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Thyroid Autoimmunity Marker and Gonadotropins in Women with Polycystic Ovary Syndrome: A Casecontrol Study from Northern India

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ABSTRACT
Polycystic ovary syndrome (PCOS) has been associated with various metabolic, cardiovascular diseases and with autoimmune conditions, predominantly autoimmune thyroid disease (AITD). This age matched case control study was conducted among Indian women (N = 80) to see if there is a relationship between autoimmune thyroid disease assessed by thyroid peroxidase antibody (anti-TPO Abs) with PCOS. Mean anti-TPO Abs levels in study group was raised significantly higher (63.55±35.36) among study participants as compare to control group (10.42±4.49). Mean LH level and FSH level and LH/FSH ratio, among the study group was 15.98±2.87, 7.69±1.41 and 2.71±0.50, respectively which were significantly raised in comparison to those of control group ($p<0.05$). The patients with PCOS are at increased risk of autoimmune thyroid and clinician should consider screening for thyroid-specific autoantibodies at the time diagnosis.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, characterized by signs and symptoms of endocrine excess, ovarian dysfunction and polycystic ovarian morphology[1]. Previously known as SteinLeventhal syndrome, PCOS presents with biochemical hyperandrogenism and insulin resistance, leading to chronic anovulation, oligomenorrhea or amenorrhea, obesity, cystic acne, hair loss, facial hirsutism, sterility and severe generalized hirsutism[2]. It is a chronic disorder with a multifactorial etiology, affecting approximately 5-20% of the population, influenced by both genetic and environmental factors[3,4]. These factors primarily affect gonadotropin secretion and insulin signaling pathways[5].

Autoimmune thyroid disorders have been directly associated with several reproductive physiological and pathological conditions. Autoimmune thyroid diseases, characterized by antithyroid antibodies, specifically anti-thyroglobulin antibody and anti-Thyroperoxide antibody, frequently cause disorders of the thyroid gland[6]. A higher prevalence of PCOS is observed in euthyroid adolescent girls with juvenile autoimmune thyroiditis and patients with PCOS have a threefold higher prevalence of autoimmune thyroiditis, suggesting a correlation with autoimmunity[7,8]. Estrogen enhances humoral immunity, while androgen and progesterone act as immune suppressors[9]. PCOS patients often experience a deficiency in progesterone, leading to an increased estrogen-to-progesterone ratio due to oligo or anovulatory cycles and their immune systems appear to be overstimulated, potentially propagating autoimmune disease. The diagnosis of PCOS coincides with a higher prevalence of elevated levels of thyroid specific antibodies (anti-TPO antibody) and anti-bodypositive patients have a higher LH:FSH ratio[7]. Autoimmune thyroid diseases encompass a spectrum of clinical conditions affecting reproductive function due to the polyclonal production of immunoglobulins against the thyroid[6].

The human ovary can be targeted by autoimmune attacks in various circumstances, including organ-specific or systemic autoimmune diseases. Clinically, this can lead to Premature Ovarian Failure, unexplained infertility, PCOS and endometriosis associated with anti-ovarian autoimmunity[10]. Studies have shown a higher incidence of autoimmune thyroiditis among women with PCOS. Therefore, it is essential to explore the prevalence and clinical significance of systemic and organ-specific autoantibodies in PCOS and investigate mechanisms linking autoimmune diseases to PCOS[9]. Considering the significant overlap in symptoms between PCOS and thyroid disease, although they are distinct conditions, this study aims to evaluate the hormonal status of LH, FSH and anti-TPO antibodies in patients with PCOS and investigate any potential relationship between anti-TPO antibodies and PCOS.

MATERIALS AND METHODS

Study setting and participants: The present hospitalbased analytical casecontrol study was conducted at Rajindra Hospital in the Department of Biochemistry and the Department of Gynaecology during the period of 2018-19. The study included a total of 80 participants aged between 18 to 50 years. The study group comprised 40 clinically diagnosed PCOS patients, identified according to the revised 2003 Rotterdam criteria[8], who were referred by the Department of Gynaecology. The control group consisted of 40 females in the reproductive age group with regular menstrual cycles, no signs of hyperandrogenism and normal ovaries based on pelvic ultrasound examination. Individuals using medications that could interfere with thyroid tests, such as estrogen and corticosteroids, were excluded from the study. Also, medical conditions leading to irregular menstrual cycles and androgen excess, like hyperprolactinemia, were excluded, as well as women taking oral contraceptive pills or corticosteroids and those who did not fulfill the Rotterdam criteria.

Data collection: A detailed history was obtained from each participant, including current age, age at menarche, history of menstrual irregularities, acne, hirsutism, infertility, obstetric history, thyroid disorders, family history of similar disorders, contraceptive methods and current medication. All participants voluntarily agreed to take part in the study and signed the informed consent form.

Sample collection: Before commencing the study, the purpose of the research was thoroughly explained to the participants and written informed consent was obtained. Fasting blood samples were collected using clot activation tubes for biochemical analysis. The samples were allowed to stand for one hour, after which the serum was separated by centrifugation at 3000 rpm for 10 min and stored for further analysis. The hormonal estimation was performed using the chemiluminescent immunoassay (CLIA) method. Assay reliability was verified using commercially derived control sera of both low and high concentrations.

Statistical analysis: Microsoft Excel was used for statistical analysis. Continuous parameters were expressed as Mean±SD. Variables that were normally distributed between the two groups (PCOS and non PCOS) were analyzed using Student's t-test. A p-value less than 0.05 was considered statistically significant.

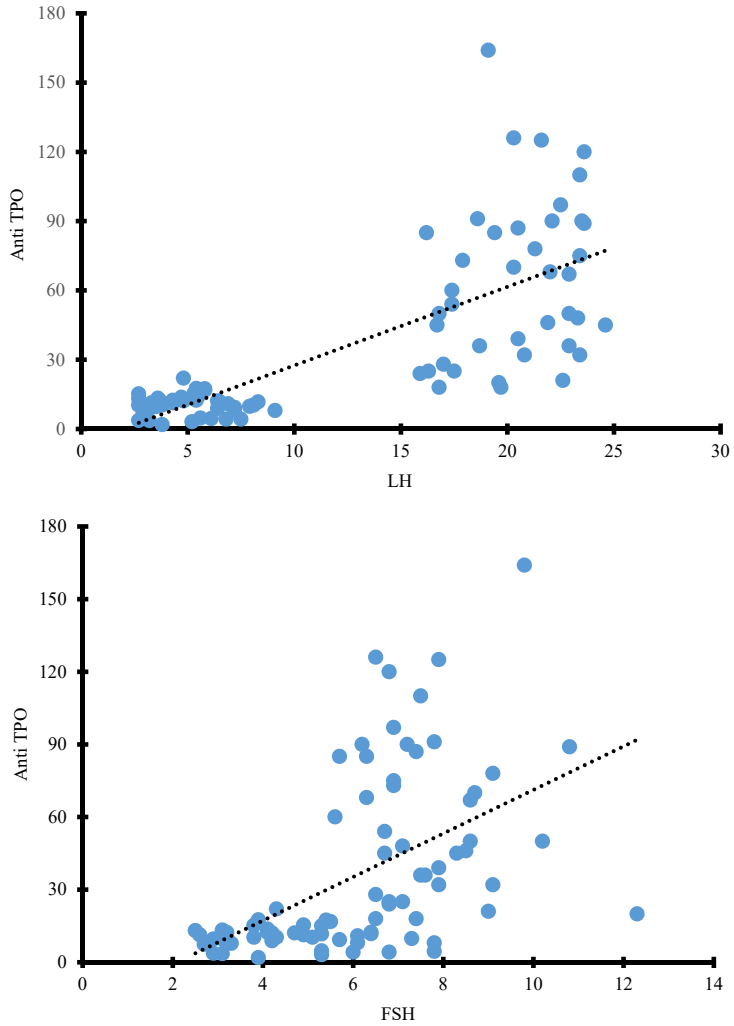

Fig. 1: Correlation between anti TPO antibodies and LH/FSH level

Table 1: Base line characteristics of study and control participants

Variable	Controls (n = 40)	PCOS (n = 40)
Age (years)	24.6±4.53	24.4±4.16
BMI*	22.30±2.40	25.75±2.73
Hb	11.5±2.44	11.1±3.22

*Basal metabolic index

Observations: In the present study, the mean age of the participants was 24.6±4.53 and 24.4±4.16 years in the study group and control group respectively without statistically significant difference (p>0.05) (Table 1).

Mean LH level and FSH level and LH/FSH ratio, among the study group was 15.98±2.87, 7.69±1.41 and 2.71±0.50, respectively which were significantly raised in comparison to those of control group. (p<0.05) Mean anti TPO levels in study group was raised significantly higher (63.55±35.36) among study participants as compare to control group (10.42±4.49). (Table 2).

Mean Prolactin level was 13.0±4.5 and 11.34±3.40 respectively in study and control group. The mean TSH levels in study and control group was 2.22±0.49 and 2.38±0.62 respectively. Both mean Prolactin and TSH level were not statistically different in two study groups (p>0.05).

There is a positive correlation between LH and anti TPO antibodies among the study participants with Pearson's correlation coefficient (r) = 0.74 and p <0.05 which is statistically significant. There is also a significant positive correlation between FSH and anti TPO antibodies with r = 0.50 (p<0.05) (Fig. 1).

DISCUSSION

TPO, described as the "thyroid microsomal antigen," is a membranebound enzyme expressed at the apical pole of thyrocytes[11]. TPO is a glycoprotein with a molecular weight of 100107 KD and consists of 933 amino acid residues. It is a hemoglycoprotein present on the thyroid cell surface and serves as an important antigenic target in autoimmune thyroid disease[12].

Table 2: Comparison of biochemical assay among study and control participants

Variable	Control group (n = 40)	Study group (n = 40)	p-value
LH	5.16±1.80	15.98±2.87	<0.05
FSH	4.70±1.45	7.69±1.41	<0.05
LH/FSH ratio	1.10±0.21	2.71±0.50	<0.05
TSH	2.38±0.62	2.22±0.49	0.21
Anti-TPO antibody	10.66±1.78	51.13±9.83	<0.05
Prolactin	11.74±3.40	13.0±4.5	0.13

Our study revealed that women with PCOS have higher levels of anti-TPO and are more likely to experience thyroid dysfunction compared to agematched controls without PCOS. This finding is consistent with Menon M et al's study, which also demonstrated elevated levels of anti-TPO in PCOS patients[13]. Similarly, studies by Al saab et al in Syria and Janseen et al in Europe have reported similar results to our study[3,7]. However, Kim *et al*.[14] casecontrol study among Korean women did not find a higher prevalence of Autoimmune thyroid disorders (AITD) in women with PCOS compared to controls.

PCOS patients often present with low levels of progesterone due to oligo/anovulation, leading to increased expression of interleukin-6 in T cells due to estrogen overstimulation of the immune system. This absence of inhibitory action of progesterone makes these patients more prone to immune disorders[15]. During a normal ovulatory menstrual cycle in young women, the follicular phase is characterized by elevated IL-6 levels, while they are decreased in the luteal phase, which also exhibits a negative correlation with progesterone[16].

The association of PCOS with autoimmunity is evident from the higher prevalence of elevated levels of thyroid-specific antibodies (anti-TPO antibody) and higher LH:FSH ratio in antibody-positive PCOS patients. This suggests that a higher LH level may contribute to autoimmunity, leading to subsequent hypothyroidism. The immunoglobulins produced against the thyroid are polyclonal and the combination of various antibodies contributes to the clinical spectrum of autoimmune thyroid diseases affecting reproductive function[17]. Interestingly, the pathophysiological mechanism of ovarian cyst formation in patients with subclinical and overt hypothyroidism is similar to those occurring in PCOS. Hypothyroidism was found to produce ovarian cysts and polycystic appearance of ovaries, which significantly improved with thyroxine treatment[18].

In our study, the LH/FSH ratio was significantly higher in PCOS women compared to control subjects (the ratio was >2). Similar findings were observed in studies by Banaszewaska *et al*.[19] and Anlakesh *et al*.[20]. Makled et al also reported a significantly higher LH/FSH ratio in affected individuals[21]. This abnormality in the hypothalamic-pituitary-ovarian or adrenal axis disturbs the pulsatile release of gonadotrophin-releasing hormone (GnRH), resulting in an excess release of LH compared to FSH due to abnormal feedback mechanisms by ovarian estrogen.

CONCLUSIONS

In conclusion, our findings indicate that patients with PCOS have an increased risk of thyroid disorders, as evidenced by increased positive results for thyroid autoantibodies. Therefore, clinicians should consider screening for thyroid function tests, including thyroid-specific autoantibodies, at the time of PCOS diagnosis, even in the absence of symptoms related to thyroid dysfunction.

Limitations: Limitations of our study include the reliance on participant-reported family and personal medical history, as we were unable to access medical files. Additionally, clinical investigations such as goiter examination and thyroid scans, which could have been valuable, were not feasible due to financial constraints.

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