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A CASE CONTROL STUDY TO ASCERTAIN THE RELATIONSHIP OF METABOLIC, BIOCHEMICAL AND HORMONAL CHANGES IN WOMAN SUFFERING FROM POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 9 -18% of women worldwide and a major cause of anovulatory infertility. PCOS is found to be a predisposing factor for the development of impaired glucose tolerance and cardiovascular diseases. This study was designed to investigate and compare the metabolic and biochemical characteristics of PCOS patients with control group. **Methods:** Young women, aged 16 to 40 years, diagnosed with PCOS (N =100) and control group (N=100) attending a tertiary care hospital was included in the study. Biochemical parameters were measured using standard procedures. Laboratory normal reference ranges were used for comparison. **Results:** 82.2% of the PCOS patients were in 16-20 years of age group. BMI range of the women with PCOS was 24.82. Fasting Blood Sugar, Random Blood Sugar and Hba1C all were deranged in cases. Reversal of LH/FSH ratio was also present with mean value of 2.48 in the cases. Lipid profile was highly deranged in cases with mean values of 210.08mg/dl (Total Cholesterol), 125.94mg/dl (Triglycerides), 125.11mg/dl (LDL), and 39.67 mg/dl (HDL). Serum Prolactin, FSH, LH, Thyroid Stimulating Hormone (TSH) DHEA (dihydroepiandesterone), SHBG (sex hormone binding globulin) testosterone, Prog-21 (progesterone on 21st day of menstrual cycle) level were also deranged among the PCOS patients in comparison to controls. **Conclusions:** BMI was high in the patients of the PCOS. Blood sugar, lipid profile and hormonal profile were deranged in PCOS patients as compared to controls.

KEYWORDS: BMI, hormonal profile, lipid profile, PCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by infertility, hirsutism; obesity; menstrual irregularities and metabolic changes.[1] PCOS is the most frequent disorder noted in woman of reproductive age group. It affects almost 9–18% of women of this age group.[2] In 73% of cases PCOS results in anovulatory cycles and infertility.[3]

The National Institute for Health (NIH) Criteria 1990 was revised; In 2003 Rotterdam criteria have been adopted worldwide. Under this criteria PCOS diagnosis can be reached when at least two of the following three criteria are met: hyperandrogenism and/or hyperandrogenemia (HA); oligomenorrhea or amenorrhea or anovulation (Oligo-An); and polycystic ovary morphology However, recently in 2006, Androgen Excess Society (AES) has come up with a consensus statement, defining PCOS as a hyperandrogenic state and emphasizes the presence of either clinical or biochemical features of hyperandrogenism along with other features of PCOS for diagnosis.[4]

PCOS is found to be a predisposing factor for the development of impaired glucose tolerance and cardiovascular diseases. Furthermore it is an important cause of concern to most women suffering from it. The underlying hormonal imbalance in PCOS is created by a combination of increased androgens and decreased insulin activity.[5-8]

Along with the clinical manifestations and ultrasonography findings, PCOS show gross changes in the biochemical parameters affecting the complete metabolism of the body. Leading to impaired blood sugar levels, lipid and hormonal profile. Ultimately this increases the risk of obesity, dyslipidemia and type II diabetes mellitus. PCOS patients are highly susceptible to cardiovascular disorders because of increased prevalence of subclinical atherosclerosis, hyperlipidemia, hypertension, inflammation and endothelial dysfunction. These women have increased risk of fetal deformities, miscarriages, premature deliveries and neonatal complications during pregnancy.[9,10]

Urbanization, sedentary lifestyle along with unhealthy diet gave rise to certain metabolic disorders including PCOS. In India, adaptation of such lifestyle especially in urban areas leads to the problem. Most of the young population does not visit health facilities until they have late sequel of the problem. Although there are no systemic studies from India, the observations by endocrinologists, gynecologists, dermatologists, etc. show a significant rise in number. Most of the studies are done in tertiary hospital set-ups and recently a few studies in school going teenagers were reported with a prevalence rate of 9.13% to 36%.[11]

METHODOLOGY

This Observational Epidemiological Case Control Study was carried out in the Central clinical laboratory at tertiary care hospital in western Maharashtra from December 2015 to February 2017. A total of 200 consented women aged 16-40 years were enrolled in the study. The subjects were divided into two groups (cases and controls). The study group consisted of 100 premenopausal women diagnosed to have Polycystic Ovarian Syndrome (PCOS) by Rotterdam criteria.[3] The control group consisted of 100 age matched healthy female volunteers with regular menstrual cycles and with no clinical or biochemical features of hyperandrogenism, thereby excluding the diagnosis of PCOS in this group. Institutional Ethical Committee approval was obtained.

Exclusion Criteria: Patients suffering from Diabetes Mellitus, hypertension, thyroid disorders, renal diseases, cardiovascular diseases, Cushing's syndrome, pregnant or lactating women, Oral Contraceptives, hypoglycemic agents / lipid lowering drugs, hormonal medications within previous 6 weeks were excluded from the study.

Sample Collection: 6 ml of Fasting blood samples was withdrawn from antecubital vein at rest in supine position, after an overnight fasting. Blood was collected from controls and PCOS patients for determination of basal endocrinological parameters. 4 ml of sample blood was taken in plain vacutainer centrifuged at 3000 rpm for 10 minutes; the serum samples were incubated for 15 minutes at room temperature.

Biochemical Methods: Thyroid stimulating hormone (TSH), Follicle stimulating hormone (FSH), Luteinizing hormone (LH), prolactin, dehydroepiandrosterone (DHEA), sex hormone binding globulin and testosterone on day 2 or 3 of menstrual cycle while serum progesterone was measured on day 21. Total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations were determined using an autoanalyzer.1 ml of blood was stored in fluoride vacutainer in order to estimate fasting blood sugar levels. Rest 1 ml was stored in EDTA vacutainer for HbA1c.

Assay methods: Quantitative determination of hormones was carried out by electrochemiluminescence immunoassay (Roche Hitachi Cobas e 411). Blood glucose was measured on autoanalyzer (Vital Scientific Microlab 300) using oxidase method. Lipid profile was determined by enzymatic colorimetric method. HbA1c was measured with the help of Erba analyzer.

Statistical tests: Data Analysis was performed using SPSS 2.0 Software. The values were expressed as mean ± Standard Deviation and the findings were analyzed by student "t" test. Pearson's correlation coefficients were calculated to assess the correlation between the biochemical parameters in the study group. A 'P' value of < 0.05 was considered statistically significant. 'P' value with single star (*) represents significance and with (**) represents high significance.

RESULTS

Table 1 shows the mean age, which was found to be 21.94±3.97 for cases and 24.53±5.07 years for controls respectively. Majority of the participants (82.2%) were adolescents (16-22 years). BMI was raised among the cases in comparison to the controls. LH/FSH ratio was also raised in the cases, which was also statistically significant. Fig. 1 shows the comparison of these variables in both the groups. Fig. 1.1 shows the age wise distribution of PCOS among the cases.

Table 1. Age, Body Mass Index & LH/FSH ratio among cases (n=100) and controls (n=100)

Sr. No.	Parameter	Cases (n=100)		Controls(n=100)		P value
		Mean	SD	Mean	SD	
1.	**AGE**	21.94	3.976	24.53	5.079	**0.0001****
2.	**BMI**	24.8216	3.0437	21.7731	2.0767	**0.0001****
3.	**LH/FSH ratio**	2.4858	0.4105	1.8021	0.2064	**0.0001****

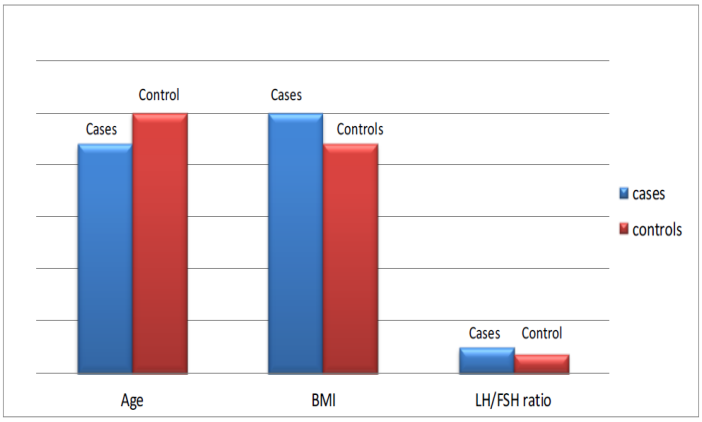

Figure 1. Comparison of Age, Body Mass Index (BMI) & LH/FSH ratio among cases (n=100) and controls (n=100)

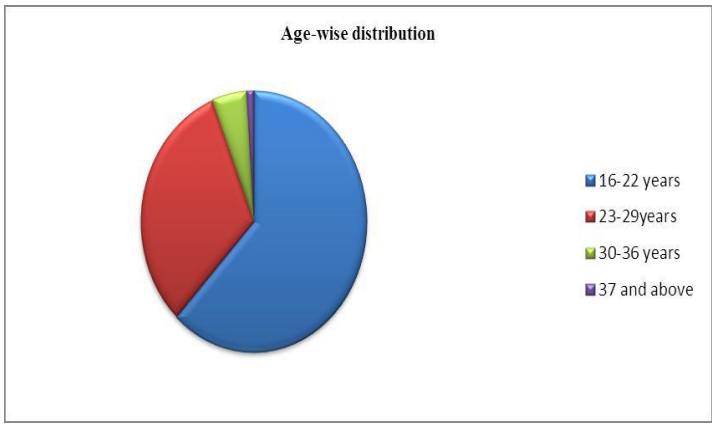

Figure 1.1 Age wise distribution of PCOS among the cases (n=100)

Table 2. Displays the changes in the blood sugar parameters among the cases and controls. These all parameters were deranged among the cases. Fig 2. Shows the comparison of these parameters with the controls. This was also statistically significant.

Table 2. Blood Sugar and related profiles in cases (n=100) and controls (n=100)

Sr. No.	Parameter	Cases (n=100)		Controls(n=100)		P value
		Mean	SD	Mean	SD	
1.	FBS(mg/dl)	113.10	10.82	87.71	6.88	0.0001**
2.	RBS(mg/dl)	153.99	19.01	128.68	13.38	0.0001**
3.	HbA1c(mg/dl)	5.999	0.851	4.167	0.321	0.0001**

FBS; Fasting blood sugar after overnight fasting, RBS; Random Blood Sugar, HbA1c: Glycated hemoglobin values.

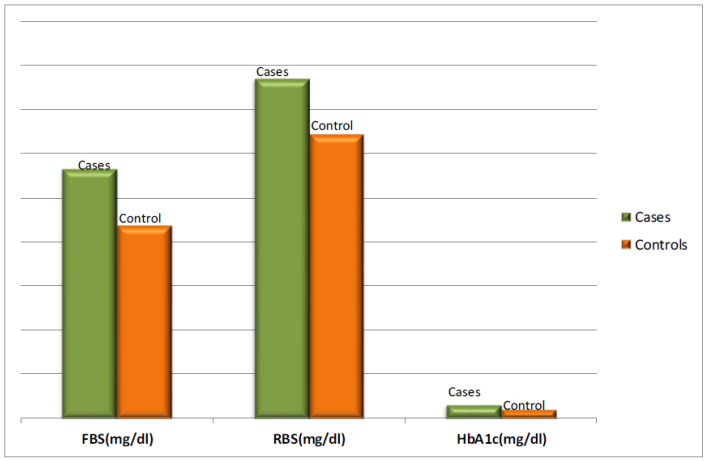

Figure 2. Comparison of blood sugar parameters among cases (n=100) and controls (n=100)

Table 3 shows the lipid profile among the cases and controls, the mean total cholesterol was found to be 210.08 ± 22.99 in cases as well 167.32±15.01 in controls. Triglycerides were also raised in cases along with derangement of LDL and HDL. This was statically significant between them (p>0.05). Figure 3 shows the comparison of these parameters in both the groups and hence shows dyslipidemia is a common feature among the PCOS patients.

Table 3. Lipid profile among cases (n=100) and control (n=100) groups

Sr. No.	Parameter	Cases (n=100)		Controls(n=100)		P value
		Mean	SD	Mean	SD	
1.	Total cholesterol(mg/dl)	210.08	22.99	167.32	15.01	0.0001**
2.	TGL(mg/dl)	125.94	21.02	107.94	11.01	0.0001**
3.	LDL(mg/dl)	125.11	19.44	91.67	3.66	0.0001**
4.	HDL(mg/dl)	39.67	6.50	52.98	3.42	0.0001**

TGL; Triglycerides, LDL: low-density lipoproteins, HDL: High -density lipoproteins.

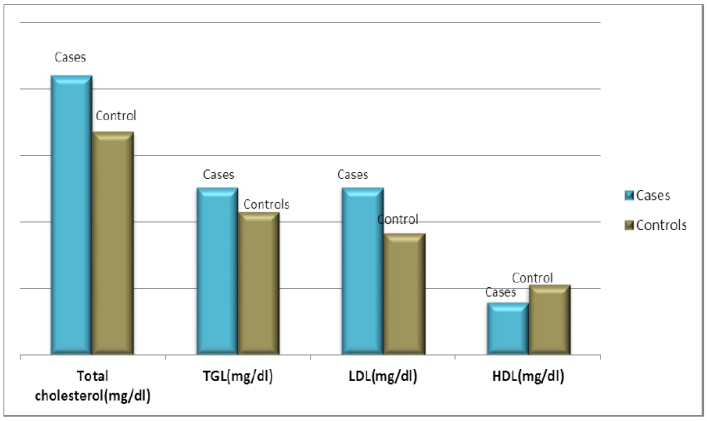

Figure 3. Comparison of lipid profile among the cases and controls

Table 4. Shows the hormonal profile along with standard deviation in cases and controls. Prolactin, FSH, LH, DHEA, TSH, SHBG, and Progesterone on day 21st of menstrual cycle these all parameters were significantly high in the cases as compared to controls, which can be seen in the figure 4 also. The Testosterone was not statically significant. Oligomenorrhea, irregular menstrual cycles, hirsuitism, acanthosis nigricans etc. was positive in the cases establishing strong association of deranged hormonal profile. As well the comparison of the hormonal profile can be well seen in the figure 4.

Table 4. Hormonal profile of cases and controls

Sr. No.	Parameter	Cases (n=100)		Controls(n=100)		P value
		Mean	SD	Mean	SD	
1.	Prolactin(ng/dl)	14.38	2.29	7.05	1.64	0.0001**
2.	FSH(mIU/l)	5.234	0.571	4.200	0.286	0.0001**
3.	LH (mIU/L)	12.897	1.879	7.530	0.687	0.0001**
4.	TSH (mIU/L)	5.431	0.943	1.888	0.410	0.0001**
5.	DHEA(ug/dL)	324.40	42.31	191.55	30.93	0.0001**
6.	SHBG (nmol/L)	26.381	1.633	61.763	15.583	0.0001**
7.	Testosterone(ng/ml)	0.3861	0.0907	0.3526	0.0965	0.0136*
8.	Prog-21 (ng/mL)	10.333	1.146	7.839	1.066	0.0001**

FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: Thyroid stimulating hormone, DHEA: dihydroepiandesterone, SHBG: sex hormone binding globulin, testosterone, Prog-21: progesterone on 21st day of menstrual cycle.

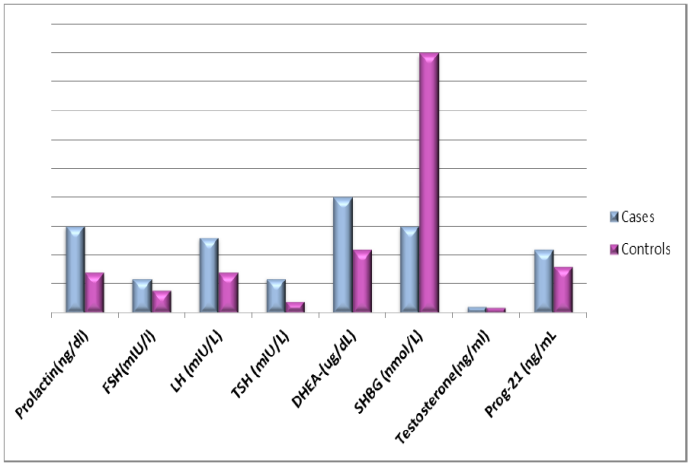

Figure 4. Comparison of hormonal parameters in cases and controls.

DISCUSSION

PCOS among adolescents is an emerging problem that needs to be assessed carefully, so that timely intervention and appropriate treatment can be introduced. In this study we found woman of younger age (16-22 years, Fig 1.1) group showing features of PCOS as also found by Solomon CG and certain other studies.[5] Age plays vital role in understanding the pathophysiology of PCOS, right from menarche the various changes in hormonal levels is the underlying cause.[2,5]

As the age advances PCOS may present with increased dyslipidemia, impaired blood sugar and higher BMI scores when compared to younger age group. These changes further expose patients to the increased risk of insulin resistance and metabolic syndrome. Impaired blood sugar profile (Fig 2.) was seen in cases as compared to controls corresponding to various literatures in the past.[12,13]

Dyslipidemia (Fig. 3) was highly significant in our study among the cases in comparison to control group. This revealed the relationship of increased adipose tissue and PCOS similar to a study by Misra et al.[14] Hence, due to impaired lipid Panel according to Gu¨lekli's reveals that PCOS patients are prone to gain weight.[15] Kalra et al. found no co-relation between BMI with various lipid parameters.[16] Whereas in our study, it was highly significant. A study by Valkenburg et al. on serum lipid profile of PCOS patients showed higher levels of total cholesterol, triglycerides and LDL compared with the controls. On the contrary serum levels of HDL were significantly lower in women with PCOS similar to our results.

Derangement in thyroid function tests can be noted with PCOS. Such patient's present with the features of hypothyroidism like alopecia, weight gain, obesity, mood disturbances intolerance to cold etc. In the present study we tried to fetch as much as data we can, but unfortunately we had the values of TSH only which was significantly raised in the cases ('P' value of < 0.05). Henceforth, putting theses cases into a category, prone to become a case of hypothyroidism in future similar to other studies (Table 4.).[17]

Reversed LH: FSH ratio is a common pathognomic feature of PCOS. In the present study, the mean LH: FSH ratio in the cases was more than two and showed significance compared to the controls.[18] Prolactin, DHEA, progesterone were also found to be significantly raised among the cases as compared to the control groups. Similar results were noted in the past.[19] Such hormonal imbalances play a vital role in inducing oligomenorrhea, amenorrhea, infertility, increased pre-menstrual syndrome and acne.[6,9,15]

Sex hormone binding globulin was found to be less amongst the cases as compared to the controls ('P' value of < 0.05). Low levels of SHBG leads to male- patterned hair growth or hair loss, menstrual irregularities, decreased breast tissue and skin abnormalities. Ultimately decreased levels of SHBG predisposes woman for developing higher cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome. Level of testosterone was not significantly raised ('P' Value of < 0.0136*) in the cases. This must be due to the less time period and young population of cases in our study. These findings are similar to Mora et al.[19] Increased testosterone in young females leads to hirsutism, acne loss of libido, infertility etc. Both of them lead to androgenization in woman.

CONCLUSION

The present study showed PCOS patients with higher BMI as compared to controls. PCOS women had significantly increased total cholesterol, triglycerides and LDL. Serum levels of HDL were significantly lower in the cases compared to controls. The findings of this study confirm the association between BMI and dyslipidemia in PCOS patients. Significant raised positive values of blood sugar were also noted. In addition, we observed derangement of hormonal profile leading to various clinical features. In conclusion, the use of these simple and cost-effective biochemical parameters might prove to be biomarkers in early

detection of these metabolic changes and may help to identify women with PCOS and also its association with risk cardiovascular diseases.

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CONFLICTS OF INTEREST
There are no conflicts of interest.

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