) ultrasonography equipment with a 14 MHz linear probe.

Statistical analysis

Data analysis was conducted with Statistical Package for the Social Sciences for Windows software, version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics with a normal distribution were presented as mean \pm standard deviation; those with a non-normal distribution were presented as median (min–max); and nominal variables were presented as number of cases and percentage (%). The significance of the difference between the two groups was evaluated with Student's *t*-test for means and the Mann-Whitney *U* test for medians. The significance of the mean difference between more than two groups was evaluated with either the ANOVA test or Kruskal-Wallis test, where applicable. In order to determine which groups differ, post hoc tests (Bonferroni) were used. Nominal

variables were evaluated using Pearson's χ^2 or Fisher's exact test. Pearson and (or) Spearman's correlation test was used to investigate the association between two continuous variables. A p -value < 0.05 was considered statistically significant.

Results

Demographic, hormonal and pelvic ultrasonography data of all three groups are summarized in Table I. The three groups were similar with regard to age, height, body mass index (BMI), age at menarche and number of children ($p > 0.05$ for all).

We found differences among groups in TSH, fT3, fT4, TPOAb and TgAb concentrations (Table I).

Post hoc tests were performed to determine which groups differ. According to their results, there was a statistically significant difference among groups in TPOAb (OH-SCH, $p = 0.002$; OH-CG, $p < 0.001$; SCH-CG, $p < 0.001$) and TSH (OH-SCH, $p < 0.001$; OH-CG, $p < 0.001$; SCH-CG, $p = 0.009$). TgAb concentrations were not different between OH and SCH groups, but comparison of OH and SCH with CG showed statistical significance (OH-CG, $p < 0.001$; SCH-CG, $p = 0.01$). Free T3 concentrations were significantly different between only OH and CG groups (OH-SCH, $p = 0.345$; OH-CG, $p = 0.03$; SCH-CG, $p = 0.092$). Additionally, fT4 concentrations were significantly different when

Table I. Demographic, hormonal and pelvic ultrasonography parameters of the study population

Parameter	OH (n = 21)	SCH (n = 21)	CG (n = 32)	P-value (ANOVA)	P-value (post-hoc)
Age [years]	35.4 \pm 5.9	34.2 \pm 4.7	32.0 \pm 5.1	0.06	
Weight [kg]	72.4 \pm 13.9	67.8 \pm 17.4	63.9 \pm 11.4	0.10	
Height [cm]	162.1 \pm 6.6	162.2 \pm 5.7	161.2 \pm 5.0	0.78	
BMI [kg/m ²]	27.6 \pm 5.7	25.8 \pm 6.8	24.5 \pm 3.9	0.13	
Waist [cm]	91.4 \pm 14.6	85.6 \pm 16.1	83.8 \pm 13.0	0.17	
TPOAb (< 115 IU/ml)	281.9 \pm 119.6	152.0 \pm 190.9	17.8 \pm 7.7	< 0.001	a: $p = 0.002^*$ b: $p < 0.001^*$ c: $p < 0.001^*$
TgAb (< 34 IU/ml)	265.8 \pm 154.6	170.5 \pm 154.9	20.3 \pm 5.2	< 0.001	a: $p = 0.08^*$ b: $p < 0.001^*$ c: $p = 0.01^*$
TSH (0.27–4.2 μ U/ml)	12.1 \pm 3.4	4.5 \pm 2.0	2.0 \pm 1.1	< 0.001	a: $p < 0.001^*$ b: $p < 0.001^*$ c: $p = 0.009^*$
fT3 (2.1–4.4 pg/ml)	1.8 \pm 0.3	2.2 \pm 0.1	2.9 \pm 0.3	0.03	a: $p = 0.345^*$ b: $p = 0.03^*$ c: $p = 0.092^*$
fT4 (0.8–2.7 ng/dl)	0.7 \pm 0.2	1.1 \pm 0.1	1.1 \pm 0.1	0.016	a: $p < 0.001^*$ b: $p < 0.001^*$ c: $p = 0.665^*$
Age at menarche [years]	12.8 \pm 1.2	13.0 \pm 1.2	12.7 \pm 1.4	0.08	
Number of children	2.5 \pm 1.0	2.4 \pm 1.1	2.4 \pm 1.0	0.09	
FSH (1.4–9.9 mIU/ml)	9.5 \pm 13.4	9.1 \pm 7.3	5.9 \pm 2.2	0.25	
LH (2.4–12.6 mIU/ml)	10.8 \pm 9.7	10.6 \pm 7.2	8.4 \pm 7.3	0.18	
E2 (12.5–166 pg/ml)	99.4 \pm 134.1	103.4 \pm 109.9	144.8 \pm 119.8	0.09	
Mean AMH concentration [ng/ml]	1.5 \pm 1.3	1.8 \pm 2.2	2.1 \pm 1.4	0.19	
Total AFC	12.8 \pm 8.6	12.5 \pm 4.8	11.6 \pm 3.8	0.80	

*Bold p-values indicate statistically significant differences ($p < 0.05$). TPOAb – anti-thyroid peroxidase antibodies, TgAb – anti-thyroglobulin antibodies, TSH – thyroid-stimulating hormone, FSH – follicle-stimulating hormone, LH – luteinizing hormone, E2 – estradiol, AMH – anti-Müllerian hormone, AFC – antral follicle count, pairwise comparison shortcuts; OH-SCH = a, OH-CG = b, SCH-CG = c, *Post hoc analysis was performed only on $p < 0.05$ values.*

comparing OH with SCH and CG groups (OH-SCH, $p < 0.001$; OH-CG, $p < 0.001$; SCH-CG, $p = 0.665$).

The mean AMH concentrations were similar between SCH, OH and CG ($p = 0.19$). All three groups had similar AFC (OH, 12.80 ± 8.62 ; SCH, 12.57 ± 4.85 ; CG, 11.68 ± 3.88 , $p = 0.80$).

When all the patients were evaluated, there was a significant positive correlation between AMH and AFC ($r = 0.559$, $p < 0.001$), significant negative correlations between AMH and BMI ($r = -0.382$, $p = 0.001$), AMH and waist ($r = -0.330$, $p = 0.004$), and AMH and age ($r = -0.400$, $p < 0.0001$). There were no correlations between serum AMH and TSH, TPOAb, TgAb, FSH, age at menarche or number of children ($p > 0.05$ for all). There was a negative correlation between AFC and BMI ($r = -0.284$, $p = 0.01$). There were no correlations between AFC and AMH and TSH, TPOAb, TgAb, FSH, age at menarche or number of children ($p > 0.05$ for all).

No significant difference was found among groups in regard to the presence of irregular periods of menstruation ($p = 0.59$). Five (12.5%) women in CG, 3 women (13.6%) in SCH and 3 women in OH (12.5%) had irregular periods of menstruation. Oligomenorrhea was the most common type of menstrual irregularity in all three groups (CG 10%, $n = 4$, SCH 9.1%, $n = 2$, OH 8.3%, $n = 2$).

Discussion

Autoimmune thyroid disease (AITD) is the most common endocrine disease among women of reproductive age. Its prevalence was reported to range from 5% to 15%. Risk of hypothyroidism by age shows a two-stage peak with an increase from 1.4 to 14 per 1000 per year at 20 to 25 and 75 to 80 years of age [4]. Since ovarian reserve decreases with increasing age, women with hypothyroidism are at increased risk for development of ovarian insufficiency. Our study is among the few studies that have investigated the association of AMH values with ovarian reserve in women with autoimmune thyroid disease. Although our study demonstrated low serum AMH concentration in women with AITD, the difference was not statistically significant.

There are several parameters for evaluation of ovarian reserve, including FSH, E2, inhibin B, AMH, AFC and ovarian volume in ultrasound, clomiphene test, and exogenous FSH ovarian reserve test. Follicle-stimulating hormone concentration increases in the early follicular phase (EFP) and this increase occurs before a significant decrease in estradiol, or progesterone concentrations, and before the luteal phase occurs [17]. Therefore, EFP FSH concentration may be a useful marker of ovarian reserve. Since high concentrations of serum estradiol on day 3 were reported to be associated with rapid

premature follicle recruitment and decreased oocyte numbers, they may also be indicative for poor pregnancy outcome after *in-vitro* fertilization (IVF) [18]. Both hormones show some variation, and this may complicate their usefulness. However, since AMH does not significantly vary throughout the menstrual cycle, its measurement seems to be more useful in detection of ovarian reserve [19]. There have been a number of studies comparing AMH and AFC where AMH concentration was found to be more strongly correlated with oocyte yield following ovarian stimulation compared to AFC [20–23]. In our study, we found no significant difference among OH, SCH and controls in regard to AMH values. Total AFC did not differ significantly in OH and SCH compared to controls. We found no significant association between AMH concentration and FSH or E2 concentrations.

Studies have demonstrated a relationship between infertility and autoimmune thyroid diseases [14–16]. Several mechanisms have been suggested to explain the high incidence of infertility in hypothyroid women, including an altered peripheral estrogen mechanism, hyperprolactinemia, coagulopathies and gonadotropin-releasing hormone secretion abnormalities leading to the abnormal pulsatile release of LH [24]. Adequate fertilization and blastocyst development are dependent on both gonadotrophins and T4 concentrations. In one recent study, Cramer *et al.* demonstrated that serum TSH concentration significantly predicted failure of fertilization in women receiving IVF [25]. This information highlights the role of thyroid hormones in oocyte physiology. In a retrospective study, prevalence of hypothyroidism was investigated in 299 infertile women having different etiologies [26]. Overall, 4% of the patients had an increased concentration of serum TSH and 3.3% had OH. In another retrospective study, Abalovich *et al.* included 244 patients presenting with infertility and 155 healthy women with confirmed fertility [27]. Although SCH is more common in infertile patients (13.9% vs. 3.9%), AITD prevalence did not differ significantly between infertile women and controls. Incidence of SCH was reported to range from 1% to 4% in infertile women [28]. In one study Polyzos *et al.* evaluated the effect of thyroid autoimmunity on ovarian reserves using AMH measurements. The authors reported that incidence of overt or subclinical hypothyroidism was not significantly different among women with low, normal or increased ovarian reserves (4.1%, 4.6% and 3.8%, respectively) [29]. Likewise, we found no significant correlation between thyroid autoantibodies and AMH concentration. Saglam *et al.* investigated the ovarian reserves of 85 euthyroid AITD patients using AMH concentration and found that prematurely aging ovaries was significantly higher [30]. Kuroda *et al.* reported

that AMH concentrations were inversely correlated with TSH concentration (despite normal TSH concentrations) in infertile women of reproductive age [31]. Our study showed no significant relationship between TSH and AMH concentrations. Tuten *et al.* found that AMH concentration was significantly higher in 32 premenopausal women with Hashimoto thyroiditis compared to controls, whereas they found no significant difference in antral follicle count [32]. The reason for this result was that their study included many patients with PCOS, who have more antral follicles than patients without PCOS, and presence of more follicles leads to secretion of more AMH. In our study, patients with PCOS were not included, since this may cause increased AMH concentrations.

Patients with hypothyroidism may have alterations in time of the menstrual cycle and amount of bleeding because of the estrogen breakthrough bleeding and decrease in coagulation factors such as factor VII, VIII, IX and XI [33, 34]. Krassas reported in his review that the most common menstruation disorder was oligomenorrhea rather than amenorrhea in patients with hypothyroidism [4]. Likewise, we found that oligomenorrhea was the most common menstrual disorder in all groups. We found no significant difference in menstrual irregularities among groups. The low incidence of menstrual disorders in other studies may be due to the early establishment of the diagnosis of hypothyroidism before clinical manifestations become apparent.

There have been several studies reporting that BMI and AMH concentration did not show a significant correlation [35, 36], whereas a significant negative correlation was demonstrated in some others [37]. In our study, we found a significant negative correlation between BMI, waist circumference and AMH concentration. Therefore, in our opinion control of body weight may be important in preservation of ovarian reserves.

Our study had several limitations. First, the effect of thyroid autoimmunity on ovarian functions might have been inadequately assessed since we included patients with newly diagnosed overt and subclinical hypothyroidism. Moreover, ovarian functions might have been found to decrease with increasing time from diagnosis. The low number of patients is among the limitations of this study.

In conclusion, we found no significant difference between patients with overt or subclinical hypothyroidism and control in regard to ovarian reserves measured by serum AMH concentration and total AFC. However, the lower AMH concentration found in OH and SCH patients may be suggestive for close follow-up of these patients. Further, larger prospective studies are needed to confirm these findings.

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Conflict of interest

The authors declare no conflict of interests.

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