Research Paper Medical SCience

Impact of BMI on clinical, endocrine and metabolic profile of Indian PCOS Women

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ABSTRACT

Objective: To assess the differences between non obese and obese subgroups of women with PCOS with regard to clinical, endocrine and metabolic profile of Indian PCOS women according to ESHRE/ ASRM criteria.

Method: Fifty healthy women who were diagnosed to have PCOS according to ESHRE/ ASRM criteria were evaluated. Patients with BMI<23 kg/m2 were put in Lean PCOS Group and patients with BMI>23 kg/m2 were labelled as overweight / obese PCOS. Patients were examined and investigated after a detailed history with special reference to menstrual cycles, features of hyper-androgenism, dyslipidaemia, metabolic syndrome, insulin resistance, hormonal profile and ultrasound morphology.

Results and conclusions: The present study reveals that obesity, seen in 56% of our patients, plays an important role in clinical, hormonal and metabolic alterations in women with PCOS. Although clinical features, glucose intolerance, and gonadotrophin alterations did not vary significantly with BMI, ovarian morphology, hyperandrogenism, and metabolic disturbances like insulin resistance were accentuated with obesity.

KEYWORDS : Polycystic ovary syndrome (PCOS), Insulin resistance, BMI, Obesity

INTRODUCTION:

Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts.[1] It is now recognized as a common heterogeneous, heritable disorder affecting women throughout their lifetime and is a leading cause of oligomenorrhea, amenorrhea, hyperandrogenism and hormonal related infertility. Besides reproductive and obstetric complications the consequences of PCOS extend beyond the reproductive axis; as women with this syndrome are at substantial risk of developing metabolic syndrome.[2] "Metabolic syndrome" (MBS) is a constellation of cardiovascular disease risk factors associated with insulin resistance, glucose intolerance, dyslipidemia, hypertension, and central obesity.[2]

Although much remains unknown regarding the underlying pathophysiology of PCOS, a form of insulin resistance intrinsic to the syndrome appears to play a central role in its development. Among many women with PCOS, the observed insulin resistance is partially explained by excess adiposity; however it is increasingly recognized that even lean women PCOS have increased insulin resistance compared to normal controls. [3]

Considering the well-established relationship between insulin resistance and obesity, the relative contribution of these two parameters to the endocrinometabolic disturbances of PCOS and their impacts on hyperandrogenism and chronic anovulation are pivotal in understanding of this complex syndrome, which has not been clearly elucidated. It is recognized that BMI could be an important determinant. [4] Nevertheless, the differential impact of insulin resistance and obesity on the disorders of the syndrome needs to be highlighted. Hence the present study was carried out to gain insight into possible pathogenetic differences between non obese and obese subgroups of women with PCOS and its resultant clinical heterogeneity.

MATERIAL AND METHODS:

Fifty healthy women who were euthyroid and had spontaneous onset of puberty and normal sexual development with age range 15-38 years who presented to gynecology OPD and diagnosed to have PCOS according to ESHRE/ASRM criteria were included in the study after obtaining a written informed consent. Women with other causes of hyperandrogenism, hypothyroidism, on oral contraceptive pills and patients on any medication known to affect carbohydrate metabolism for at least 3 months before the study, were excluded from the study.

Patients were examined and investigated after a detailed history. History of hirsutism, acne, alopecia, infertility, menstrual irregularity, history of voice change, history of weight gain and detailed obstetric history etc was noted. BMI (body mass index) was calculated by the formula weight in kg/ height in meter square, after measuring height in meter and weight in kg in all PCOS women. Patients with BMI$\leq$23 kg/m^2 were put in **Lean PCOS Group** and patients with BMI>23 kg/m^2 were labelled as **overweight / obese PCOS**. Waist to hip ratio was calculated. Abnormal waist to hip ratio is taken as $\geq$0.85. General physical examination was done with special emphasis on Blood Pressure, hirsutism (Ferriman Gallway score $\geq$8), acne, oily skin, alopecia, acanthosis nigricans, and clitoromegaly.

All studies were performed in the follicular phase, 2 to 4 days after a spontaneous or progestin-induced menses. All women were subjected to a set of blood investigations which comprised of fasting lipid profile (Cholesterol, LDL, HDL and Triglyceride), 75 g Oral glucose tolerance test, fasting serum Insulin, HbA1c, Fasting Insulin: glucose ratio (HOMA-IR), hormonal profile including LH, FSH, total Testosterone, Prolactin, DHEAS and TSH. Hormonal estimation was done by ELISA. Deranged lipid profile was considered if any of the cholesterol, triglycerides, and HDL-cholesterol were $\geq$200, $\geq$150, and <50 mg/ dL, respectively. Insulin resistance was calculated by HOMA-IR=serum insulin (in micro IU/mL) × fasting glucose (mg/dl) ÷ 405. HOMA-IR>2.5 was considered abnormal.

Trans-abdominal scan was done for unmarried and trans-vaginal scan was done for married women. The size of ovaries, volume, morphology, and the number and size of follicles was noted. Polycystic ovarian morphology was defined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume more than 10 cm^3 along with stromal hyperplasia. The various clinical, metabolic, and hormonal characteristics were entered in Microsoft excel sheet for both the two groups and compared using unpaired, two-tailed Student's t-test chi-square test, and fisher exact test. Significance was set at $P < 0.05$.

RESULTS

Out of 50 women who were diagnosed to have PCOS according to ESHRE/ASRM criteria, there were more obese or overweight women (56%) with BMI > 23 and mean BMI of 29.52$\pm$2.43 than the rest 22 (44%) who were lean with BMI $\leq$ 23 (Mean BMI 21.87$\pm$1.19). The women in obese group were of older, belonging to a higher socioeconomic status than the lean group, with no difference in their parity (Table 1).

The most common presentations were menstrual irregularities in the form of amenorrhea, oligomenorrhoea, polymenorrhoea, and inter-menstrual bleeding irrespective of their weight. The other manifestations' were hirsutism, infertility, acne and obesity (Table 2). Weight gain, obesity especially of abdominal type with higher waist to hip ratio (>8.5) were present in all obese women as it was the main criterion for group B. There was a more significant association of family history of PCOS and diabetes in obese than in lean women. There was no difference in features of hyperandrogenism in both groups as evident by hirsutism, acne, oily skin and clitoromegaly. Although the incidence of hirsuitism was similar in obese and non-obese but its severity as judged by Ferriman Gallway Score was more in obese women (Table 2).

Table 1: Characteristics of PCOS women

	LEAN PCOS BMI<23Kg/m^2 (GROUP A)	OBESE PCOS BMI>23kg/m^2 (GROUP B)	P Value
NUMBER OF PATIENTS	**22** (44%)	**28** (56%)	
MEAN BMI	21.87±1.19	29.52±2.43	
MEAN AGE	23.32±3.14	26.28±4.18	0.029
SOCIOECONOMIC CLASS ≥ middle class ≤ Lower Class	 0% 100%	 39.3% 60.7%	 0.001
NULLIPARITY	12 (54.5%)	11(39.3%)	0.233

Table No. 2 Clinical Presentation of PCOS women

CLINICAL FEATURES	GROUP A (LEAN PCOS) N=22		GROUP B (OBESE PCOS) N=28		P value
	NUMBER	%	NUMBER	%	
MENSTRUAL IRREGULARITY	20	90.9	27	96.4	0.576
HIRSUTISM	18	81.8	24	85.7	0.718
INFERTILITY	10	45.4	11	39.2	0.661
ACNE/OILY SKIN	2	9.1	7	25	0.266
WEIGHT GAIN	0	0	15	53.6	<0.001
OBESITY	0	0	28	100	<0.001
WAIST TO HIP RATIO >8.5	1	4.5	28	100	0.001
ALOPECIA	0	0	2	7.1	0.497
CLITOROMEGALY	0	0	1	3.6	1.0
ACANTHOSIS	2	9.1	4	14.3	0.683
FAMILY H/O PCOS	1	4.5	11	39.3	<0.001
FAMILY H/O DIABETES	1	4.5	10	37.7	0.04
HIRSUTISM SCORE **Ferriman Gallway Score** No(<8) Mild(9-16) Moderate(17-25) Severe(>25) MEAN SCORE	 4 18 0 0 8.59± 1.94	 18.2 81.8 0 0	 4 6 15 3 16.61± 6.64	 14.3 21.4 53.6 10.7	 <0.001

Independent of obesity per se, PCOS is associated with a higher prevalence of insulin resistance, impaired glucose tolerance and type 2 diabetes as evident by a high incidence of deranged GTT, high HOMA-IR score (>2.5) and high HbA1c (>6.5) in both the groups with comparable values. The fasting insulin level was higher in obese group (13.58µIU/ml) than in lean group (11.3µIU/ml). p value =<0.001(statistically significant). 88% of all PCOS were insulin resistant (HOMA-IR>2.5) with a preponderance in obese women. (Table No.3)

Mild hypertension (>130/85) was seen in 24% of all PCOS and all of them were obese. None of lean PCOS was hypertensive. Obese women with PCOS had higher concentrations of total cholesterol, LDL, low HDL than their lean counterparts. (Table No.3)

TABLE 3: Glucose metabolism and other metabolic features

	GROUP A (LEAN PCOS)		GROUP B (OBESE PCOS)		P value
	No	%	No	%	
NORMAL GTT	18	81.8	17	60.8	0.15
IMPAIRED GTT	4	18.2	8	28.6	
DIABETES	0	0	3	10.7	
FASTING INSULIN >10 microlU/ml	19	86.4	25	89.29	
MEAN FASTING INSULIN	11.30±1.91		13.58±2.15		<0.001
FASTING INSULIN: GLUCOSE RATIO	0.13±0.02		0.15±0.03		0.001
HOMA-IR >2.5	19	86.4	25	89.3	0.009
MEAN HUMA IR	2.44±0.45		2.93±0.75		
MEAN HbA1c	6.29±0.30		6.18±0.48		
HbA1c < 5.7 HbA1c 5.7-6.5 HbA1c >6.5	0 18 4		2 21 5		0.363
MEAN HDL(mg/dl)	56.27±5.17		52.89±7.65		0.082
MEAN LDL(mg/dl)	128.22±14.03		141.43±24.12		0.027
MEAN TRIGLYCERIDE(mg/dl)	123.18±14.73		139.93±28.17		0.015
MEAN TOTAL CHOLESTEROL(mg/dl)	176.50±16.92		201.46±36.91		0.005
DERRANGED LIPID PROFILE	3	13.6%	11	39.3%	0.45
MILD HYPERTENSION	0	0%	12	42.9%	<0.001

Serum gonadotrophin derangement with low FSH and high LH was seen in PCOS women irrespective of their BMI. A high LH: FSH ratio (>2) was seen in 40% of all PCOS women. The mean LH: FSH ratio was 2.31.The difference in LH: FSH ratio was not statistically significant between obese (2.16) and lean (2.51) groups. Serum prolactin and thyroid profile were found to be within normal range in all subjects. Elevated serum testosterone and high DHEAS were seen more commonly in obese PCOS than their lean counterpart (Table No. 4) Ovarian morphology consisted of enlarged ovarian volume, necklace appearance, and large number of follicles. The mean ovarian volume of all the PCOS women was 15.78±4.96. However it was higher in obese group (18.99) than in lean group (11.69). Though there was no difference in number of follicles, necklace appearance was more often seen in obese PCOS. Endometrial thickness was unremarkable in study groups. (Table No.4)

Table 4: Endocrine Profile of PCOS Women and Ultrasound Morphology

	GROUP A (LEAN PCOS)		GROUP B (OBESE PCOS)		P Value
SERUM FSH <10 (mIU/ml)	21	95.5%	28	100%	0.440
SERUM LH >10 (mIU/ml)	15	68.2%	13	46.4%	0.248
MEAN LH:FSH RATIO	2.51±1.20		2.16±1.07		0.274
S.PROLACTIN (microg/l)	12.82±3.67		13.57±4.26		0.513

SERUM DHEAS(µg/dl)	313.32±67.16		405.57±50.51		<0.001
SERUM TESTOSTERONE(ng/ml)	0.39±0.31		1.24±0.60		<0.001
TSH(microg/dl)	1.80±0.46		2.73±0.48		
OVARIAN VOLUME <10cm^3	0	0%	0	0%	
OVARIAN VOLUME 10-25cm^3	22	100%	27	96.4%	0.001
OVARIAN VOLUME >25cm^3	0	0%	1	3.6%	
MEAN OVARIAN VOLUME	11.69±0.84		18.99±4.45		
MEAN NUMBER OF FOLLICLES	15.78±4.96		13.68±1.47		
NUMBER OF FOLLICLES <12 >12	10 12	45.5% 54.5%	6 22	21.4% 78.6%	0.483
NECKLACE APPEARANCE	6	27.28%	28	100%	<0.001
ENDOMETRIAL THICKNESS >4	1	4.5%	3	10.7%	0.621

DISCUSSION

PCOS is now recognized as a common, heterogeneous, heritable disorder affecting women anytime in their life. The clinical presentation of PCOS varies from menstrual disturbances, clinical features of hyper-androgenism, and infertility. The use of many and varied definitions of the syndrome by investigators has seriously confused the literature and has hampered the scientific clarification of the genetics, aetiology, clinical associations and assessment of the treatment and later sequelae of this prevalent syndrome. [5]

The prevalence of obesity varies in these women, and in present study it was more common as 56% were found to be obese/ overweight with BMI>23kg/m^2. Asian Indians have higher percentage body fat, abdominal adiposity at lower or similar BMI levels as compared to white Caucasians. Asian Indians are more predisposed to develop insulin resistance and cardiovascular risk factors at lower levels of BMI as compared to other ethnic groups. [6]

Obese PCOS usually presents in older age group than lean PCOS as in present study, mean age was higher in obese group (26.28±4.18 years) than in lean group (23.32±3.14 years). A J Morales et al (1996) observed that the mean age of lean PCOS was 26.7+1.9 years and obese PCOS was 27.9+2.1 years which is comparable to our study. [7] PCOS has its origin during adolescence and its metabolic abnormalities worsen as the age increases and with obesity. PCOS was more common in obese women from affluent society than in lean women.

Clinical presentation in terms of menstrual abnormalities, hirsutism, acne and infertility were comparable in both the groups, however the degree of hirsutism was exaggerated in obese. The presence of family history of PCOS and obesity was seen to be more in obese group than in lean group. The prevalence of central obesity was higher in obese group (Mean WHR 0.97) than in lean group (Mean WHR 0.82).

Independent of obesity and consistent with the increased insulin resistance, women with PCOS displayed an increased prevalence of impaired glucose tolerance and type 2 diabetes in our study as evident by a high incidence of deranged GTT, high HOMA-IR score (>2.5) and high HbA1c (>6.5). Several studies have pinpointed insulin resistance (IR) as the fundamental link associating PCOS and metabolic syndrome, although IR may be present in PCOS independently of obesity. [8] Boudreaux et al., 2006 reported a 5-fold risk of developing DM2 over a period of 8 years in women with PCOS, compared with the risk calculated using age- and weight-matched controls. [9]

The prevalence of mild hypertension was more in obese group than in lean group which is comparable with other studies. [10,11] Obese PCOS had significantly higher deranged lipid profile than the lean PCOS women. Jan Holte (1994) studied serum lipoprotein lipid profile in women with PCOS and their BMI matched controls and observed obese women with PCOS had higher concentrations of total cholesterol, LDL, low HDL than their lean counterparts. But he also inferred that the atherogenic lipoprotein pattern is entirely accounted by obesity and there is no significant effect of PCOS or hyperinsulinism on lipoprotein profile. [12]

PCOS women had high prevalence of elevated serum LH and low Serum FSH level, but they were comparable in both groups. Serum LH: FSH ratio (>2) did not differ in both groups. Dipankar et al (2005) noted that LH/FSH ratio>2 in 46.93% and mean LH: FSH ratio 2.011.46. [13]

Obese women with PCOS show higher levels of testosterone and adrenal androgens, than non obese women as seen in other studies. [12, 13] Hyperandrogenism per se may play a role in favouring insulin resistance and the simultaneous development of the abdominal obesity phenotype in PCOS. Thus a vicious circle between hyperandrogenism and hyperinsulinemia represent the specific biological basis for the development of obese PCOS phenotype in PCOS women.

The mean ovarian volume was higher in obese group (18.9) than lean (11.69) with mean follicle number of lean and obese PCOS as 15.78±4.96 and 13.68±1.47. Necklace appearance on ultrasound was also more in obese group. Pelvic ultrasonography may be very helpful in the evaluation as well, but polycystic ovaries are not specific for PCOS with over 20% of "normal" women having this finding. [14]

CONCLUSION

The present study reveals that obesity, seen in 56% of our patients, plays an important role in clinical, hormonal and metabolic alterations in women with Polycystic Ovarian Syndrome.

Although the clinical features like menstrual disturbances, infertility, hirsutism, acne, and acanthosis nigracans were present in most PCOS women irrespective of their weight, the endocrine and metabolic effects were exacerbated by obesity.

A higher degree of hyper-androgenaemia as evidenced by increased Testosterone and DHEAS levels and higher magnitude of hirsutism (FG Score) was present in obese PCOS as compared to their lean counterpart. The polycystic ovarian morphology was significantly accentuated in obese cases. However, altered gonadotropin milieu, with raised LH and a high LH: FSH ratio, did not correlate well with BMI.

The consequences of PCOS extend beyond the reproductive axis. Hyper-insulinaemia and Glucose intolerance were present in both Lean and obese PCOS, but obesity aggravates the underlying insulin resistance, as judged by a higher HOMA-IR score in obese PCOS. Metabolic abnormalities like hypertension and deranged lipid profile and the concurrent cardiovascular health risks were more frequently observed in obese patients. Thus they are at substantial risk of developing metabolic syndrome and obesity was a significant contributor to its development.

Hence it is suggested that life style modification such as exercise and weight reduction and periodic monitoring should be done in all PCOS women and more so in obese. The most important aspect of long term care of PCOS is managing cardiovascular risks such as obesity, insulin resistance, diabetes, hypertension and elevated blood lipids. Early recognition and intervention should be considered the cornerstones of PCOS treatment.

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