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Evaluation of the levels of the antithyroid peroxidase antibodies in females suffering from polycystic ovary syndrome (PCOS)

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Abstract
Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common endocrine disorders in the general population. Although the etiopathogenesis of hypothyroidism and PCOS is completely different, these two entities have many features in common. Whether this is due to some common factors predisposing an individual to both disorders, or due to a pathophysiological connection between the two disorders has not been established until now. Hence the present study was planned to assess the Antithyroid Peroxidase Antibodies in females suffering from polycystic ovary syndrome.
The present study was done in the Department of Obstetrics Gynaecology, Indira Gandhi Institute of Medical Science, Patna from Aug 2018 to Dec 2018. Total 50 females were included in the study. 25 patients diagnosed with the Polycystic Ovary Syndrome (PCOD) coming to outdoor of this hospital, were enrolled in the present study. 25 females in reproductive age with regular menstrual cycles, no signs of hyperandrogenism, normal ovaries on pelvic ultrasound examination and normal level of free testosterone were enrolled in control group. Various parameters like TSH, free T4, antithyroid peroxidase antibody, total testosterone were measured in the all patients. The type of assay used was chemiluminescent immunoassay (CLIA).
There is enough literature support to argue that prevalence of subclinical hypothyroidism/thyroid autoimmunity is increased in women with PCOS patients. Thyroid disorders in the course of PCOS, are observed significantly more frequently than in the general population. However, their concomitance in the context of fertility disorders has not been investigated extensively.

Keywords: antithyroid peroxidase antibody PCOS Thyroid profile

Introduction
Polycystic ovary syndrome (PCOS) is a condition resulting from hormonal disturbance and most commonly effects young girls. Common features include oligomenorrhea or amenorrhea, hirsutism, acne, infertility, polycystic ovaries on ultrasound.
Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer [1].
PCOS is due to a combination of genetic and environmental factors. Risk factors include obesity, a lack of physical exercise, and a family history of the condition. Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and high blood levels of prolactin [2].
Treatment may involve lifestyle changes such as weight loss and exercise. Oral contraceptive pills may help with improving the regularity of periods, hirsutism, and acne. Metformin and anti-androgens may also help. Other typical acne treatments and hair removal techniques may be used. Efforts to improve fertility include weight loss, clomiphene, or metformin. In vitro fertilization is used by some in whom other measures are not effective [3].
PCOS is the most common endocrine disorder among women between the ages of 18 and 44. It affects approximately 2% to 20% of this age group depending on how it is defined. When someone is infertile due to lack of ovulation, PCOS is the most common cause [1].

Common signs and symptoms of PCOS include the following:

- Menstrual disorders: PCOS mostly produces oligomenorrhea (cycles of more than 35 days duration) or amenorrhea, but other types of menstrual disorders may also occur.
- Infertility: This generally results directly from chronic anovulation (lack of ovulation).
- High levels of masculinizing hormones: Known as hyperandrogenism, the most common signs are acne and hirsutism (male pattern of hair growth, such as on the chin or chest), but it may produce hypermenorrhea (heavy and prolonged menstrual periods), androgenic alopecia (increased hair thinning or diffuse hair loss), or other symptoms [17, 19]. Approximately three-quarters of women with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.
- Metabolic syndrome: This appears as a tendency towards central obesity and other symptoms associated with insulin resistance. Serum insulin, insulin resistance, and homocysteine levels are higher in women with PCOS.

Asians affected by PCOS are less likely to develop hirsutism than those of other ethnic backgrounds [4].
Women with PCOS tend to have central obesity, but studies are conflicting as to whether visceral and subcutaneous abdominal fat is increased, unchanged, or decreased in

women with PCOS relative to reproductively normal women with the same body mass index. In any case, androgens, such as testosterone, androstanolone (dihydrotestosterone), and nandrolone decanoate, have been found to increase visceral fat deposition in both female animals and women [5]. Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common (and perhaps overlooked) endocrine disorders in women. Although hypothyroidism and PCOS are very different, these two conditions share many similar features. Hypothyroidism, and in particular, Hashimoto's thyroiditis, is more common in women with PCOS than in the general population. Both genetic and environmental factors are believed to be contributing to thyroid disorders in PCOS. Hypothyroidism is known to cause PCOS-like ovaries and overall worsening of PCOS and insulin resistance. Hypothyroidism can increase testosterone by decreasing the level of sex hormone binding globulin (SHBG), increasing the conversion of androstenedione to testosterone and estradiol, and reducing the metabolic clearance of androstenedione. An increased estrogen and estrogen/progesterone ratio seem to be directly involved in high thyroid antibody levels in PCOS patients [6].

Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common endocrine disorders in the general population. Although the etiopathogenesis of hypothyroidism and PCOS is completely different, these two entities have many features in common. An increase in ovarian volume and cystic changes in ovaries have been reported in primary hypothyroidism. In the other direction, it is increasingly realized that thyroid disorders are more common in women with PCOS as compared to the normal population. Whether this is due to some common factors predisposing an individual to both disorders, or due to a pathophysiological connection between the two disorders has not been established until now. Hence the present study was planned to assess the Antithyroid Peroxidase Antibodies in females suffered from polycystic ovary syndrome.

Methodology

The present study was done in the Department of Obstetrics Gynaecology, Indira Gandhi Institute of Medical Science, Patna from Aug 2018 to Dec 2018 on outdoor basis. Total 50 females were included in the study. 25 females diagnosed with the Polycystic Ovary Syndrome (PCOD) were enrolled in the present study. The 25 females were enrolled in the control group cases as females in reproductive age with regular menstrual cycles, no signs of hyperandrogenism, normal ovaries on pelvic ultrasound examination and normal level of free testosterone. The various parameters like TSH, free T4, antithyroid peroxidase antibody, total testosterone were measured in the all patients. The type of assay used was chemiluminescent immunoassay (CLIA).

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]

In all patients informed consent was taken. The aim and the objective of the present study were conveyed to them.

Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

Antithyroid antibodies are observed in 5-10% of women of reproductive age. [9] The presence of antibodies alone does not automatically influence thyroid function. Although overt hypothyroidism may manifest with serious reproductive disorders, they should retreat after introducing an appropriate treatment. However, patients with HT in euthyreosis may still have difficulties conceiving or delivering at term [10].

Singla *et al*. [11] 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*. [12].

In 2012, the Endocrine Society published Guidelines for Thyroid Dysfunction in Pregnancy. According to them, universal screening of healthy women for thyroid dysfunction, as well as the presence of anti-TPO antibodies, before and during pregnancy is not recommended. In the case of screening for thyroid disorders in newly pregnant women, the committee is incoherent. Some members recommend screening of all pregnant women by the ninth week or at the time of their first visit. Others recommend targeted screening, among others, in women: over age of 30 years, with thyroid antibodies, with other autoimmune diseases, with a prior history of miscarriage or preterm delivery and, finally, with infertility. If serum TSH is greater than 2.5 mIU/L in the first trimester or above 3 mIU/L in the second and third trimesters, LT4 therapy should be instituted. If the hypothyroidism has been diagnosed before pregnancy, adjustment of LT4 dose to reach serum TSH not higher than 2.5 mIU/L before pregnancy is recommended. However, in the case of nothing except antithyroid antibody presence in pregnancy, LT4 treatment is not advised. During pregnancy and breast feeding, suggested iodine intake should reach 250 μg per day [13].

Table 1: Comparison of variables between controls and PCOS Variable

Groups	Group A	Group B
Type of Cases	**Controls**	**PCOS**
Total Cases	**25**	**25**
Age (years)	20– 35years	20 – 32 years
Oligomenorrhoea/amenorrhoea	8	18
Hirsutism	5	19
Serum testosterone (ng/dL)	0.11 – 0.38	0.52 – 0.93
21 days progesterone (ng/dL)	0.63 – 1.24	0.28 – 0.98
Ultrasound for polycystic ovaries	0	18

Table 2: Thyroid dysfunction based on TSH and FT4 levels

Groups	Group A	Group B
Type of Cases	**Controls**	**PCOS**
Total Cases	25	25
Hyperthyroid	3	3
Euthyroid	16	17
SCH	1	1
Hypothyroid	5	4
Total	25	25

Table 3: Comparison of biochemical characteristics

Groups	Group A	Group B
Type of Cases	**Controls**	**PCOS**
Total Cases	**25**	**25**
Fasting Blood Sugar	85 -105 mg/dL	91 – 119 mg/dL
TSH	1.34 – 6.8 mU/L	4.2 – 7.5 mU/L
Anti-Thyroid Peroxidase	12.7 – 16.8 IU/mL	23.3 -28.7 IU/mL

The pitfall of this pathway is that it fails to explain increased incidence of thyroid autoimmunity in patients with PCOS. 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 (compatible with thyroiditis) when compared to controls [14]. Thyroid peroxidase (TPO) antibodies have been shown to be present in 27% of the patients when compared to 8% in controls [15].

Are we right in saying, therefore that women with PCOS are more predisposed to autoimmune diseases? There seem to be some theoretical basis for this statement. PCOS is known to be a hyper estrogenic state. Hyperestrogenism has been proposed as one explanation for the occurrence of increased autoimmune diseases in females when compared to males [16]. Estrogen receptors have a proliferative action on B-lymphocytes and estrogen receptors are also present on T-cell as well as macrophages [17].

The prevalence of subclinical thyroid dysfunction in the general population has been estimated around 10%, but in reproductive years this prevalence is considerably low at 4-6% [18-19]. In recent years, a number of publications have reported increased incidence of thyroid disorders in females with PCOS. Sinha *et al*. compared 80 PCOS females with 80 controls and found significant higher prevalence of goiter (27.5% vs. 7.5%) and subclinical hypothyroidism (22.5% vs. 8.75%) in PCOS patients as compared to controls [11]. An another study conducted in young women with PCOS found prevalence of subclinical hypothyroidism (defined as TSH > 4.5 μIU/ml) to be 11.3% (mean TSH level of 6.1 ± 1.2 mIU/L). There was no difference in two groups (with or without subclinical hypothyroidism) with respect to BMI, waist circumference or Ferriman-Gallwey score. Low-density lipoprotein cholesterol (LDL-C) was found to be significantly higher in the cohort with subclinical hypothyroidism [12].

In fact, there are some reports of increased autoimmunity in PCOS patients towards organs other than thyroid as well. Positive anti-ovarian antibodies for at least one isotype (IgG - 27%, IgA - 3%, IgM - 27%) were present in 15 (44%) of 34 of the PCOS women [20]. In another study comparing 109 women with PCOS to 109 age-matched healthy controls, women with PCOS had significantly elevated serum levels of antihistone and anti-double-stranded deoxyribonucleic acid antibodies whereas serum levels of antinuclear antibodies (ANAs) and antinucleo some antibodies were similar [21]. A more recent study has reported ANA positivity in 8.6% of PCOS patients, while none in the control group was positive [22]. Raised levels of smooth muscle antibody have also been reported [23]. Keeping this data in mind and also numerous reports of increased thyroid autoimmunity, increased incidence of thyroid autoimmunity cannot be ignored and refuted anymore. As of now, the pathophysiological explanation of this phenomenon is unclear. There seem to be a complex interplay of PCOS, adiposity, thyroid dysfunction and autoimmunity, working to produce varying clinical pictures, all belongs to different parts of a wide spectrum. The relative contribution of each aspect, to the propagation of other factors, as well as the direction of causality, is far from certain. A multi-directional link seems to be the best explanation as of now.

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

There is enough literature support to argue that prevalence of subclinical hypothyroidism/thyroid autoimmunity is increased in women with PCOS patients. Thyroid disorders in the course of PCOS, are observed significantly more frequently than in the general population. However, their concomitance in the context of fertility disorders has not been investigated extensively.

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