Thyroid Peroxidase Antibodies in Infertile Women with Polycystic Ovary Syndrome

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Abstract

To compare the rate of positive thyroid peroxidase antibodies (TPO Ab) between women with different polycystic ovary syndrome (PCOS) phenotypes and women without PCOS. This is a retrospective cohort study. Women with PCOS at My Duc Hospital between June 1, 2020, and March 27, 2021, were matched with non-PCOS women by age. TPO Ab (cut-off: 34 IU/mL) and thyroid-stimulating hormone (TSH) levels were measured as markers of Hashimoto thyroiditis and thyroid function, respectively. One thousand eight hundred eight infertile women were included, 904 with PCOS (mean age 29.0 ± 3.58 years) and 904 without PCOS (29.1 ± 3.4 years; controls). Women with PCOS had a higher body mass index (22.8 ± 3.84 vs. 19.9 ± 2.23 kg/m^2, $p < 0.001$), but most were not overweight/obese. Rates of positive TPO Ab in women with versus without PCOS were 8.2% and 8.4%, respectively ($p = 0.932$). Rates of positive TPO Ab in patients with PCOS phenotype A, B, C, or D were not statistically different (7.5%, 2.9%, 20.0%, and 7.8%, respectively). Median TSH concentrations were similar in the PCOS and control groups (1.84 mIU/L vs. 1.78 mIU/L, respectively; $p = 0.194$). Based on a linear regression model, there was no correlation between either BMI or the estradiol to progesterone ratio and TPO Ab status. In a large population of infertile women with PCOS who were mostly lean patients, rates of positive TPO Ab across all four PCOS phenotypes did not differ significantly from those in women without PCOS. These findings did not support the hypothesis that PCOS is a risk factor for Hashimoto thyroiditis.

Keywords Polycystic ovary syndrome · Phenotypes · Thyroid peroxidase antibodies · Infertility · Hashimoto thyroiditis · Lean PCOS

Introduction

The prevalence of autoimmune thyroid diseases (AITDs) is 4% and up to 15% in women of childbearing age [1]. AITDs cover a spectrum of disorders ranging from thyrotoxicosis to hypothyrodism which is caused by infiltration of lymphocytes to the thyroid gland, production of antibodies against self-structures, and cytotoxic action of T cells on thyrocytes. Thyroid autoimmunity and subsequent thyroid dysfunction induce abnormal sex hormone metabolism and menstrual irregularities and contribute to infertility [2, 3].

The etiology of AITDs is thought to include a combination of genetic susceptibility and environmental factors. Either thyroid specific (TSHR, thyroglobulin) or immunoregulatory genes (FOXP3, CD25, CD40, CTLA-4, and HLA) play essential roles in the development of AITDs, e.g., Graves' disease and Hashimoto's thyroiditis (HT) [4]. However, the development of AITDs cannot be solely predicted from susceptibility genes. Environmental factors contributing to the development of AITDs include viral infections, stress, body mass index, and sex steroid hormones. Compared with men, women had a five to tenfold higher chance of acquiring AITDs, which has been correlated with their

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higher estrogen levels. Estrogen is implicated as an enhancer of humoral immunity, while androgens and progesterone are thought to be protective as natural immune suppressors. Thyroid peroxidase antibody (TPO Ab) and thyroglobulin antibody (Tg Ab) are fundamental markers of HT, which is one of the most common types of AITDs leading to hypothyroidism. A study by Poppe et al. [2] showed that TPO Ab is significantly higher in infertile patients compared with controls (18% vs. 8%, respectively). In a Danish population, Feldthusen et al. [5] also reported impaired fertility associated with TPO Ab. However, population-based study conducted in Iran showed no association between infertility and TPO Ab [6]. These studies had several limitations, e.g., not focusing on the analysis of different metabolic disorders or on the correlation between TPO Ab and body mass index (BMI) or sex hormones. Moreover, thyroid autoimmunity is also associated with miscarriage, thyroid disorders during pregnancy, and in the postpartum period [3]. Ning et al. [7] found a strong association between TPO Ab positivity and preterm birth in euthyroid women with a female fetus.

In addition to AITDs, polycystic ovary syndrome (PCOS) is another common endocrine disorder that includes irregular menstrual cycles, hyperandrogenism, and infertility. Obesity, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disorders are the most common comorbidities related to PCOS. PCOS was subdivided into four clinical phenotypes [8]. Phenotype A is characterized by clinical and/or biochemical hyperandrogenism (HA), menstrual dysfunction (oligo/amenorrhea) (OA), and polycystic ovarian morphology (PCOM) in ultrasonography. Phenotype B is recognized when HA and OA are present, phenotype C is characterized by HA and PCOM, and the fourth phenotype, D, is defined by the presence of OA and PCOM. It is still unclear whether metabolic problem are the same in PCOS patients with the milder versus more severe phenotypes. Some studies claimed that phenotype A results in the most severe endocrine and metabolic abnormalities [9], while these were less extreme in phenotype D (the normoandrogenic phenotype) [10].

Several evidences suggested that PCOS is an independent risk factor for HT. In 2018, a meta-analysis of data from 1210 patients with PCOS and 987 non-PCOS women reported that the prevalence of positive TPO Ab was 26% and 9.7%, respectively (odds ratio [OR] 3.27, 95% confidence interval [CI] 2.32–4.63) [11]. Of note, the risk of AITDs in women with PCOS persisted for Asians (OR 4.56). However, it has also been reported that the rate of positive TPO Ab does not differ significantly between women with and without PCOS from Korea and Poland [12, 13]. Until now, only one single study explored the rate of TPO Ab positivity between PCOS phenotypes with clinical and/or biochemical hyperandrogenism and the control group [13]. In the current study, we reported the prevalence of TPO Ab in a large cohort of Vietnamese women with different phenotypes of PCOS compared with non-PCOS women. We also examined the correlation between BMI or the estradiol to progesterone ratio with TPO Ab status using a linear regression model.

Materials and Methods

Study Design

This retrospective cohort study was conducted at IVFMD center (My Duc Hospital), Ho Chi Minh City, Vietnam, between June 1, 2020, and March 27, 2021. The study was approved by the Institutional Ethics Committee of My Duc Hospital (02/2021/MĐ-HĐĐĐ).

Study Population

Women (aged ≥ 18 years) who sought infertility treatment and had at least two of the following diagnostic criteria of PCOS were eligible for the study: irregular menstrual cycles (> 35 days or < 21 days); clinical and/or biochemical signs of HA; and/or PCOM on ultrasound, after exclusion of other disorders that mimic PCOS. Biochemical HA was defined as elevated testosterone (1.8 nmol/L) or free testosterone index > 6. For PCOM, using endovaginal ultrasound transducers with a frequency bandwidth that includes 8 MHz, the threshold for PCOM on either ovary was > 20 follicles per ovary, ensuring no corpora lutea, cysts, or dominant follicles were present. The four different PCOS phenotypes were A (OA + HA + PCOM), B (OA + HA), C (HA + PCOM), and D (OA + PCOM). Age-matched controls were female patients who visited the hospital because of problems unrelated to PCOS, had normal menses, and did not seek advice for thyroid dysfunction. Individuals with hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, hypertension, hepatic or renal insufficiency, and diabetes mellitus and those who had used preparations containing selenium in the previous 3 months were excluded.

Assessments

For all participants, at the first time of visit, thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels were quantified using the Access 2 Immunoassay System (Beckman Coulter, Inc., USA). Chemiluminescent competitive immunoassay (Roche Cobas® E 411, Roche Diagnostics, German) was utilized for measurement of TPO Ab, estradiol, and progesterone levels. The reference range for TPO Ab was < 34 IU/mL; level above this threshold was considered positive.

Outcome Measures

The primary outcome was the rate of TPO Ab positivity or median antibody levels between patients with and without PCOS and among different PCOS phenotypes.

Statistical Analysis

Data were analyzed using descriptive statistics (mean and standard deviation for normally distributed variables or median and interquartile range for skewed variables). Between-group differences were analyzed using one-way ANOVA with post hoc Tukey HSD test or Kruskal Wallis test for normally distributed or skewed variables, respectively, and the chi-square test for categorical variables. Univariable and multivariable logistic regression analyses were performed to identify factors associated with TPO Ab positivity. All variables with a p value < 0.25 in the univariate analysis were included in the multivariable analysis. All analyses were performed using the R statistical package (R version 3.3.3). Statistical significance was defined as $p < 0.05$.

Results

Study Population

Of 3182 women seeking fertility treatment at IVFMD over the study period, 904 had confirmed PCOS. The same number of non-PCOS women were randomly matched with PCOS patients by age (mean age 29 years) (Table 1). Although mean BMI was significantly higher in women with versus without PCOS women (22.8 vs. 19.9 kg/m^2; $p < 0.05$), the majority of women with PCOS were lean. As expected, the anti-Müllerian hormone (AMH) level, luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio, and the free testosterone index (FTI) were significantly higher in the women with versus without PCOS (Table 1). Duration of infertility was comparable in the two groups, but most of the patients with PCOS had primary infertility ($p < 0.05$) (Table 1).

Thyroid Peroxidase Antibody and Thyroid Hormonal Status

There were no significant differences between patients with and without PCOS or between different PCOS phenotypes with respect to rates of TPO Ab positivity or median antibody levels (Table 2, Fig. 1). Although the median concentration of fT4 was slightly lower in the PCOS group than in the non-PCOS group, TSH levels were not statistically different between groups (Table 2).

Influence of PCOS Phenotype

The prevalence of TPO Ab was slightly higher in PCOS patients with phenotype C, but between-group differences did not reach statistical significance (Table 3). Neither

Table 1 Clinical and laboratory profiles of study participants

Variables	PCOS ($n = 904$)	Non-PCOS ($n = 904$)	p value
Age, years	29.0 ± 3.58	29.1 ± 3.40	0.576
Body mass index, kg/m^2	22.8 ± 3.84	19.9 ± 2.23	< 0.001
Body mass index, n (%)			< 0.001
< 23 kg/m^2	550 (60.8)	843 (93.3)	
23 to < 25 kg/m^2	142 (15.7)	33 (3.7)	
≥ 25 kg/m^2	212 (23.5)	28 (3.1)	
Duration of infertility, years	2.00 [1.00, 3.50]	2.00 [1.00, 4.00]	< 0.001
Types of infertility, n (%)			< 0.001
Primary	669 (74.0)	593 (65.6)	
Secondary	235 (26.0)	311 (34.4)	
LH/FSH ratio	2.23 [1.58, 2.90]	NA	NA
Estradiol concentration, pg/mL	45.1 [33.7, 60.1]	45.8 [31.7, 97.6]	0.427
Estradiol/progesterone ratio	331 [172, 625]	NA	NA
Free testosterone index	4.13 [2.40, 6.60]	NA	NA
Anti-Müllerian hormone, ng/mL	8.07 [5.78, 10.9]	3.78 [2.18, 5.84]	< 0.001
Antral follicle count	30.0 [21.0, 38.0]	16.0 [10.0, 22.0]	< 0.001

Values are mean ± standard deviation, number of patients (%), or median [interquartile range]

FSH, follicle-stimulating hormone; *LH*, luteinizing hormone; *NA*, not available; *PCOS*, polycystic ovary syndrome

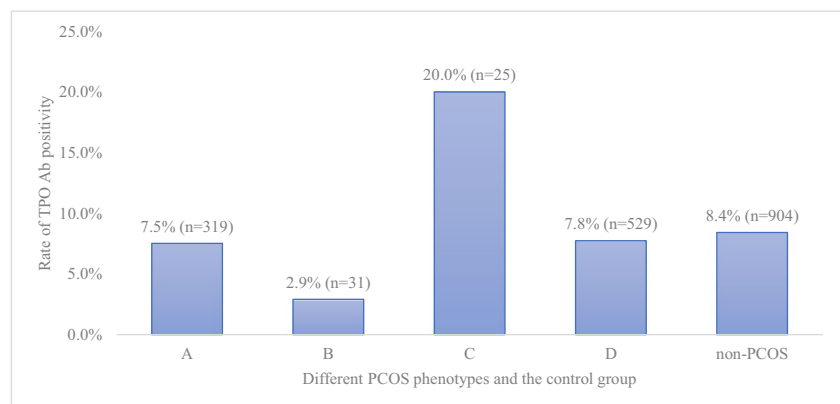**Table 2** Thyroid peroxidase antibody and thyroid hormonal status

Variables	PCOS (n=904)	Non-PCOS (n=904)	p value
Positive TPO Ab status	74 (8.2)	76 (8.4)	0.932
TPO Ab level, IU/mL	13.8 [10.9, 18.2]	14.2 [11.2, 18.1]	0.404
Thyroid-stimulating hormone, mIU/L	1.84 [1.27, 2.61]	1.78 [1.19, 2.56]	0.194
Free thyroxine, ng/dL	1.05 [0.89, 1.30]	1.11 [0.92, 1.34]	0.002

Values are number of patients (%) or median [interquartile range]

TPO Ab, thyroid peroxidase antibody; *PCOS*, polycystic ovary syndrome

BMI nor estradiol to progesterone ratio had any significant association with TPO Ab status on univariate analyses. Multivariate analyses also confirmed that PCOS was not correlated to TPO Ab positivity (Table 4).

Discussion

This was a large-scale retrospective study. Based on the large cohort of women included, our study provides robust data showing that neither the prevalence nor median level of TPO Ab increased in women with versus without PCOS. In addition, a PCOS diagnosis was not a risk factor for positive TPO Ab on multivariate analysis. In terms of clinical studies, plenty of authors reported the presence of a higher anti-TPO, and TSH levels as well as a higher frequency of anti-TPO positivity in women with PCOS than in age-matched healthy women [14, 15]. However, these studies usually had relatively small sample sizes (the largest included 210 patients) and the mean BMI of PCOS patient were higher than ours (24.9 ± 3.6 and 30.0 ± 7.9) [14, 15]. A meta-analysis study also confirmed the association between PCOS and AITDs (OR 3.27, 95% CI 2.32–4.63) [11]. Nevertheless, AITD diagnosis was made according to the authors' chosen criteria, so these criteria were not identical, and the study also found the large heterogenity between the included studies

Fig. 1 Comparison of rates of positive thyroid peroxidase antibodies between patients with different phenotypes of polycystic ovary syndrome (PCOS) or without PCOS ($p=0.212$). PCOS, polycystic ovary syndrome; TPO Ab, thyroid peroxidase antibody

Table 3 Biochemical profile and thyroid peroxidase antibody distribution based on polycystic ovary syndrome phenotype

Variables	PCOS-A (n=319)	PCOS-B (n=31)	PCOS-C (n=25)	PCOS-D (n=529)	Non-PCOS (n=904)	p value
Body mass index, kg/m²	23.9±4.1[ab]	23.5±4.7[c]	22.3±3.7[d]	22.1±3.4[ae]	19.9±2.2[bcde]	<0.001
LH/FSH ratio	2.45 [1.93, 2.98][a]	1.92 [1.59, 3.31]	2.30 [1.61, 2.80]	2.05 [1.35, 2.80][a]	NA	<0.001
Estradiol/progesterone ratio	323 [199, 600]	269 [151, 467]	265 [185, 418]	340 [155, 667]	NA	0.106
Free testosterone index	7.24 [5.51, 9.68][a]	6.03 [3.78, 7.62][b]	5.23 [2.97, 8.65][c]	2.83 [1.75, 4.30][abc]	NA	<0.001
Anti-thyroid peroxide antibody, IU/mL	13.7 [10.5, 18.2]	15.8 [12.4, 21.1]	13.0 [9.76, 21.9]	13.8 [10.9, 17.5]	14.2 [11.2, 18.1]	0.349
Thyroid-stimulating hormone, mIU/L	1.86 [1.25, 2.71]	2.06 [1.61, 2.92]	1.58 [1.30, 2.43]	1.80 [1.26, 2.54]	1.78 [1.19, 2.56]	0.283
Free thyroxine, ng/dL	1.03 [0.88, 1.33]	1.11 [0.92, 1.23]	1.05 [0.89, 1.27]	1.07 [0.89, 1.30]	1.11 [0.92, 1.34]	0.393

Values are mean±standard deviation, number of patients (%), or median [interquartile range]. Comparison was performed between phenotypes and between different phenotypes with non-PCOS group whenever it was available

FSH, follicle-stimulating hormone; *LH*, luteinizing hormone; *NA*, not available; *PCOS*, polycystic ovary syndrome; *TPO Ab*, thyroid peroxidase antibody

[a,b,c,d,e]Post hoc p value <0.05

Table 4 Factors associated with positive thyroid peroxidase antibodies

Variables	TPO Ab		Univariate analysis	Multinomial logistic regression
	Negative ($n = 1658$)	Positive ($n = 150$)	OR [95% CI]; p value	Adjusted OR; [95% CI]; p value
Age, years	29.1 ± 3.5	29.1 ± 3.2	1.00 [0.96, 1.05]; 0.925	
Body mass index, kg/m^2	21.3 ± 3.4	21.5 ± 3.6	1.02 [0.97, 1.06]; 0.495	
Duration of infertility, years	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	0.96 [0.89, 1.03]; 0.298	
LH/FSH ratio	2.2 [1.5, 2.9]	2.2 [1.3, 3.1]	1.01 [0.80, 1.24]; 0.956	
Estradiol/progesterone ratio	330.8 [171.5, 618.1]	293.6 [126.6, 590.6]	1.00 [0.97, 1.00]; 0.793	
Non-PCOS women	882 ± 53.2	81 ± 54.0	Reference	
PCOS women	776 ± 46.8	69 ± 46.0	0.97 [0.69, 1.36]; 0.865	0.98 [0.68, 1.40]; 0.909
Anti-Müllerian hormone, ng/mL	6.0 [3.7, 8.9]	5.1 [3.3, 9.0]	1.00 [0.96, 1.04]; 0.848	
Antral follicle count	17.0 [11.0, 24.0]	16.0 [10.0, 26.0]	1.00 [0.98, 1.02]; 0.869	
Thyroid-stimulating hormone, mIU/L	1.8 [1.2, 2.5]	2.0 [1.1, 2.9]	1.11 [0.95, 1.27]; 0.170	1.11 [0.95, 1.27]; 0.171
Free thyroxine, ng/dL	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	0.98 [0.64, 1.20]; 0.907	

Values are mean ± standard deviation, number of patients (%), or median [interquartile range]

FSH, follicle-stimulating hormone; *LH*, luteinizing hormone; *NA*, not available; *PCOS*, polycystic ovary syndrome; *TPO Ab*, thyroid peroxidase antibody

[11]. Some studies on the Asian population showed that AITD was not more prevalent in women with PCOS than in controls, and subjects with AITD showed significantly higher adiposity than those without AITD [12, 13]. Moreover, the mean BMI of those PCOS population was similar to our population (20.4 ± 2.8 and 22.8 ± 3.84). Although the median BMI in the PCOS group was significantly higher than that in the non-PCOS group in our study, the majority of our patients had a normal BMI (Table 1). Other studies attributed an increase in the prevalence of HT to obesity, which is usually seen in women with PCOS. In one meta-analysis, obesity was significantly correlated with 93% increased risk of detection of positive TPO Ab [16]. Adipocyte-derived leptin, which serves as a cytokine polarizing T cells towards the T helper 1 cell phenotype and suppressing regulatory T cell activity, triggers and perpetuates the autoimmune process [16]. Furthermore, reciprocal crosstalk between estradiol and leptin may occur potentiating immune T cell responses [17]. This contrasts with Caucasian populations of PCOS patients, who are usually overweight or obese.

Interestingly, the estradiol to progesterone ratio in our lean patients with PCOS did not differ from that in the study showing a positive correlation between this ratio and the frequency of positive TPO Ab [14]. Median values for AMH and AFC in our PCOS population were also in the typical ranges for these patients. Therefore, we postulated that sex hormone imbalance per se did not elicit HT in the absence of obesity.

Phenotype D was the most common among our infertile PCOS women as well as in China [18], and type D was considered to be more common in East Asian patients than in Caucasian patients [19]. Although the highest rate of positive TPO Ab was seen in phenotype C group which had only a small number of patients, there were no statistically significant differences between other phenotypes or between the different phenotypes and the control group. Because PCOS is a very heterogeneous disorder, it is essential to analyze the relationship between PCOS and HT in different phenotypes. Until now, only one previous study reported TPO Ab-positive frequency in the four different PCOS phenotypes [13]. In that study, the frequency of positive TPO Abs was the highest in phenotype C and lowest in phenotype D, but differences between phenotypes and the control group were not statistically significant. However, it is hard to explain the frequency of TPOAbs in these phenotypes observed in our study.

Some authors suggested that higher TSH level was associated with hyperandrogenism in euthyroid patients with PCOS and that this relationship was independent of age, BMI, and thyroid autoimmunity [20]. However, we did not observe any clinically significant increase in TSH level or decrease in fT4 level between HA PCOS phenotypes A, B, and C compared with phenotype D (Table 3).

Our study had few limitations. First, we did not measure Tg Ab, similar to other reports. Therefore, some HT may be misdiagnosed in the PCOS and control groups. Second, this study did not include the LH/FSH ratio among non-PCOS patients because the current practice at our hospital did not capture this information. Third, this is a retrospective study, and we could not determine the time from PCOS diagnosis to the occurrence of TPO Ab meaning that exposure time could not be included in our study.

In conclusion, our study provides substantial evidence that the prevalence of positive TPO Ab was not increased in infertile women with PCOS, most of whom were lean. The

rate of TPO Ab did not differ significantly between PCOS phenotypes. Therefore, routine screening for thyroid disorders has limited value in infertile PCOS women.

Declarations

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