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# An Observational Study on the Prevalence of Thyroid Disorders in Reproductive Aged Women with PCOS

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## Abstract

Polycystic ovarian syndrome (PCOS), the commonest endocrinological abnormality of women in the reproductive age, is adversely affected by associated thyroid dysfunction. Both have independent risks for ovarian failure and complications related to pregnancy.

*Aim of the study:* The present study aims to investigate the prevalence of different thyroid disorders in PCOS patients.

*Settings and Design:* Observational case control study.

*Materials and methods:* This hospital based observational case-control study was done in 90 cases who were defined as having PCOS according to the revised 2003 Rotterdam criteria and another 90 age-matched women were studied as the control population. Thyroid function was evaluated by measuring serum thyroid stimulating hormone (TSH), free T3 and free T4 levels, anti-thyroperoxidase antibody (anti-TPO Ab) and thyroid morphology by clinical examination and ultrasound (USG) of the thyroid gland.

*Statistical Analysis:* It was done by Student's *t*-test and *Chi*-square test using appropriate software (SPSS version 25).

*Results:* This case-control study revealed statistically significant higher prevalence of autoimmune thyroiditis, detected in 17 patients (18.9% vs. 1% of control) as evidenced by raised anti-TPO antibody levels. PCOS patients were found to have higher mean TSH level than that of the control population (4.52 ± 2.56 and 2.54 ± 3.15 respectively; p value < 0.05). Also a high prevalence of goiter was observed among PCOS patients (27.8% vs. 8.9% of control, p value < 0.001). On thyroid USG, 16.67%of PCOS patients and 4.44% of controls had hypoechoic USG pattern which was also compatible with the diagnosis of autoimmune thyroiditis.

*Conclusions:* High prevalence of thyroid disorders in PCOS patients necessitates the importance of early screening and correction of hypothyroidism in managing infertility associated with PCOS.

**Keywords:** Anti-thyroperoxidase antibody; Autoimmune thyroiditis; Hypothyroidism; Infertility; Polycystic ovarian syndrome.

## Introduction

Polycystic ovarian syndrome (PCOS), the most common endocrinological abnormality of reproductive aged women is characterized by chronic anovulation associated with androgen excess and it occurs in 5-10% of reproductive aged women.[1] PCOS is a heterogeneous endocrinological disorder of multifactorial etiology. It is also associated with increased risk of metabolic syndrome, diabetes mellitus and cardiovascular risk factors.[2] These risks are linked to insulin resistance and compounded by the common occurrence of obesity, although insulin resistance

is also present in non-obese women with PCOS. During the reproductive years, PCOS is associated with infertility, irregular menstrual bleeding and increased pregnancy loss.

Thyroid dysfunction and anatomic abnormalities of the thyroid gland are very common in the reproductive aged women. Abnormalities in the supply of thyroid hormone to the peripheral tissue is associated with alteration in a number of metabolic processes. Early stages of thyroid dysfunction leads to subtle changes in ovulation and endometrial receptivity, which may have profound effect on fertility. Infantile hypothyroidism if untreated, leads to sexual immaturity. Untreated juvenile hypothyroidism causes a delay in the onset of puberty followed by anovulatory cycles. In adult women, severe hypothyroidism may be associated with diminished libido and failure of ovulation. Primary ovarian failure can also be seen in patients with Hashimoto's thyroiditis as a part of autoimmune polyglandular syndrome. Rarely, in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhoea. Pregnancy complications are associated with overt and subclinical hypothyroidism, although the impact has varied among different studies.

Hence, it is evident that both hypothyroidism and PCOS have profound effect on fertility and reproductive biology. Hypothyroidism can initiate, maintain or worsen the syndrome. Hence, different studies regarding thyroid disorders in PCOS patients, have explored the PCOS-thyroid interface. Mostly the studies showed higher incidence of elevated TSH levels and higher prevalence of autoimmune thyroiditis in PCOS subjects.[3] Again, routine screening for thyroid dysfunction in hyperandrogenic patients is not required since the incidence of these disorders is not higher in hyperandrogenic patients than in normal reproductive aged women.[4] With this background, the present study has been done to identify the prevalence of different thyroid disorders in PCOS patients attending a tertiary care hospital in south India.

## Materials and Methods

An observational case control study was conducted in the female patients attending the Gynecology outpatient department of Karpagam Faculty of Medical Sciences and Research, Othakkalmandapam, Coimbatore, for a period of one year, from January 2018 to December 2018 with the following inclusion and exclusion criteria.

### *Inclusion criteria for cases*

1. Ultrasound diagnosis of PCOS.
2. History of menstrual irregularities-amenorrhoea/oligomenorrhoea.
3. Presence of hirsutism.
4. Presence of acanthosis nigricans.
5. Age between 15 to 45 years.
6. Consented women to take part in the study.

### *Exclusion criteria for cases*

1. Women with steroid drug intake in the preceding 3 months.
2. Women with previously diagnosed diabetes.
3. Women with oral contraceptive intake in the preceding 3 months.
4. Pregnant women.
5. Women already diagnosed with hyperprolactinemia, hypothyroidism, cushings syndrome, congenital adrenal hyperplasia.
6. Women aged less than 15 years and more than 45 years.
7. Women who have not consented to take part in the study.

### *Inclusion criteria for controls*

1. Age between 15 to 45 years.
2. Normal menstrual cycles.
3. Absence of acanthosis nigricans.
4. Normal pelvic findings in Ultrasound.
5. Consented women to take part in the study.

### Exclusion criteria for controls

1. Women with steroid drug intake in the preceding 3 months.
2. Women with previously diagnosed diabetes.
3. Women with oral contraceptive intake in the preceding 3 months.
4. Pregnant women.
5. Women already diagnosed with hyperprolactinemia, hypothyroidism, cushings syndrome, congenital adrenal hyperplasia.

6. Women aged less than 15 years and more than 45 years.
7. Women who have not consented to take part in the study.

Rotterdam's criteria was used to define PCOS in the event of: (1) menstrual abnormalities like amenorrhoea (no cycles in the past 6 months), oligomenorrhoea (cycles lasting longer than 35 days), or long cycles, (2) clinical and/or biochemical hyperandrogenism, (3) ultrasound (USG) appearance of polycystic ovaries (multiple cysts >12 in number of 2-9 mm size). The presence of two of these three criteria was required to define PCOS once all other diagnosis, like congenital adrenal hyperplasia, virilising tumor, cushing syndrome and prolactinoma was ruled out.[5] Clinical hyperandrogenism was defined as hypertrichosis (Ferriman–Gallwey score >8) and/or acne, and/or androgenic pattern of alopecia.[6,7] Biochemical hyperandrogenism was defined by elevated testosterone. A luteinizing hormone (LH) to follicle stimulating hormone (FSH) ratio above 2 was considered elevated. Pelvic USG was performed to detect the presence of polycystic ovaries.

Detailed clinical history, clinical examination and laboratory investigations like blood glucose (fasting and 2 h post 75 g glucose), serum LH, FSH, thyroid stimulating hormone (TSH), free thyroxine levels (free T3 and free T4), anti-thyroperoxidase antibody (anti-TPO Ab), free testosterone measured by an automated immune-enzyme assay systems, were performed in both PCOS and control population.

Normal serum levels of different hormones and peptides were defined as (1) freeT3 -2.4-4.2 pg/ml, (2) free T4 -0.7-1.24 ng/dl, (3) TSH -0.34-4.25 mIU/ml, (4) anti-TPO antibody- <35 IU/ml, (5) prolactin -1.9-25 ng/ml, (6) free testosterone -3-19 pg/ml. LH and FSH were measured on the 2nd day of menstruation.

USG thyroid was performed using a 7.5 MHz transducer with duplex sonography, GE Voluson S8. The thyroid was considered hypoechoic when its signal was equal or below the echogenicity of the surrounding neck muscle.

Statistical analysis was done by Student's *t*-test and Chi-square test using appropriate software (SPSS version 25).

## Results

The study was conducted among 90 patients of PCOS in the age group of 15-45 years. Screening was done in a total of 120 patients with menstrual abnormalities and hirsutism. PCOS was diagnosed in 90 patients according to Rotterdam classification of PCOS and rest were excluded from this study. Many clinical characters and laboratory parameters

**Table 1:** Comparison of Thyroid Abnormalities in cases and controls.

| Thyroid Abnormalities | PCOS (n=90) | Controls(n=90) |
|---|---|---|
| Goiter | 25(27.8%) | 8(8.9%) |
| Subclinical hypothyroidism | 20(22.2%) | 8(8.9%) |
| Overt hypothyroidism | 3(3.3%) | 1(1.1%) |
| Autoimmune thyroiditis | 17(18.9%) | 1(1.1%) |

**Table 2:** Statistical values of various variables and their correlation with PCOS cases and controls.

| Variables | PCOS(n=90) | Controls(n=90) | p value |
|---|---|---|---|
| Goiter | 25(27.8%) | 8(8.9%) | <0.05 |
| Hirsutism | 67(74.4%) | 0 | <0.05 |
| FG Score | 17.55+/-4.18 | 8.58+/-4.12 | 0.04 |
| LH(m IU/mL) | 10.92+/-4.61 | 9.15+/-3.56 | <0.001 |
| FSH(m IU/mL) | 4.81+/-1.57 | 4.152+/-2.7 | <0.05 |
| Free T3(pg/mL) | 2.85+/-1.42 | 2.08+/-1.15 | <0.001 |
| Free T4(ng/mL) | 1.48+/-3.15 | 1.15+/-3.05 | <0.001 |
| TSH(m IU/mL) | 4.52+/-2.56 | 2.54+/-3.15 | <0.001 |
| AntiTPO Antibody(IU/mL) | 27.15+/-8.52 | 24.20+/-7.58 | 0.03 |
| Free Testosterone(pg/mL) | 22.58+/7.92 | 14.8+/-5.98 | <0.01 |
| Hypoechoic USG | n =15(16.67%5) | n =4(4.44%) | <0.001 |

FG-Ferriman-Gallwey score, LH-Luteinising Hormone, FSH-Follicle Stimulating Hormone, TSH-Thyroid Stimulating Hormone, TPO-Thyroperoxidase,USG-Ultrasonogram

were compared among the study population and a control group of age matched healthy women concentrating mainly on thyroid related investigations.In the PCOS study population, maximum numbers of PCOS patients were in the age group of 15-25 years (56 patients; 62%) followed by 26-30 years (24 patients; 27%).70 patients (77.78%) had oligomenorrhoea and 14 patients (15.5%) had amenorrhoea. Clinical Hirsuitism as per modified Ferriman–Gallwey score (>8) was present in 67 patients (74.4%; mean F-G score 17.55 ± 4.18) of PCOS. 45 patients (50%) had BMI of more than 25.60 patients (66.7%) had normal blood pressure. 19 patients (21.1%) had prehypertension and only 4 patients (4.44%) were hypertensive. Estimation of glycemic status of PCOS patients showed impaired glucose tolerance (IGT) in 26 patients (28.89%) and rest had normal glycemic status. Raised serum free testosterone level was detected in 67 patients (74.4%). 45 patients (50%) had elevated LH-to-FSH ratio above 2.0.

Goiter was detected in 25 (27.8%) out of 90 patients with PCOS as compared to only 8(8.9%) of control population($p<0.001$). Subclinical hypothyroidism was detected in 20 patients (22.2%; 8.9% of controls), 3 patients had clinically overt hypothyroidism (3.3%), and autoimmune thyroiditis was detected in 17 patients (18.9% vs. 1.1% of control) as evidenced by raised anti-TPO antibody levels (mean 27.15 ± 8.52 and 24.20 ±7.58 respectively; $p = 0.03$). PCOS patients had higher mean TSH level than control group (4.52 ± 2.56 and 2.54 ± 3.15 respectively; $p < 0.001$).On thyroid USG, a significantly higher percentage of PCOS patients (16.7%; controls 4.44%) had hypoechoic USG pattern compatible with the diagnosis of autoimmune thyroiditis.

## Discussion

In the present study, the occurence of PCOS is maximum between 15-25 years and has decreased significantly after 30 years. This may be due to the fact that, menstrual abnormalities begin from puberty itself which leads to early presentation.

In this study, patients having symptoms of menstrual abnormalities in the form of oligomenorrhoea was 77.7% and amenorrhoea was 15.5%. This is also reflected in other studies which report 60-85% patients suffering from gross menstrual dysfunction.[8] 93% PCOS patients had oligomenorrhoea or amenorrhoea as observed by Najem, et al.[10]

The present study states that clinical hirsutism as detected by modified F-G score was present in 74.4% of the patients. Raised serum free testosterone was detected in 75% patients. This finding also correlates with other studies stating that hirsutism affects 65-75% of white, black and south-east Asian woman.[8,9] Also hirsutism was present in 91% of 175 PCOS subjects and elevated testosterone was present in 69% of 175 patients as observed by Jassen, et al.[3] Najem, et al. in their study among 318 PCOS patients, detected hirsutism among 91% patients.[10] In study by Marco c Amato, et al. done over 130 PCOS patients, 57% patients were observed to have hirsutism, 61% of the patients had elevated free testosterone.[11]

Obesity was detected in 50% patients of our study, which is also similar to other studies which states prevalence of obesity is approx 50%; in a Delhi based study with 33 PCOS subjects, obesity was observed in 46%. 57% prevalence of obesity among 318 PCOS patients as observed by Najem, et al., 54% overweight in study of Gomathi, et al.[10] However, obesity varies significantly with country of origin.

In the present study, 21.1% patients were pre-hypertensive, 4.44% patients were detected to have hypertension. Prevalence of hypertension was 4% in study conducted by Najem, et al. and pre-hypertension was detected in 8% as detected by Huang Jia, et al.[10,12] In study of Azevedo, et al., 18.6% patients were detected to have BP >130/85.[14] In study of Christiano, the prevalence of hypertension as a whole was 20.3% (n = 14).[15] The prevalence was higher among overweight and obese patients.

Glucose intolerance in this study was reflected as IGT in 28.89% of patients. This is also reflected in other studies where using 2 h glucose tolerance test.[9] Other studies show-impaired glucose tolerance and type 2 diabetes mellitus (T2DM) in 40% of PCOS; Huang Jia, et al. detected impaired glucose tolerance in 10.2% patients; Shaheen Ara Anwary, et al. observed raised (7.8 mmol/dl) blood sugar (2 h post 75 g glucose) in 30% PCOS and in study of Lergo, et al., IGT was detected in 31%, while T2DM was detected in 7.5%.[12,13] In study by Marco c Amato, et al. done over 130 PCOS patients, 12% had IFG and T2DM; Najem, et al. detected diabetes among 9% of 318 patients.[10,11]

In the present study, 56% PCOS subjects had elevated level of LH/FSH (>2) while, 44% patients had LH/FSH <2. This has been also seen in other studies-ShaheenAraAnwary, et al. found raised LH (>14) in 56% patients, Banaszewaska, et al. found raised LH/FSH ratio in 45.4% of their patients and

Anlakesh, et al. detected a prevalence of raised LH/FSH in 64% of their 107 PCOS patients.[16,17] Five patients in the present study had oligomenorrhoea, hyperandrogenism but no polycystic ovary. These patients were also considered as having PCOS without morphology of polycystic ovary in USG. In study conducted by Najem, et al. 74% had USG features of polycystic ovaries while ShaheenAraAnwary, et al. found that 100% patients had polycystic ovaries.[10]

In this study goiter was present in 27.8% patients, subclinical hypothyroidism was present in 22.2% and clinical overt hypothyroidism was present in 3.3% cases. Among these hypothyroid patients, autoimmune thyroiditis was present in 18.9% patients. Thus this prospective case-control study revealed significant higher prevalence of thyroid disorders(72.2%) among young PCOS patients compared to age matched controls. Among the most recently held studies, Kachuei, et al. from Iran has also shown significantly higher prevalence of autoimmune thyroiditis and goiter in PCOS patients than that in control subjects (goiter 62.3% vs. 35.7%, P = 0.0001). These findings are very close to the multicenter study done by Janssen, et al. where they observed a prevalence of autoimmune thyroiditis (biochemically) in 26.9% of their 175 patients.[3] Some other studies reported even higher prevalence of autoimmune thyroiditis in PCOS subjects. DidemOzdemir, et al. among 107 patients found a prevalence of 30.5% Thyroid nodules were detected in 29 (27.1%) patients, 10 had solitary and 19 had multiple nodules. Thyroid pathologies were observed in half of the patients with PCOS.[19]

Lastly, review of Indian literature explores, Wakim, *et al*. in their research on human reproductive biology also reestablished the hypothesis that hypothyroidism worsens PCOS by further decreasing sex hormone binding globulin levels, increasing the conversion of androstenedione to testosterone and aromatization to estradiol and reducing the metabolic clearance rates of androstenedione and estrone. Since thyroid hormones are involved in the gonadotropin induced estradiol and progesterone secretion by human granulosa cells, hypothyroidism would interfere with ovarian function and fertility.[20] Sridhar, *et al*. conducted a 30 months-duration study from Visakhapatnam to show how hypothyroidism was significantly related to PCOS.[21] They opined that hypothyroid could initiate, maintain or worsen the syndrome and thereby correcting hypothyroid state, PCOS could be managed in a better way.

## Conclusion

High prevalence of thyroid disorders in PCOS patients necessitates the importance of early screening and correction of hypothyroidism in managing infertility associated with PCOS.

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