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ORIGINAL ARTICLE

Antithyroid Peroxidase Antibodies in Women with Polycystic Ovary Syndrome

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About the Author

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Abstract

Objective To find the prevalence of thyroid autoimmunity in PCOS women of reproductive age group.

Methods Study design: Observational study was done at ESIMC and PGIMSR K.K. Nagar March 2013–Feb 2014. Ninety cases of women with PCOS based on Rotterdam's criteria and an equal number of age-matched controls (women without PCOS) were included in the study. Thyroid profile, antithyroid peroxidase titre, serum progesterone, testosterone and fasting blood sugar were estimated using standardised techniques.

Results Menstrual irregularity (oligomenorrhoea and amenorrhoea) was the most common abnormality found in patients with PCOS compared with non-PCOS ($p < 0.0001$). Hyperandrogenism was the second most common manifestation present in PCOS of our study group. Hirsutism was the striking hyperandrogenic feature that was present in study group. PCOS patients had higher BMI compared to controls ($p < 0.0001$). The prevalence of thyroid dysfunction was not significantly different in both the groups ($p < 0.80$). Anti-TPO titre was higher in PCOS

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patients (25.8 ± 2.9 IU/ml) compared to the controls (14.5 ± 2.3 IU/ml) ($p < 0.009$).
Conclusion The present study shows that PCOS was associated with increased anti-TPO titres, thus emphasising the importance of screening all PCOS patients for anti-TPO along with routine thyroid profile.

Keywords Autoimmune thyroiditis · Antithyroid peroxidase antibody · PCOS · Thyroid profile

Introduction

PCOS is a common metabolic disorder in women of reproductive age group and is associated with multitude of endocrine abnormalities. The present prevalence of PCOS is around 5–20 % and is on the rise in parallel with the rise in obesity and sedentary life style [1]. A variety of theories both genetic and environmental has been postulated for the etiopathogenesis of PCOS of which hyperandrogenism theory and the insulin resistance theory are widely accepted [2]. Inflammatory and autoimmune causes are also reported to have contribution to the pathogenesis of PCOS [3]. Its close association with insulin resistance and thyroid disorders has led to a recent boon in the research and literature in this field. Autoimmune thyroid diseases (AITD) are common autoimmune disorders that affect 5–20 % of women in childbearing age [4]. AITD is the most frequent cause of hypothyroidism in young women and it may present without thyroid dysfunction for many years; hence, it is often ignored and results in hypothyroidism later in life [5]. AITD is an important cause of overt hypothyroidism with an incidence of 0.35 % per year and a prevalence of 3.5 % in iodine sufficient areas of the world [6]. Half of them manifest overt (1/3rd) or subclinical (2/3rd) hypothyroidism and the rest are euthyroid clinically and biochemically. Association between thyroid autoimmunity and adverse pregnancy outcomes has been reported; most patients with PCOS are in the childbearing age; therefore, it is important to maintain normal thyroid function before and during pregnancy to ensure the best possible outcome of the mother and progeny. This study aimed to determine whether women with PCOS were at greater risk of developing thyroid dysfunction and thyroid autoimmune diseases.

Methods

This is a prospective case control study done in March 2013–Feb 2014 at ESIC Medical College and PGIMSR Chennai. Women with signs of hyperandrogenism/oligomenorrhoea visiting obstetrics and gynaecology clinics were included in our study. PCOS was defined according to revised 2003 Rotterdam criteria [7] which require the presence of at least two of the three following indications.

1. Ovulatory disturbances mainly oligomenorrhoea or amennorhoea.
2. Hyperandrogenism as defined either clinically by hirsutism, severe acne, seborrhoea, or biologically by the elevated levels of total or free testosterone.
3. Polycystic ovaries at ultrasonography [8]

Controls were females in reproductive age with regular menstrual cycles, no signs of hyperandrogenism, normal ovaries on pelvic ultrasound examination and normal level of free testosterone.

A total of 203 patients were screened for PCOS based on their history and clinical examination. After excluding 13 patients for whom laboratory values were not complete and another 10 subjects based on exclusion criteria, 180 patients were analysed: 90 patients satisfied Rotterdam's criteria for PCOS and 90 age-matched non-PCOS patients were included in the study as controls.

A detailed history was taken that included current age, age at menarche, history of menstrual irregularity, acne, hirsutism, infertility, obstetrics history, thyroid disorders, history of similar disorder in the family, contraceptive methods and current medication. Informed and written consent was obtained from the volunteers who wished to participate in the study.

Measurement of Laboratory Parameters

Blood samples were collected using clot activation tube in the morning between day 2 and day 5 of menstrual cycle. Serum was separated after a standardised time and was kept frozen at −80° centigrade for further analysis. The following serum measurements were performed: TSH, free T4, antithyroid peroxidase antibody, total testosterone. The type of assay used was chemiluminescent immunoassay (CLIA). Assay reliability was determined by the use of commercially derived control sera of low and high concentration. Fasting blood sugars after 8 h of overnight fasting were measured using glucose oxidase test.

Statistical Analysis

A statistical power >80 % and an error <5 % were used. Variables between the two groups (PCOS and non-PCOS) that were normally distributed were analysed using Student's t test; p value <0.05 was considered statistically significant.

Table 1 Comparison of variables between controls and PCOS

Variable	Controls	PCOS
Age (years)	31.4 ± 8.6	30.02 ± 8.51
BMI*	21.3 ± 2.8	24.6 ± 4.0
Oligomenorrhoea/amenorrhoea (*N* %)*	30 (33.3)	65 (73.3)
Hirsutism (N %)*	19 (21.8)	64 (74.1)
Serum testosterone*	0.18 ± 0.21	0.74 ± 0.20
21 days progesterone*	0.90 ± 0.3	0.60 ± 0.45
Ultrasound for polycystic ovaries (*N* %)*	22 (24.5)	61 (67.8)

* $p < 0.05$ significant

Results

Table 1 shows the mean age and BMI between the control and PCOS patients which was statistically significant. Menstrual irregularity (oligomenorrhoea and amenorrhoea) was the most common abnormality found in patients with PCOS. Hyperandrogenism was the second most common characteristic manifestation present in PCOS. The clinical features, biochemical hyperandrogenism and USG ovary with number of follicles 12 or more, each measuring 2–9 mm were significantly higher in the PCOS group.

Based on TSH and FT4 levels subjects were categorised into hyperthyroid, euthyroid, subclinical hyperthyroidism and frank hypothyroidism and analysed using Chi-square test The prevalence of thyroid dysfunction was 32.5 and 35.5 % among controls and PCOS which was not statistically significant ($p = 0.8$) as documented in Table 2.

Table 3 shows the comparison of biochemical characteristics between patients and control which shows higher FBS in PCOS. Comparison of anti-TPO antibody titre between the cases and controls was done using the independent sample *t* test which showed a significant higher value in PCOS. The prevalence of autoimmune thyroiditis between PCOS and controls as defined by an elevated anti-TPO titre >60 IU/ml as positive ATPO and <60 IU/ml as negative ATPO is shown in Fig. 1.

Discussion

Patients with PCOS often have defective progesterone secretion which leads to an increased oestrogen-to-progesterone ratio. Oestrogen can increase the expression of interleukin-6 in T cells, and the absence of inhibitory action of progesterone may lead to overstimulated immune system and makes these patients more prone to autoimmune disorders [9]. Inflammatory and immune markers may have a role in pathogenesis of Insulin resistance and hyperinsulinemia in PCOS has taken a front seat. Chronic lymphocytic thyroiditis (CLT) is the most prevalent cause of hypothyroidism in areas with sufficient iodine intake and is characterised by high levels of thyroid autoantibodies, lymphocytic infiltration of the thyroid gland [10]. 21 days progesterone levels are found to be low in PCOS patients as documented in our study. In healthy women the influence of oestrogen on the immune system can be inhibited by progesterone after ovulation, but the absence of this kind of inhibition in PCOS would lead to overstimulated immune system [11].

Thyroid hormones have an important role before and during pregnancy to ensure the best possible outcome of the mother and progeny. Study done in India [12] on iodine-depleted areas showed positive results for ATPO in 22.5 % of 80 patients with PCOS when compared to 1.25 % of 80 controls.

Al Saab et al. [1] compared euthyroid PCOS and non-PCOS patients and observed that of 56 euthyroid patients with PCOS 19.6 % patients had positive results for anti-TPO, in comparison with only 3.3 % woman in the control group. Janseen et al. [3] study showed elevated levels of ATPO in 47 (26.9 %) of 175 patients with PCOS in comparison with only 14 (8.3 %) out of 168 controls. In our study, ATPO positive titre among PCOS patients was 25 % when compared to the control 5 % that was statistically significant ($p < 0.05$). Patients with ATPO are likely to develop thyroid dysfunction later in life.

Increase in BMI is an integral part of PCOS. The link between thyroid functions and obesity is proposed by the pathophysiological pathway where increased adipose tissue stimulate pro inflammatory markers and increase insulin resistance through decreased deiodinase-2 activity at pituitary level resulting in relative T3 deficiency and increase in TSH levels. Adiposity increases leptin which increases TRH from hypothalamus. Leptin also mediates autoimmunity by up-regulation of effector T cells and down-regulation of regulator T cells [13]. Thus, thyroid autoimmunity is increased in patients of PCOS. Females with PCOS have higher thyroid antibody levels, larger thyroid volumes and their thyroids are more hypoechogenic.

Are we right in saying PCOS are more predisposed to autoimmunity? PCOS is an hyperestrogenic state where oestrogen has an immune stimulatory activity due to anovulation and absence of inhibitory action of progesterone would lead to overstimulated immune system, which may propagate autoimmune disease. In our study, low level of progesterone would appear to be the likely aetiology, for ATPO positive values in PCOS.

Anaforoglu et al. [14] did a similar study found that metabolic syndrome and its components appear to be related to thyroid volume, function and antithyroid

Table 2 Thyroid dysfunction based on TSH and FT4 levels between controls and PCOS

Group	Hyperthyroid	Euthyroid	SCH	Hypothyroid	Total
Control	10 (11.1 %)	58 (64.4 %)	5 (5.55 %)	17 (18.8 %)	90
PCOD	7 (7.7 %)	61 (67.7 %)	6 (6.6 %)	16 (17.7 %)	90
Total	17	119	11	33	180

$p = 0.80$ (not significant)

Table 3 Comparison of biochemical characteristics between controls and PCOS

Variable	Controls	PCOS	p value
FBS	95.54 ± 10.53	103.51 ± 15.07	0.000*
TSH	8.09 ± 2.4	5.99 ± 1.8	0.50
Free T4	0.91 ± 0.26	0.99 ± 0.33	0.06
Anti-TPO	14.58 ± 2.3	25.8 ± 2.9	0.009*

* $p < 0.05$ significant

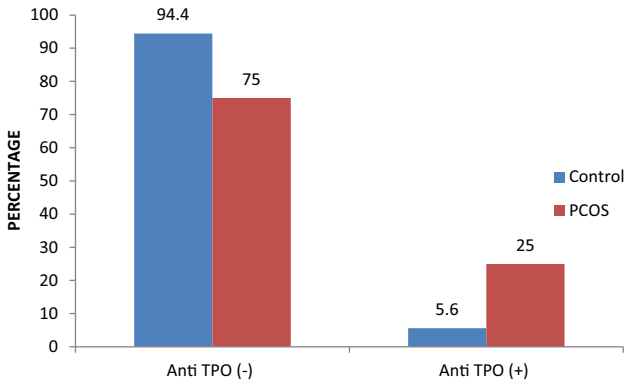

Fig. 1 ATPO titre between PCOS and controls

antibody levels and concluded that there was no significant association between PCOS and AIT ($p > 0.05$). Petrikova et al. [9] observed when comparing PCOS ($N = 64$) and non-PCOS ($N = 68$) that antibody titres were higher in PCOS group, but was not statistically significant to propose an association. Cevdetduran et al. [15] observing the frequency of nodular goitre and autoimmune thyroiditis in patients with polycystic ovarian syndrome found that the percentage of patients with thyroid parenchymal heterogenicity, positive ATPO, antithyroglobulin and AITD is similar in both PCOS and control group.

Singla et al. [13] found that females with PCOS have higher thyroid antibody levels, larger thyroid volumes and their thyroids were more hypoechogenic (compatible with thyroiditis) when compared to controls. Similarly, ATPO have been shown to be present in 27 % of the patients when compared to 8 % in controls in a study done by Garelli et al. [16].

Controversy exists as to find an association between PCOS and ATPO. It is evident from our study that significant higher titres of thyroid autoantibodies were observed in patients with PCOS compared to the controls supporting the association of ATPO and PCOS.

In the presence of hypothyroidism, ovarian morphology becomes polycystic. Thus, thyroid disorders should be exclusion criteria before making a diagnosis of PCOS in any women [12]. The pathophysiological pathway connecting the thyroid disorder and PCOS has not been clearly delineated as of now. In our study, the prevalence of thyroid dysfunction (hypothyroidism, euthyroidism and hyperthyroidism) was similar in both groups. Irrespective of thyroid function, patients with PCOS had a higher prevalence of thyroid autoantibodies.

Thus, AIT is often ignored as it may be present without thyroid dysfunction as is evident from our results. Keeping these data in mind and also numerous reports of increased thyroid autoimmunity, PCOS is a kind of autoimmune disease and has a close association with autoimmune thyroiditis that cannot be ignored and refuted anymore.

Conclusion

This prospective study demonstrates higher prevalence of ATPO in PCOS. Our data suggest that all patients with PCOS should be screened for thyroid function and thyroid specific autoantibodies even without evidence of overt thyroid dysfunction, as it is known that patients with thyroid peroxidase antibodies are likely to develop thyroid dysfunction later in life.

Compliance with Ethical Standards

Conflict of interest All the authors note that there is no conflict of interest.

Ethical Approval All procedures performed in study involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the Helsinki Declaration revised 2008.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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