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A study of correlation of PCOS with Age, BMI, Menstrual irregularities and Thyroid profile

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS) is a heterogenous endocrine and metabolic disorder characterized by a constellation of attributes which chiefly include Hyperandrogenemia (either clinical or biochemical), chronic oligo/anovulation and Polycystic ovarian morphology (PCOM). 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.

Material and Methods: This is a Prospective, observational and single centre study conducted in the Department of Obstetrics and Gynaecological at a tertiary care centre. The obstetrics and gynaecology department includes the reproductive medicine unit. Women visiting outpatient facility and diagnosed to have PCOS are included in the study. The patients after consultations with the Gynaecologist are given appointment to meet the researcher. Patients were given the choice to participate in the study.. Blood samples are collected and sent for Analyses of Thyroid profiles.

Results: In our study, most of the patients belong to 26-35 years (49.7%) followed by 15-25 years (39.4%) and 36-45 years (10.9%). The mean Body Mass Index (BMI) of the healthy control subjects was 23.73± 3.19 kg/m^2 which varies from 25.61± 3.06Kg/m^2 among PCOS which is statistically significant difference ($p =< 0.005$) Mean Serum triiodothyronine (T3) level varies from 2.05±0.34 pg/ml in healthy control subjects and 4.99±2.02 pg/ml in PCOS patients which is statistically significant. Serum tetraiodothyronine (T4) level varies from 2.09±0.18 ng/dl in healthy control subjects and 3.39±0.45 ng/dl in PCOS patients which

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statistically significant. The serum TSH levels varied from 3.71±0.45 mIU/ml in healthy control subjects and 6.54±1.71 mIU/ml in PCOS patients were statistically significant.

Conclusion: The positive correlation between serum TSH levels and the presence of higher BMI in our study threw bright light that female patients with PCOS must be investigated for the presence of Subclinical hypothyroidism which is proved to be a metabolic risk factor. As there is high prevalence of thyroid disorders in PCOS patients, all women in their reproductive age with and without PCOS, should have their thyroid function tests evaluated.

Keywords: PCOS, BMI, Menstrual irregularities, Thyroid profile

Introduction

Polycystic ovarian syndrome (PCOS) is a heterogenous endocrine and metabolic disorder, represented by approximately 6% (diagnosed as per older restrictive criteria) to 20% (diagnosed as per new criteria) of reproductive age women. [1] It is characterized by a constellation of attributes which chiefly include Hyperandrogenemia (either clinical or biochemical), chronic oligo/anovulation and Polycystic ovarian morphology. The metabolic consequences associated with the syndrome includes increased risk of Obesity, Dyslipidemia, Insulin resistance, Type II Diabetes mellitus, and Premature Atherosclerosis. [2] Besides these, infertility is the most alarming problem associated with this syndrome. The long-term aftermath of the syndrome include Breast, Ovarian and Endometrial cancer. [3]

Interaction between the hypothalamus, pituitary and ovaries regulate the phases of menstrual cycle and ovulation. Normal reproductive function includes monthly follicular development, ovulation and preparation the endometrium for implantation. The gonadotropin releasing hormone (GnRH) is secreted by hypothalamus at puberty in a pulsatile fashion. [4] GnRH activity is first evident at puberty. Release of GnRH is modulated by external neural signals. The hypothalamus exerts slow pulse frequency releasing GnRH. This surge initiates anterior pituitary to produce Follicle stimulating hormone (FSH) which is the initial step of the menstrual cycle. [5]

Many studies over the years have shown a higher presence of autoimmune thyroiditis (AIT) in specifically polycystic ovary syndrome patients [6]. Studies show AIT having a prevalence rate of about 18-40% in women with PCOS, depending on PCOS diagnostic criteria and ethnicity [7]. AIT is one of the most frequent causes of hypothyroidism in young women living in iodine sufficient regions [8]. Autoimmune thyroiditis also called Hashimoto's thyroiditis (HT), or chronic lymphocytic thyroiditis (CLT), is the most prevalent autoimmune disease that affects up to 5-20% of females in their reproductive years leading to chronic inflammation of the thyroid, with the eventual development of full-blown hypothyroidism [9]. Most patients with thyroiditis are usually positive for antibodies such as thyroid peroxidase (TPO) and/or thyroglobulin (Tg) antibodies. However, many women may have detectable levels of antibodies in the upper limit of normal observed for many years without

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noticeable thyroid dysfunction, this phenomenon is known as subclinical hypothyroidism (SCH). Often ignored, these patients later in life will develop AIT [10].

Many women with PCOS and AIT share many similar clinical findings, such as menstrual irregularities, infertility, obesity, insulin resistance, and dyslipidemia [11]. Some studies have also indicated evidence between thyroid autoimmunity and pregnancy outcomes such as miscarriages and preterm birth [12]. Many of these shared findings may be further aggravated as a result of the co-existence of PCOS and AIT, which may be more the reason to further test the associations between PCOS and thyroiditis. [13]

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. [15] 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.

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- The diagnostic criteria for PCOS was based on the unified standards formulated by the Rotterdam International Conference in 2003. Patients with any two of the following three conditions were diagnosed with PCOS:

(1) Infrequent ovulation or anovulation;
(2) Hyperandrogenism or clinical manifestations of high blood androgen; and
(3) Polycystic ovaries on USG - multiple small follicles (>10–12) and (2–9 mm in diameter) tightly spaced along the periphery of the ovary.

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The Rotterdam classification are used to define PCOS in the event of:
(1) Menstrual anomalies 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 are required to define PCOS once all other diagnosis, like congenital adrenal hyperplasia, virilising tumor, cushing syndrome and prolactinoma are ruled out.
(4) Clinical hyperandrogenism are defined as hypertrichosis (Ferriman–Gallwey score >7) and/or acne, and/or androgenic pattern of alopecia. [16]

Study Procedure:

The patients after consultations with the Gynaecologist are given appointment to meet the researcher. Patients were given the choice to participate in the study. Blood samples are sent for Analyses of Thyroid profiles.

Blood samples (5ml) should collected from the patients in tubes containing EDTA and immediately centrifuged at 4ºC for 20 min at 1600xg.

USG of the thyroid was done in presence of goitre. USG thyroid was performed using a 7.5 MHz transducer with duplex sonography. The thyroid was considered hypoechoic when its signal was equal or below the echogenicity of the surrounding neck muscles. Fine needle aspiration cytology (FNAC) of thyroid nodule was done in nodular goitre.

Ultrasound scanning
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Statistical analysis
The data collected was entered into an excel sheet and analysis was done using relevant statistical methods. Frequency tables and percentages were calculated. The prevalence of lean PCOS was expressed in percentage. Student's *t*-test and Chi-square test using appropriate software. All groups were compared using ANOVA.

RESULTS
In our study, most of the patients belongs to 26-35 years (49.7%) followed by 15-25 years (39.4%) and 36-45 years (10.9%) in table 1.

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Table 1: Distribution of Age

Age distribution	PCOS (n=165)	Control (n=165)
15-25 years	65 (39.4%)	69 (41.8%)
26-35 years	82 (49.7%)	85 (51.5)
36-45 years	18 (10.9%)	11 (6.6)
Total	**165 (100%)**	**165** (100%)

Table 2: Distribution of BMI

Variables	PCOS (n=165)	Control (n=165)	P value
BMI (Kg/m^2)	25.61±3.06 (18-32)	23.73±3.19 (18-30)	0.041 Significant

The mean Body Mass Index (BMI) of the healthy control subjects was 23.73±3.19; which varies from 25.61±3.06 kg/m^2 among PCOS which is statistically significant difference (p =< 0.005) was observed in BMI of PCOS patients when results were compared with the healthy control subjects in Table 2.

Table 2: Distribution of Goiter and Hirsuitism

Variables	PCOS (n=165)	Control (n=165)	P value
Goiter (%)	29.7 (n=122)	9.7 (n=76)	Significant
Hirsuitism (%)	74.6 (n=58)	17 (n=12)	Significant

Table 4: Distribution of Menstrual Complaints of cases

	Menstrual Complaints	No. of Cases	Percentage
Menstrual Complaints	Secondary Amenorrhoea	35	21.2
	Oligomenorrhoea	95	57.6
	Polymenorrhoea	3	1.8
	Normal	32	19.4
	Total	165	100
Infertility	Primary	115	69.7
	Secondary	50	30.3
Hyperandrogenism	140		84.8

Table 5: Statistical values of different variables and their correlation among polycystic ovarian syndrome subjects and controls

Variables	PCOS (n=165)	Control (n=165)	P value
Free T3 (pg/ml)	4.99±0.624 (2-12)	2.05±0.34 (1.8-4.2)	<0.001
Free T4 (ng/dl)	3.39±0.45	2.09±0.18	<0.001

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	(0.2-20)	(0.3.-1.32)	
TSH (mIU/ml)	6.54±1.71	3.71±0.45	<0.001
	(0.3-16)	(0.6-8.48)	
Anti-TPO Ab (IU/ml)	30.041±11.245	27.75±10.33	0.035
	(15-49)	(12-50)	
Hypoechoic ultrasound (%)	14.8 (n=10)	4.8 (n=2)	<0.001

Mean Serum triiodothyronine (T3) level varies from 2.05±0.34 pg/ml in healthy control subjects and 4.99±2.02 pg/ml in PCOS patients which is statistically significant. Serum tetraiodothyronine (T4) level varies from 2.09±0.18 ng/dl in healthy control subjects and 3.39±0.45 ng/dl in PCOS patients which statistically significant. The serum TSH levels varied from 3.71±0.45 mIU/ml in healthy control subjects and 6.54±1.71 mIU/ml in PCOS patients were statistically significant in Table 4.

DISCUSSION

In our study, most of the patients belongs to 26-35 years (49.7%) followed by 15-25 years (39.4%) and 36-45 years (10.9%) in table 1. The mean Body Mass Index (BMI) of the healthy control subjects was 23.73± 3.19 kg/m^2 which various from 25.61± 3.06kg/m2; among PCOS individual. This is statistically significant difference (p =< 0.005) and was observed in BMI of PCOS patients when results were compared with the healthy control subjects. The PCOS group tends to be overweight or obese with a higher BMI other than the control. The increase in BMI is maybe related to two causes, the first one is PCOS and the second cause may be hypothyroidism. Forty-five percent of PCOS in this study are obese according to Deepa et al [6] are in coordination with these findings. They had a mean age is 26 ± 4.2 and a BMI of 29 ± 4.4 with 32% of PCOS patients are obese. Wild RA et al [17] studied the correlation of thyroid dysfunction with the PCOS prevalence and found spatially hypothyroidism increased in PCOS incidence and obese women. Talbott E et. al. [18] found an increase in BMI in PCOS women.

Polycystic ovarian syndrome (PCOS) is an intense problem which manifests later as infertility, obesity, insulin resistance, dyslipidemia, endothelial dysfunction and overt diabetes mellitus. PCOS is often associated with abnormalities of other endocrine glands. Women with PCOS may be four times more likely to suffer from hypothyroidism. [19] In our study, we found that the BMI values in the cases were significantly higher than in the control group. Valkenburg O et al (2014) observed a statistically high-significant difference (p=<0.0001) in BMI of PCOS patients as compared to healthy control subjects. [20] Hypothyroidism can aggravate PCOS symptoms. It can lead to low levels of sex hormone binding globulin (SHBG) which in turn can lead to higher concentrations of free testosterone throughout the body. [21]

High level of testosterone is one of the factors which contribute to PCOS symptoms like infertility, polycystic ovaries, hirsutism, male pattern hair loss and acne. If hypothyroidism is

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diagnosed and treated early, some of PCOD symptoms may diminish. [22] Our study showed that the mean TSH level were significantly higher in the cases than those in the control group which was consistent with Sam S et al (2015). [23] This study did not show a statistically significant difference between cases and controls regarding T3 and T4 levels which was consistent with study by Legro RS et al (2015). [24] Mean serum TSH values were highly significant ($t=4.53$, $p<0.001$) in PCOS patients in our study. Similar result was obtained by Dahiya K et al (2012) in his study, which demonstrated a threefold higher prevalence of hypothyroidism in patients with PCOS. [25]

In fewer other studies same results obtained, like Didem Ozdemir et al (2011) observed a statistically highly-significant relation (p in serum TSH levels between normal individuals (2.67± 3.11 mIU/ml) and PCOS patients (4.55± 2.66 mIU/ml). [26] Velija-Asimi Z et al (2015) also reported a highly significant relation ($p<0.05$) in Thyroid stimulating hormone (TSH) levels (μIU/mL) between normal individuals (1.26±0.45) and PCOS patients (7.13±1.60). [27]

The study also evaluated that there is no relationship between thyroid hormones and PCOS disease which is similar with few old literatures. Krassas GE et al (2015) reported a non-significant relation ($p>0.05$) in triiodothyronine (T3) levels (ng/ml) between normal individuals (1.26 ± 0.21) and PCOS patients (1.30±0.16) [28.] Janssen OE (2014) also observed a non-significant relation ($p>0.05$) in triiodothyronine (T3) levels between normal healthy subjects and PCOS patients. [29] Our findings of serum triiodothyronine (T3) levels were in accordance with the above studies.

Conclusion

The positive correlation between serum TSH levels and the presence of higher BMI in our study threw bright light that female patients with PCOS must be investigated for the presence of Subclinical hypothyroidism which is proved to be metabolic risk factors. As there is high prevalence of thyroid disorders in PCOS patients, all women in their reproductive age with and without PCOS, should have their thyroid function tests evaluated. Secondly correcting subclinical hypothyroidism will lead to improvement of overall hormonal and metabolic health of these females.

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26-35 years	82 (49.7%)	85 (51.5)
36-45 years	18 (10.9%)	11 (6.6)
Total	**165 (100%)**	**165** (100%)

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Table 2: Distribution of BMI

Variables	PCOS (n=165)	Control (n=165)	P value
BMI (Kg/m^2)	23.73±3.19 (18-30)	25.61±3.06 (18-32)	0.041 Significant
Goiter (%)	29.7 (n=122)	9.7 (n=76)	Significant
Hirsuitism (%)	74.6 (n=58)	17 (n=12)	Significant

The mean Body Mass Index (BMI) of the healthy control subjects was 25.61± 3.06; which varies from 23.73± 3.19 kg/m^2 among PCOS which is statistically significant difference (p =< 0.005) was observed in BMI of PCOS patients when results were compared with the healthy control subjects in Table 2.

Table 3: Distribution of Menstrual Complaints of cases

	Menstrual Complaints	No. of Cases	Percentage
Menstrual Complaints	Secondary Amenorrhoea	35	21.2
	Oligomenorrhoea	95	57.6
	Polymenorrhoea	3	1.8
	Normal	32	19.4
	Total	165	100
Infertility	Primary	115	69.7
	Secondary	50	30.3
Hyperandrogenism	140		84.8

Table 4: Statistical values of different variables and their correlation among polycystic ovarian syndrome subjects and controls

Variables	PCOS (n=165)	Control (n=165)	P value
Free T3 (pg/ml)	4.99±0.624 (2-12)	2.05±0.34 (1.8-4.2)	<0.001
Free T4 (ng/dl)	3.39±0.45 (0.2-20)	2.09±0.18 (0.3.-1.32)	<0.001
TSH (mIU/ml)	6.54±1.71 (0.3-16)	3.71±0.45 (0.6-8.48)	<0.001
Anti-TPO Ab (IU/ml)	30.041±11.245 (15-49)	27.75±10.33 (12-50)	0.035
Hypoechoic ultrasound (%)	14.8 (n=10)	4.8 (n=2)	<0.001

Mean Serum triiodothyronine (T3) level varies from 2.05±0.34 pg/ml in healthy control subjects and 4.99±2.02 pg/ml in PCOS patients which is statistically significant. Serum tetraiodothyronine (T4) level varies from 2.09±0.18 ng/dl in healthy control subjects and 3.39±0.45 ng/dl in PCOS patients which statistically significant. The serum TSH levels

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varied from 3.71±0.45 mIU/ml in healthy control subjects and 6.54±1.71 mIU/ml in PCOS patients were statistically significant in Table 4.

DISCUSSION

In our study, most of the patients belongs to 26-35 years (49.7%) followed by 15-25 years (39.4%) and 36-45 years (10.9%) in table 1. The mean Body Mass Index (BMI) of the healthy control subjects was 25.61± 3.06; which varies from 23.73± 3.19 kg/m^2 among PCOS which is statistically significant difference (p =< 0.005) was observed in BMI of PCOS patients when results were compared with the healthy control subjects. The PCOS group tends to be overweight or obese with a higher BMI other than the control. The increase in BMI is maybe related to two causes, the first one is PCOS and the second cause may be hypothyroidism. Forty-five percent of PCOS in this study are obese according to Deepa et al [6] are in coordination with these findings. They had a mean age is 26 ± 4.2 and a BMI of 29 ± 4.4 with 32% of PCOS patients are obese. Wild RA et al [17] studied the correlation of thyroid dysfunction with the PCOS prevalence and found spatially hypothyroidism increased in PCOS incidence and obese women. Talbott E et. al. [18] found an increase in BMIO in PCOS women.

Polycystic ovarian syndrome (PCOS) is an intense problem which manifests later as infertility, obesity, insulin resistance, dyslipidemia, endothelial dysfunction and overt diabetes mellitus. PCOS is often associated with abnormalities of other endocrine glands. Women with PCOS may be four times more likely to suffer from hypothyroidism. [19] In our study, we found that the BMI values in the cases were significantly higher than in the control group. Valkenburg O et al (2014) observed a statistically high-significant difference (p=<0.0001) in BMI of PCOS patients as compared to healthy control subjects. [20] Hypothyroidism can aggravate PCOS symptoms. It can lead to low levels of sex hormone binding globulin (SHBG) which in turn can lead to higher concentrations of free testosterone throughout the body. [21]

High level of testosterone is one of the factors which contribute to PCOS symptoms like infertility, polycystic ovaries, hirsutism, male pattern hair loss and acne. If hypothyroidism is diagnosed and treated early, some of PCOD symptoms may diminish. [22] Our study showed that the mean TSH level were significantly higher in the cases than those in the control group which was consistent with Sam S et al (2015). [23] This study did not show a statistically significant difference between cases and controls regarding T3 and T4 levels which was consistent with study by Legro RS et al (2015). [24] Mean serum TSH values were highly significant (t=4.53, p<0.001) in PCOS patients in our study. Similar result was obtained by Dahiya K et al (2012) in his study, which demonstrated a threefold higher prevalence of hypothyroidism in patients with PCOS. [25]

In fewer other studies same results obtained, like Didem Ozdemir et al (2011) observed a statistically highly-significant relation (p in serum TSH levels between normal individuals (2.67± 3.11 mIU/ml) and PCOS patients (4.55± 2.66 mIU/ml). [26] Velija-Asimi Z et al (2015) also reported a highly significant relation (p<0.05) in Thyroid stimulating hormone

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(TSH) levels (μIU/mL) between normal individuals (1.26±0.45) and PCOS patients (7.13±1.60). [27]

The study also evaluated that there is no relationship between thyroid hormones and PCOS disease which is similar with few old literatures. Krassas GE et al (2015) reported a non-significant relation ($p>0.05$) in triiodothyronine (T3) levels (ng/ml) between normal individuals (1.26 ± 0.21) and PCOS patients (1.30±0.16) [28.] Janssen OE (2014) also observed a non-significant relation ($p>0.05$) in triiodothyronine (T3) levels between normal healthy subjects and PCOS patients. [29] Our findings of serum triiodothyronine (T3) levels were in accordance with the above studies.

Conclusion

The positive correlation between serum TSH levels and the presence of higher BMR in our study threw bright light that female patients with PCOS must be investigated for the presence of Subclinical hypothyroidism which is proved to be metabolic risk factors. As there is high prevalence of thyroid disorders in PCOS patients, all women in their reproductive age with and without PCOS, should have their thyroid function tests evaluated. Secondly correcting subclinical hypothyroidism will lead to improvement of overall hormonal and metabolic health of these females.

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