ORIGINAL RESEARCH PAPER

Endocrinology

CLINICAL AND METABOLIC PROFILE OF POLYCYSTIC OVARIAN SYNDROME IN EASTERN INDIAN POPULATION.

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is most common endocrine abnormality in women of reproductive age. Several studies of diverse populations have estimated its prevalence at 6% - 10%.Most patients with PCOS have metabolic abnormalities such as insulin resistance with compensatory hyperinsulinemia, obesity, and dyslipidemia. All of these metabolic features may play a role in the development of glucose intolerance or type 2 diabetes mellitus and hypertension, thereby increasing cardiovascular diseases.

Aim : To evaluate the prevalence of metabolic & clinical manifestation of poly cystic ovarian syndrome in eastern Indian population.

Material and method: This was a single centre observational Cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from march 2017 to January 2019.

Results: The mean BMI were 24.73 and 22.25 kg/m2 & there is significant difference in the BMI. There was significant difference in the Waist hip ratio among the case and the control. The mean systolic and mean diastolic blood pressure were significantly higher among the cases .The most of the cases had mild Hirsutism with a median score of 8. Acne were significantly higher in the PCOS group as compare to control group (<0.001).The grade 1 was the most common pattern & The cases have significantly less number of cycle per year (p 0.001) and the 83.33% cases and 14.49% control had oligomenorrhea.

INTRODUCTION :

Polycystic ovarian syndrome (PCOS) is most common endocrine abnormality in women of reproductive age. Several studies of diverse populations have estimated its prevalence at 6% - 10%[1,2,3]. The first description of PCOS was given by Stein and Leventhal in 1935.They described a constellation of amenorrhea, oligomenorrhea, obesity and hirsutism in presence of polycystic ovary. The disorder has since being known as PCOS, although considerable change in its definition and known path physiology has occurred. Most patients with PCOS have metabolic abnormalities such as insulin resistance with compensatory hyperinsulinemia, obesity, and dyslipidemia. All of these metabolic features may play a role in the development of glucose intolerance or type 2 diabetes mellitus and hypertension, thereby increasing cardiovascular diseases [4,5] PCOS has long term consequences which include irregular uterine bleeding, anovulatory infertility, androgen excess, chronically elevated levels of free estrogen associated with an increased risk of endometrial cancer and insulin resistance and associated with an increased risk of CVD and diabetes mellitus.PCOS as estimated till now with prevalence of 9 to 11% in India will have huge impact on health expenditure of government and individual, adding to frustration of tackling largest diabetic population of the world.[6,7]

Aim :

To evaluate the prevalence of metabolic & clinical manifestation of poly cystic ovarian syndrome in eastern Indian population.

MATERIAL AND METHOD:

This was a single centre observational Cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from march 2017 to January 2019.

Total number of study subjects were 207 out of which 138 were cases. Adolescents and young woman of reproductive age group between 16-40 yrs attended the in-patient and outpatient clinic of the Department of Endocrinology and metabolism in whom PCOS was diagnosed according to the Rotterdam criteria and participated by signing the consent form . Subject should had least two of the following elements

1. Hyperandrogenism (H): Modified Ferriman-Gallwey score ≥8 or serum total testosterone (TT) ≥80 ng/dL (≥2.77 nmol/L)[8]
2. Ovulatory dysfunction (O): Oligomenorrhea (cycles longer than 35 days OR less than 9 cycle in a year) or amenorrhea (no menses in the last 6 months) after a negative screening pregnancy test. In patients with regular menses, progesterone level <4 ng/mL (12.72 nmol/L) in the luteal phase of two consecutive cycle.

3.Polycystic ovaries (P): 12 or more follicles of 2 to 9 mm diameter and/or increased ovarian volume (>10 mL) in at least one ovary by ultrasonography .

Body mass index (BMI):Body weight in kilograms divided by the square of the height, expressed in meters (kg/m2). Waist/hip ratio (W/H): the waist was recorded as the median of three measurements performed in mid distance between the last rib margin and the anterior-superior iliac crest and hip circumference was the largest measurement over the buttocks. Blood pressure: the average of two measurements in the non dominant arm, in sitting position and after a 5-minute rest, using a mercury sphygmomanometer. Hirsutism: defined as a Ferriman-Gallwey score ≥8[9].Acne: scoring based on its number, type and distribution done by global acne grading scale.[10]AcanthosisNigricans :Grading 1-4

Informed consent was taken from all the subjects involved in the study including controls and from the parents in case of age less than 18 years.

Inclusion criteria: Female between 16-40 age group with features of PCOS, as defined by Rotterdam criteria 2003, characterised by at least two of the following three features;
1) Oligo or anovulation
2) Clinical and/or biochemical hyperandrogenism, and
3) Ultrasound appearance of polycystic ovaries.

Exclusion criteria :
Other causes of hyperandrogenism like Cushing's syndrome, late-onset congenital adrenal hyperplasia andandrogen-secreting tumours were excluded with appropriate diagnostic tests. Thyroid dysfunction,, except euthyroid on stable dose of medication for 3 month. Hyperprolactinemia, Pregnancy , OCP or any other hormonal contraception

Descriptive statistical analysis were carried out with SAS (Statistical Analysis System) Version 21.0 for windows, SPSS, Inc., Chicago, IL, US.Results on continuous measurements were presented as Mean ± SD .Results on categorical measurements are presented in Number (%). The level of Significance was assessed at 5%.*Unpaired t-test* was used to find the significant changes between the quantitative parameters between two groups i.e. PCOS and Controls.*Chi-square test* use for qualitative data to compare the test of significance difference between proportions . *Spearman correlation test* was done to find out whether any significant correlation exists between the two variables.

RESULTS:
The mean age were 22.5 year and 23.25 year in the case and control respectively & the difference was nonsignificant. The mean height were 154.33 cm and 155.14 cm among the case and control group & the difference in the mean height were not significant. The mean BMI were 24.73 and 22.25 kg/m2 in the case and control respectively & there is significant difference in the BMI. There were nonsignificant difference among the Neck circumference, Waist circumference and Hip circumference among the case and control groups. The was significant difference in the Waist hip ratio among the case and the control. The mean systolic and mean diastolic blood pressure were significantly higher among the cases as compare to control.(table:01)

Table 01: Clinical parameters of PCOS and control

Group Statistics			
	Group	Mean ±Std. Deviation	p
AGE(year)	PCOS	22.5.0 ± 4.529	0.265
	Non-PCOS	23.25 ± 4.603	
Height (cm)	PCOS	154.33 ± 4.830	0.254
	Non-PCOS	155.14 ± 4.772	
Weight (kg)	PCOS	58.44 ± 11.546	0.002
	Non-PCOS	53.52 ± 7.611	
BMI kg/m2	PCOS	24.73 ± 4.364	<0.001
	Non-PCOS	22.25 ± 2.948	
NC (cm)	PCOS	33.41± 2.706	0.069
	Non-PCOS	32.83 ± 1.534	
WC (cm)	PCOS	82.65 ± 12.025	0.062
	Non-PCOS	79.70 ± 7.297	
HC (cm)	PCOS	96.30 ± 10.534	0.232
	Non-PCOS	97.96 ± 6.307	
W/H	PCOS	0.88 ± 0.06	<0.001
	Non-PCOS	0.81 ± 0.05	
SBP(mmhg)	PCOS	117.93 ± 9.257	0.026
	Non-PCOS	114.96 ± 8.336	
DBP (mmhg)	PCOS	78.39 ± 5.520	0.013
	Non-PCOS	75.62 ± 10.320	

P =< 0.05 is significant BMI- Body mass index (kg/m2),NC-neck circumference, HC- hip circumference, W/H-waist hip ratio, SBP-systolic Blood pressure,DBP-Diastolic blood pressure

There were significant difference in the mean values of Fasting plasma glucose, 2 hour OGTT , fasting Insulin and HOMA-IR (homeostatic model of assessment of insulin resistance) among the case and control groups . There were nonsignificant difference in the Total cholesterol,HDL ,LDL and TGs among the case and the control groups.(table;02)

Table 02: Biochemical Parameters in the case and control group

	Group	Mean ± Std. Deviation	p
FPG(mg/dl)	PCOS	88.77 ±1 3.077	0.008
	Non-PCOS	83.75 ± 11.587	
75g OGTT(mg/dl)	PCOS	125.14 ± 20.238	<0.001
	Non-PCOS	102.86 ± 21.828	
Fasting .Insulin (uIU/ml)	PCOS	11.56 ± 8.118	<0.001
	Non-PCOS	7.65 ± 5.625	
HOMA IR	PCOS	2.55 ± 2.026	<0.001
	Non-PCOS	1.59 ± 1.287	
HDL	PCOS	49.83 ± 8.757	0.161
	Non-PCOS	51.65 ± 8.875	
LDL	PCOS	100.78 ± 29.191	0.936
	Non-PCOS	101.12 ± 27.258	
VLDL	PCOS	47.23 ± 24.379	0.565
	Non-PCOS	46.19 ± 24.678	
TG	PCOS	169.19 ± 52.165	0.569
	Non-PCOS	164.93 ± 53.960	
T CHL	PCOS	175.83 ± 35.269	0.686
	Non-PCOS	177.87 ± 32.045	

FPG –fasting plasma glucose,75 g OGTT-75 gram oral glucose tolerance test, HOMA-IR-homeostatic model assessment-of insulin resistance, HDL-high density lipoproteins, LDL-low density lipoproteins, VLDL-very low density lipoprotien, TG-triglycerides TCHL-total cholesterol.

The WHO-ASIAN classification of obesity was used to classify the obesity. There were 47.1%, 26.8% and 26.1% obese , overweight and lean respectively among the PCOS group while in control group the 13.0%,14.5% and 72.5% were obese ,overweight and lean subjects. The difference was statistically significant among the PCOS and control group (p <0.001)(figure1)
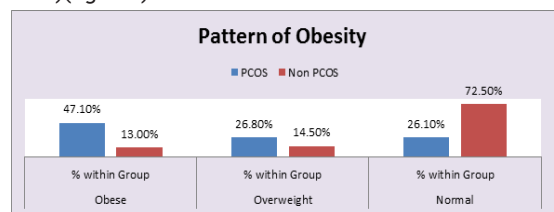

Figure 1 : pattern of obesity in the case and control group.

Central obesity was defined by waist circumference >= 80 in the female patients

The 64.5% of PCOS subjects were centrally obese as compare to 42.0% control subjects .The difference in the waist circumference were statistically significant (p 0.001). The waist hip ratio >= 0.85 were present in 59.4% of case group as compare to 24.6% control (p <0001) .There were more PCOS patients had android pattern of body fat distribution as compare to control. The systolic blood pressure were higher in the case group as compare to control (p 0.003) and the 10.9% of case had systolic blood pressure more than >=130mmhg .There were non-significant differences among the diastolic blood pressure among the case and the control group (p 0.23). The 7.2% of PCOS subjects had diastolic blood pressure more than 85 mug as compare to 5.8% subjects in control group.

The fasting plasma glucose were impaired in the 23.02% case as compare to 8.69% control group (p <0.0001). The 16.6% of PCOS subjects had impaired 75 gram 2 hour oral glucose tolerance test.

There were extremely significant differences among the modified Farriman Gallwey score, number of menstrual cycle and Acne score in the case and control groups.

The most of the patients had mild Hirsutism with a median score of 8 in the case group while no Hirsutism in the control. The most common pattern of the menstrual cycle was oligomenorrhea, and the most of the PCOS had 6 to 8 menstrual cycle per year. The most of the case have grade 1 acne.(table:03)

Table:03 Relation of Modified FG Score, Number of Cycle per year and Acne score

Group	PCOS	Non-PCOS	p
	Median (IQR)	Median (IQR)	
MFG. SCORE	8 (4-12)	1 (0-2)	<0.001
NO. CYCLE/YR	7 (6-8)	11 (11-12)	<0.001
ACNE SCORE	1 (0-1)	0.00	<0.001

The Severity of Hirsutism was defined as per the modified Ferriman gallwey score (MFG). The Hirsutism were present in the 61.6% of cases and 0.00% in the control group (p <0.001), the mild Hirsutism was the most common pattern it was present in the 39.1% of PCOS patients and 22.5% patients have sever Hirsutism. The 15.2% of lean PCOS had Hirsutism.(figure:02)
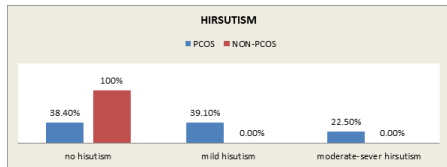

Figure 02 pattern of hirsutism in PCOS & Control

The Acanthosis nigricans were significantly higher in the case group as compare to control group (p 0.015) and the grade 4 was most common in the case group. The grade 0 , grade 1 , grade 2, grade 3 and grade 4 Acanthosis nigricans were present in the 23.2%, 0.0%, 23.9%, 20.3 % and 32.6% PCOS patients respectively as compare to 55.0% , 15.9% , 24.6% , 4.3% and 0.00% in the control group respectively . The Acanthosis was present in the 76.8% of PCOS as compare to 45% of the control

The GAGS scoring was used to define the severity of Acne score (GAGS SCORE).

Acne were significantly higher in the PCOS group as compare to control group (<0.001). The grade 1 was the most common. The grade 1 , grade 2 grade 3 and grade 4 acne were in the 38.4% , 13.8% ,0.0% and 2.2% of the PCOS as compare to 2.9%, 1.4% ,0.00%, and 0.00% of the control .

The Kendall's tau_b correlation showed the positive but weak correlation between the acne severity score and AMH level in the PCOS (r 0.366 , p <0.001) but there is no correlation between the AMH and Acne Score in the control group(figure03)
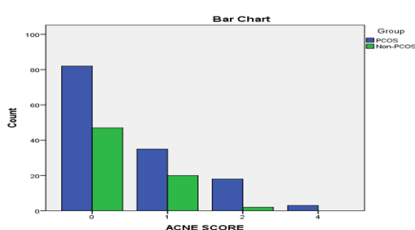

Figure 03 distribution of acne among PCOS and Control .

The cases have significantly less number of cycle per year (p 0.001) and the 83.33% cases and 14.49% control had oligomenorrhea .(table04)

Table 04 ; Pattern of menstrual cycle :

Menstrual Cycle	PCOS	NON-PCOS	P
Normal menstrual Cycle	7.97%	85.5%	0.001
Oligomenorrhea	83.33%	14.49%	
Secondary Amenorrhea	8.69%	0.00%	

DISCUSSION:
The Rotterdam criteria was used to diagnose the cases of PCOS in the present study. The most patients were of the younger age (mean age -22.5 yr) & 80.43 % patients were less than 26 year of age. There were no-significant differences in the age among the case and control groups.

PCOS is not only an endocrine- reproduction disease, but also is a metabolic disorder. In our study there were 47.1%, 26.8% and 26.1% obese , overweight and lean(BMI<23kg/m2) respectively among the PCOS group while in control group 13.0%,14.5% and 72.5% were obese ,overweight and lean subjects . 64.5% of PCOS had central obesity as per the ATP - 3 metabolic syndrome criteria and 42% of the control were centrally obese . Our finding was consistent with Conway GS et al , who found genralized obesity in the 40-50% of PCOS patients [11] while the A Majumdar et al from north india found obesity in 92% PCOS patients. Yildiz et al [12] found that 17 % of PCOS were lean , while in our study 26,1% of the PCOS were lean(BMI<23kg/m2). Two Indian study by Varghese J et al & Indu NR et al showed that 86.6% and 62.7% of PCOS had waist circumference more than 80 cm & 88 cm respectively[13,14]

There is great ethnic and environmental variability in the phenotype of the PCOS. In the eastern Indian subset the lean PCOS is common as compare to southern India and the western countries. Multiple studies have now confirmed that diagnostic criteria that center on polycystic ovaries, with either hyperandrogenism or oligomenorrhea, tend to identify a population that was thinner and had a lower prevalence of metabolic abnormalities such as hyperglycemia, dyslipidemia, or hypertension [15,16,17,18]. In isolation Polycystic ovaries was common in normal younger women without considering any pathology.[18]

Therefore, diagnostic schema that rely on the presence of polycystic ovaries primarily likely to identify a younger population, who are likely healthier and thinner. Increasing age during the reproductive years remains one of the most significant associations or predictors of increasing weight as well as the development of major morbidities such as cardiovascular disease and cancer.

The prevalence of systolic blood pressure ≥130 mmHg were 10.9% in the PCOS group and none of the control had systolic blood pressure ≥130 mmHg .Diastolic blood pressure ≥85 mmHg was present in the 7.2% of the PCOS and 5.8% of the control group. However most of the patients were normotensive in both the group despite increase prevalence of obesity and our finding was consistent with ZimmermannS et al [19]

On the contrary Ben Salem Hachmi L et al found 12% prevalence of hypertension in their study. Several other studies have also suggested an increased prevalence of hypertension in women with PCOS compared to the general population[20,21,22,23,24,25,26,27]. However, a factor complicating the interpretation of such studies was that obesity was present in most of the PCOS patients which itself a significant risk factor for hypertension . Moreover, in the studies which did adjust the analyses for BMI, either statistically or by study design involving matched control for BMI , the association between hypertension and PCOS was not always clear.

The impaired fasting glucose was present in 23.02% cases as compare to 8.69% controls. The 16.6% of PCOS subjects had impaired glucose tolerance . Our finding was similar to the Gambinen et al who reported the prevalence's of impaired glucose tolerance in 15.5% of Italian PCOS [28] . Some Previous studies in the United States have shown that women with PCOS have a higher prevalence of diabetes (8%–12%) and impaired glucose tolerance (30%–35%) than normal women of the same age.[29,30] In a Dutch follow-up study of lean PCOS patients the prevalence of diabetes was increased compared with the general female population, especially in women aged 45–54 years.[31] So in the present study the low Prevalence of impaired glucose tolerance may be due to younger age , lower BMI as compare to other studies.[29,30,31]

The severity of hirsutism was defined as per the modified Ferriman gallwey score (MFG). The hirsutism was present in 61.6% of cases and 0.00% in controls . Mild Hirsutism was the most common pattern. It was present in 39.1% of PCOS patients and 22.5% patients had severe hirsutism. The 15.2% of lean PCOS had hirsutism. Our finding was consistent with Choudhary A et al who reported a prevalence of 64.4% [42] . According to Azzize et al the majority of women with hirsutism (70% to 80%) had PCOS and more than 80% of women had androgen excess [32,33] .The prevalence of hirsutism in different parts of the world varied from 3% in Japanese women to 70% in Caucasians women. [34,35] The prevalence of variable hirsutism may be due to differential susceptibility of pilosebaceous unit to the androgens across the different ethnic group.

Acanthosis was present in the 76.8% of PCOS as compare to 45% of the control. According to Shivaprakash G.et al acanthosis nigricans was prevalent in 58% patients [36] It is a marker of insulin resistance. The variable prevalence of acanthosis nigricans across the Indian studies (7 to 30-40%)[37] is probably due to normal variance observed in the general population .

The GAGS scoring was used to define the severity of acne score . Acne were significantly higher in the PCOS group as compare to control group .The mild acne (score≤18) were the most common. The 54.4% of the PCOS and 4.3% of control had acne and the moderate to severe acne was present in 16%(score 19-38) PCOS The Chaudhury A et al reported a prevalence of 58.5% which was similar to our study . The Kilkenny et al (1998) reported that moderate to severe acne was 17% in their patients[38] . The Cibula et al had reported acne of moderate severity in 22% PCOS [39].However the acne commonly present in PCOS but variable prevalence of acne may be due to difference in ethnicity.

The oligomenorrhea and secondary amenorrhea were present in the 83.33% and 8.69% of the PCOS and the 14.49 % of the control had oligomenorrhea . The prevalence of infertility could not be evaluated because most of the PCOS patient were unmarried .Our finding was consistent with Hart.r et al, who showed oligomenorrhea as most common menstrual abnormality and the 85%–90% of women with oligomenorrhea PCOS[40.] According to Khoury et al study, oligomenorrhea was seen in 60% of patients [41] . According to Choudhary A et al from north India the oligomenorrhea was present in the 40% of PCOS.[42] So as per the different studies from the different part of the world and India as well there was a variable prevalence of oligomenorrhea observed [40.41,42,43]

The difference in the menstrual irregularities in the different part of the world may be due to different ethnicity , envionrnmental factors and the difference in the life style. The Menstrual disorders, particularly oligomenorrhea after the ages of menarche, can be a beginning of ovulatory dysfunction and infertility , and complications resulting from abnormal increase in estrogens and androgens in later years. In fact, the complications of PCOS can be prevented to some extent by early diagnosis [43].

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