International Journal of Medical and Health Research
ISSN: 2454-9142; Impact Factor: RJIF 5.54
Received: 21-05-2019; Accepted: 23-06-2019
www.medicalsciencejournal.com
Volume 5; Issue 8; August 2019; Page No. 211-215

Clinical evaluation of levels of antithyroid peroxidase antibodies in women with polycystic ovary syndrome from Bihar

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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. 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. Hence the present study was planned to evaluate the levels of antithyroid peroxidase antibodies in women with polycystic ovary syndrome.

The present study was planned in Department of Obstetrics and Gynaecology, Patna medical college and Hospital, Patna Bihar and JLNMCH Bhagalpur ,Bihar from October 2018 May 2019. Total 30 females were enrolled in the present study. Out of the 30 females, 15 females were evaluated in the group I as study group patients with polycystic ovarian diseases. Remaining 15 cases were evaluated in the control group cases. These control group females are with 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 and Hypothyroidism are closely related. There is increased prevalence of hypothyroidism in PCOS. The symptoms of both PCOS and hypothyroidism are similar. PCOS patients with hypothyroidism have increased prevalence of menstrual complaints like oligomenorrhoea and secondary amenorrhoea. The pathophysiological pathway and contributing factors behind this association are yet to be elucidated. Long-term studies are required to assess the significance of thyroid dysfunction in patients with PCOS, especially on fertility.

Keywords: polycystic ovary syndrome, PCOD, Bihar region, etc

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders among women of reproductive age. PCOS is common diagnosis in women presenting with infertility. The exact prevalence of PCOS is not known as the syndrome is not defined precisely. Prevalence of PCOS is highly variable ranging from 2.2% to 26% globally. In few Asian countries prevalence figures are ranging from 2% to 7.5% in China and 6.3% in Srilanka. There are few studies conducted in India. Studies done in South India and Maharashtra, prevalence of PCOS (by Rotterdam's criteria) were reported as 9.13% and 22.5% (10.7% by Androgen Excess Society criteria) respectively.

PCOS was first reported by Stein and Leventhal in 1935, described as symptoms complex with amenorrhea, hirsutism, and enlarged ovaries with multiple cysts. Polycystic ovary syndrome causes irregular menstrual cycles, excessive body or facial hair and polycystic ovaries as its main symptoms. Polycystic means "many cysts," and PCOS often causes clusters of small, pearl-sized cysts in the ovaries. The cysts are fluid-filled and contain immature eggs. Women with PCOS produce slightly higher amounts of male hormones known as androgens, which contribute to some of the symptoms of the condition.

Early diagnosis of PCOS is important as it has been linked to an increased risk for developing several medical conditions including insulin resistance, type 2 diabetes, high cholesterol, high blood pressure and heart disease. PCOS is an emerging health problem during adolescence therefore promotion of healthy lifestyles and early interventions are required to prevent future morbidities [1].

Polycystic ovary syndrome (PCOS) is a set of symptoms due to elevated androgens (male hormones) in females. Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin. Associated conditions include type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer. 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 someone with the condition. Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts. Cysts may be detectable by ultrasound [9]. Other conditions that produce similar symptoms include adrenal hyperplasia, hypothyroidism, and high blood levels of prolactin [2].

PCOS has no cure. Treatment may involve lifestyle changes

such as weight loss and exercise. Birth control pills may help with improving the regularity of periods, excess hair growth, 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. The earliest known description of what is now recognized as PCOS dates from 1721 in Italy [4].

Common signs and symptoms of PCOS include the following:

- Menstrual disorders: PCOS mostly produces oligomenorrhea (fewer than nine menstrual periods in a year) or amenorrhea (no menstrual periods for three or more consecutive months), but other types of menstrual disorders may also occur.
- Infertility: This generally results directly from chronic anovulation (lack of ovulation) [5].
- 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.
- 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 [6].

Asians affected by PCOS are less likely to develop hirsutism than those of other ethnic backgrounds. 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 [7].

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of androgenic hormones, in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility) [8].

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles not cysts. The follicles have developed from primordial follicles, but the development has stopped ("arrested") at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination.

Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio. A majority of women with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased SHBG binding. Furthermore, excessive insulin, acting through its cognate receptor in the presence of component cAMP signalling, upregulates 17α-hydroxylase activity via PI3K, 17α-hydroxylase activity being responsible for synthesising androgen precursors. The combined effects of hyperinsulinemia contribute to an increased risk of PCOS. Insulin resistance is a common finding among women with a normal weight as well as overweight women [9].

Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese women creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback). PCOS may be associated with chronic inflammation, with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms. Similarly, there seems to be a relation between PCOS and increased level of oxidative stress. It has previously been suggested that the excessive androgen production in PCOS could be caused by a decreased serum level of IGFBP-1, in turn increasing the level of free IGF-I, which stimulates ovarian androgen production, but recent data concludes this mechanism to be unlikely [10].

PCOS has also been associated with a specific FMR1 sub-genotype. The research suggests that women with heterozygous-normal/low FMR1 have polycystic-like symptoms of excessive follicle-activity and hyperactive ovarian function. Transgender men may experience a higher than expected rate of PCOS due to increased testosterone, if they choose to take hormone therapy as part of their gender presentation.

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. Hence the present study was planned to evaluate the levels of antithyroid peroxidase antibodies in women with polycystic ovary syndrome.

Methodology

The present study was planned in Department of Obstetrics and Gynaecology, Patna medical college and Hospital, Patna Bihar and JLNMCH Bhagalpur ,Bihar from October 2018 May 2019. . Total 30 females were enrolled in the present study. Out of the 30 females, 15 females were evaluated in the group I as study group patients with polycystic ovarian diseases. Remaining 15 cases were evaluated in the control group cases. These control group females are with 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).

All the patients were informed consents. 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.
Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria
Women with complaints of any two of the following were included: oligomenorrhoea/amenorrhoea and inability to conceive, hirsuitism and polycystic ovaries in ultrasonography. None of these women received any hormonal contraceptives, vitamin supplements or any other significant drug therapy. None of them were alcoholics or chronic smokers and did not suffer from any other illnesses.

Exclusion Criteria
1. Congenital hypothyroidism
2. Thyroidectomy patients
3. History of radiation to head and neck in cancer patients.
4. Women who are not willing for examination and further investigations and follow up.

Results & Discussion
Dysfunction and anatomic abnormalities of the thyroid are among the most common diseases of the endocrine gland. Abnormalities in the supply of thyroid hormone to the peripheral tissue are associated with alteration in a number of metabolic processes. Early stages of thyroid dysfunction (before symptoms are obvious) can lead to subtle change 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 woman, 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.
In the presence of hypothyroidism, ovarian morphology becomes poly-cystic. Hence, thyroid disorders are one of the exclusion criteria before making a diagnosis of PCOS in any women. Rise in thyrotropin-releasing hormone (TRH) in primary hypothyroidism leads to increased prolactin and thyroid stimulating hormone (TSH). Prolactin contributes toward polycystic ovarian morphology by inhibiting ovulation as a result of the change in the ratio of follicle stimulating hormone (FSH) and luteinizing hormone and increased dehydroepiandrosterone from the adrenal gland. Increased TSH also contributes due to its spill-over effect on FSH receptors. Increased collagen deposition in ovaries as a result of hypothyroidism has also been suggested.

Table 1: Comparison of variables between controls and PCOSVariable

Groups	**Group I**	**Group II**
Type of Cases	**Controls**	**Polycystic Ovarian Diseases**
Total Cases	15	15
Age (years)		
21 – 30 years	7	10
31 – 40 years	5	3
41 – 50 years	2	2
Education		
Literacy	12	11
Illiterate	3	5
Economical Class		
Lower	3	5
Middle	11	8
Upper	1	2

Table 2: Type of Cases

Groups	**Group I**	**Group II**
Type of Cases	Controls	Polycystic ovarian diseases
Oligomenorrhoea/amenorrhoea	9	10
Hirsutism	6	5
Serum testosterone (ng/dL)	0.10 – 0.40	0.48 – 0.85
21 days progesterone (ng/dL)	0.61 – 1.24	0.35 – 0.81
Ultrasound for polycystic ovaries	4	11

Table 3: Thyroid dysfunction based on TSH and FT4 levels

Groups	**Group I**	**Group II**
Type of Cases	Controls	Polycystic ovarian diseases
Total Cases	15	15
Hyperthyroid	3	3
Euthyroid	16	17
SCH	1	1
Hypothyroid	5	4

Total	25	25

Table 4: Comparison of biochemical characteristics

Groups	Group I	Group II
Type of Cases	Controls	Polycystic ovarian diseases
Total Cases	15	15
Fasting Blood Sugar	86.5– 107.3mg/dL	92.3 – 118.6mg/dL
TSH	7.3 – 9.6mU/L	3.9 – 7.1mU/L
Anti-Thyroid Peroxidase	11.6 – 15.9IU/mL	22.4 -27.6IU/mL

The severity of ovarian morphology also depends on duration and severity of underlying primary hypothyroidism. In most severe cases like long standing untreated cases of congenital hypothyroidism ovarian morphology can be very striking and can even be mistaken for ovarian malignancies. These cases have been given an eponym Van Wyk and Grumbach syndrome, after the scientist who first described the case [11].
In a study, on somewhat less severe primary hypothyroidism, by Muderris *et al*., 26 treatment naïve females with primary hypothyroidism, with mean TSH 57.1 mcg/dl, underwent evaluation of ovarian volume before and after replacement with thyroxine [12]. Twenty-six healthy normal controls were also recruited. Ten of 26 hypothyroid females had polycystic appearing ovaries on ultrasound sonography test at baseline. All women with primary hypothyroidism had significantly higher ovarian volumes than controls. Even the subgroup without polycystic appearing ovaries had significantly higher ovarian volumes. However, there was no correlation of TSH levels with cyst formation. The most remarkable finding of this study was normalization of ovarian volume in all patients, with or without polycystic appearing ovaries, after replacement of thyroxine.
Lastly, review of Indian literature explores Ghosh, *et al*. who tried to evaluate the role of hypothyroidism in the causation of PCOS. Their comparative analysis suggested that hypothyroidism led to lowering of sex hormone binding globulin level and increment of testosterone level but not invariably directed towards estriol overproduction [13]. Two years later 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 [14]. Sridhar, *et al*. conducted a 30 months-duration study from Visakhapatnam to show how hypothyroidism was related to PCOS. Two women of primary hypothyroidism (2/13; 1.04%) presented with features of PCOS [15].
Earlier studies had reported increasing levels of anti-TPO antibodies and serum TSH levels with advancing age [16-17]. This increase in TSH with age might be due to increased presence of anti-TPO antibodies in the participants. When anti-TPO positive group was excluded, no age-dependent change was noticed in our study. Data from this study can be used as a reference for future investigations and also for comparisons with other cohorts who have a high risk of thyroid dysfunction and autoimmunity.

Conclusion

PCOS and Hypothyroidism are closely related. There is increased prevalence of hypothyroidism in PCOS. The symptoms of both PCOS and hypothyroidism are similar. PCOS patients with hypothyroidism have increased prevalence of menstrual complaints like oligomenorrhoea and secondary amenorrhoea. The pathophysiological pathway and contributing factors behind this association are yet to be elucidated. Long-term studies are required to assess the significance of thyroid dysfunction in patients with PCOS, especially on fertility.

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