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Analysis of Metabolic Syndrome in females with Polycystic Ovarian Syndrome

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Abstract
Backgrounds: *The metabolic syndrome (MBS) is a cluster of cardiovascular risk factors associated with excess of fat. The MBS is more common among women in PCOS than in normal women particularly in those with hyperinsulinemia and obesity.*
Objectives: *To determine the prevalence of metabolic syndrome and its main determinants in women with PCOS.*
Methods: *Hundred women, 50 with polycystic ovarian syndrome (PCOS) and 50 ages matched normal women served as a control. A prospective observational study was conducted in the age groups of 17-40 years in the gynaecological OPD in two tertiary centres from July 2016 to June 2017. Sociodemographic data, waist circumference (WC), height, weight, BMI and blood pressure were recorded. A fasting blood sample was obtained for serum glucose and lipid profile determination. For assessment of the metabolic syndrome (MBS) in the study groups, the NCEP ATPIII guideline was used.*
Results: *The prevalence of MBS was 40% (20/50) in PCOS, 4 fold higher than that reported for women in the control group. Thirteen patients (57%) belonged to 26-40 years and 7 (26%) in 17-25 years. Waist circumference ≥ 88 cm and BP(≥ 130/85 mm of Hg) were found among 52% and 40% of patients with PCOS respectively in comparison to 18% and 10% of control women respectively(P=0.001).The study showed significant rise in triglyceride(≥ 150 mg/dl), HDL-cholesterol (< 50 mg/dl) and fasting insulin (≥25μIU/ml)levels. The main menstrual disorders associated with PCOS was oligomenorrhea, observed in 92% of women compared to 12% in control women (P=0.001). Hirsutism was found among 62% of PCOS women in comparison to 4% of control (P =0.001).Multiple logistic regression analysis shows that BMI (OR=2.053; 95% CI: 1.349-3.123; Wald statistics 11.284; P=0.001) and age (OR = 0.858; 95% CI: 0.703 -1.048; Wald statistics 2.256; P=0.133) are the associated factors for MBS among PCOS patients.*
Conclusion: *The prevalence of metabolic syndrome in PCOS is high. Age above 25 years and waist circumference >88 cm with elevated BMI were powerful predictors of metabolic syndrome amongst PCOS women.*

Keywords: *metabolic syndrome, polycystic ovarian syndrome, hyperinsulinemia, prevalence*

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I. Introduction

Polycystic ovarian syndrome is a heterogeneous disorder characterized by chronic anovulation, hyperandrogenism and polycystic ovaries. It affects only 5-10% of women in the reproductive age group and is considered one of the most common endocrine disorders in premenopausal women[1]**.** The Diagnosis of PCOS is based on the presence of any two of the following three components of Rotterdam European Society for Human Reproduction and Embryology/ The American Society of Reproductive Medicine (ESHRE/ASRM) – sponsored PCOS consensus workshop group revised 2003 ciieteria[2]; oligoovulation, and or anovulation, hyperandrogenism (clinical and /or biochemical) and polycystic ovaries (ultrasonographical) in absence of other causes of hyperandrogenism.

Metabolic syndrome is characterized by a cluster of metabolic abnormalities including abdominal obesity, glucose intolerance, hypertension and dyslipidemia. The diagnosis of MBS identifies patients at increased risk of developing cardiovascular disease [3, 4, 5]. A number of expert groups have attempted to develop a unifying definition for the MBS. One of the most widely accepted of these definitions have been produced by

The National Cholesterol Education Program- Third Audit Treatment Panel (NCEP ATP III) (Executive Summary of the third report of the national cholesterol education program, 2001)[6]. According to this programme MBS includes the presence of any three or more factors of the five components—increased waist circumference(≥88cm), high fasting plasma glucose level (≥110 mg/dl), increased blood pressure (≥130/85 mm of Hg), serum triglyceride level ≥150 mg/dl and low serum HDL cholesterol level (< 50 mg/dl).

Women with PCOS have basal and glucose stimulated hyperinsulinemia, suggesting the presence of insulin resistance. It is now become clear that the syndrome also has a component of metabolic disorder, beyond reproductive morbidities. MBS is associated with high risk of atherosclerosis, cardiovascular disease, thrombotic events and mortality. The prevalence of type II diabetes in menopausal women with previous PCOS was higher than observed in the general population; 15% versus 2.3%[7].

The aim of this study is to establish the relation between PCOS and metabolic syndrome and to define the different risk factors (characteristics) associated with it and to compare them with MBS and without MBS.

II. Materials and methods

The prospective observational study was conducted in the Dept. of Obstetrics and Gynecology at Burdwan Medical College and Hospital, Burdwan and R.G. Kar Medical College and Hospital, Kolkata on 100 subjects (50 women having PCOS designated as a case and another 50 apparently healthy woman without PCOS as a control) in the reproductive age groups of 17-40 years over a period of one year from 1st July 2016 to 30th June 2017.The study was approved by instititutional research and ethics committee. Written informed consent was taken from the studied women in local languages.

All women in the present study attending institutional gynaecological OPD underwent questionnaire and examination with predesigned and pretested schedule. The diagnosis of PCOS was based upon the presence of any two the following three decisive factors[2].

i. Oligo-ovulation, and or anovulation,
ii. Hyperandrogenism (Clinical and /or biochemical)
iii. Polycystic ovaries (Ultrasonographical) in absence of other causes of hyperandrogenism

Inclusion criteria

- Age groups 17-40 years
- Diagnosed cases of PCOS
- Apparently healthy woman without PCOS

Exclusion criteria

Patients who were diabetic and hypertensive, or having thyroid dysfunction, hyperprolactinemia, non classical congenital adrenal hyperplasia (NCCAH), Cushing's syndrome, acromegaly or use of medications known to affect sex steroid metabolism, such as oral contraceptive pills or insulin sensitizing drugs and other hormonal agents known to affect menstrual cycle for at least 3 months before collection of samples, were excluded from the study.

Detailed history was taken from every participant and through clinical examinations was carried out. Measurements such as waist circumference, weight and height and blood pressure readings were recorded. Waist circumference in centimetre was measured at a point midway between the lowest rib and the iliac crest using a soft non-stretchable tape and was taken at the end of normal expiration. Blood pressure recording was obtained from the right arm of the patients at 5 minutes intervals using a standard sphygmomanometer machine after 30 minutes of rest. All the measurements were done by same person to reduce any bias. Weight in kilogram was weighted while the clothes on using weighing machine and height were recorded in centimetre. BMI was calculated as weight in kilogram divided by the square of height in meter (kg/m^2). According to WHO, overweight is defined as BMI 25.0-29.0 kg/m^2 and obese as ≥30 kg/m^2.

Collection of blood samples: 10 ml of clotted venous blood was collected after an overnight fasting of 12 hours. Serum was separated and the following parameters were estimated

- Estimation of fasting blood glucose level
- Estimation of total cholesterol
- Estimation of high density lipoprotein (HDL) cholesterol
- Estimation of triglycerides
- Fasting insulin
- Fasting glucose/insulin ratio

For assessment of the metabolic syndrome (MBS) in the study groups the NCEP ATPIII[6] guideline was used.

Statistical analysis

The sample size was calculated based on the formula, $n=Z^2 \times (p) \times (1-p)/\Delta^2$, where n = the sample size; Z= Z value (e.g. 1.96 for 95% confidence level); Δ is the confidence interval i.e. 0.04 for ± 4% and p = percentage

picking a choice i.e. 5%, expressed as decimal to 0.05. So, $n = (1.96)^2 \times (0.05) \times (1-0.05) / (0.04)^2$. n=114, if there is 10% drop out rate; the calculated sample size is 103.

Categorical variable was expressed as a number of patients and percentage and Chi-square test was used for comparison between groups as regard qualitative variables. Pearson's correlation co-efficient was used to compare correlations. A multiple logistic regression was chosen as the dependent variables of the binary outcome. Findings of the final model were presented with an adjusted odds ratio (OR), its 95% confidence interval and corresponding P- value. P<0.05 was considered to be statistically significant. All statistical analysis was done in Microsoft XL and SPSS16.

III. Results

The median range of women with PCOS was 25 years (range 17-37 years). Among the 50 women with PCOS, 20 met the criteria of metabolic syndrome (MBS). It has been observed that more women in higher age group (56.52%) were suffering from features of MBS in comparison to only 25.93% in younger age group and there was a significant age difference in prevalence of MBS in women with PCOS (p <0.028) (Table 1)

As shown in Table 2, the most prevalent of MBS components among the PCOS women were waist circumference ≥ 88cm in 52 % of cases , followed by low HDL (< 50mg/dl) , high blood pressure(≥ 130/85 mm of Hg) and high triglyceride level (≥150 mg /dl) in 42%, 40% and 38% of cases respectively. The least prevalent component was high fasting blood glucose level (≥ 110mg/ dl) and it was noted only in 16% of PCOS women. Concerning the marker of insulin resistance (fasting blood sugar /insulin ratio < 4.5) was significantly more prevalent in women with PCOS than those without PCOS (p=0.005).

Table 3 illustrates the clinical manifestations in women with PCOS and control groups. The most common presentations of PCOS feature was oligomenorrhea (92%). Infertility was present in 82% of such women. USG diagnosed 90% of these women with polycystic ovaries.

The positive and negative predictive values are very important to assess the presence or absence of individual component of MBS. The presence of fasting blood glucose of 110 mg/dl or greater had the highest positive predictive value (100%) for the presence of MBS. However only eight women met this criterion. Concerning blood pressure (≥ 130/85 mm of Hg) 100% of women met also the criteria of metabolic syndrome. On the other hand 95% of women with HDL cholesterol less than 50 mg/dl met the criteria of MBS. Elevated triglyceride is a common finding, also had high positive predictive value for the presence of metabolic syndrome in 74% (14 out of the 19 women having triglyceride level greater than or equal to 150 mg/dl). Waist circumference greater than equal to 88 cm had 77% positive predictive value. WC, HDL cholesterol, triglycerides and blood pressure each had high negative predictive value. Of the 24 women whose WC was less than 88cm, 24(100%) did not met the criteria for the MBS. Of the 29 women with an HDL-C more than 50 mg/dl, all (100%) did not meet the criteria of MBS. Finally 25 of the 31 (80.65%) woman with a triglyceride level less than 150 mg/dl also did not met the criteria of metabolic syndrome. The negative predictive value of hypertension were also 100% but that of elevated fasting level of glucose was 71.43% only (Table 4)

Fig1. Shows correlation between BMI (kg/m^2) and waist circumference (WC, cm) of studied women with PCOS patients (n=50, age range17-37 years).Waist circumference of 88 cm corresponded to BMI of 25.8 kg/m^2(r=0.67; P=0.000000)

IV. Discussion

The present study indicates 40% prevalence of metabolic syndrome in PCOS women. This is closely related to the observations of 42% and 47.3% prevalence made by Dey et al[8] and Dokras

et al[9]. Our study indicates that the prevalence of MBS was higher (56.52%) in the age group of 26-40 years in comparison to only 26% in 17-25 years of age. Dey R et al[8] in their study found that the prevalence of MBS in the age group of 15-25 years was 20.7% where as it was 71.4% in 25-35 years. So more women at higher age groups were suffering from features of MBS in comparison to younger age groups and there was a significant age difference in prevalence of MBS in women with PCOS in our study(P=0.028)[Table 1]

The present study noted the waist circumference which depicts central obesity ≥ 88cm in 52% of cases and 18% of controls (P <0.001) (Table 2) . Our finding corresponds with the result of Alwaeely et al[10] who observed 60% of women with PCOS were with waist circumference of > 88 cm as compared to 25% of control (P<0.001), but differ from the study done by Ehrmann et al[11] which supports high value of waist circumference by citing 80% of subjects above 88 cm. Dislipidemia in association with PCOS is a constant observation in several studies[12-15]. Our study exhibits abnormal lipid profile with increased TG levels and elevated HDLC level in PCOS patients. Fasting insulin level was increased in 26% of cases and 8% of control (P=0.017)(Table 2). It shows a significant difference among women with metabolic syndrome in comparison to those without metabolic syndrome as supported by Dokra et al study in 2005[9].

Menstrual abnormalities particularly oligomenorrhea and hirsutism are consistent finding in association with PCOS. We found oligomenorrhea in 92% and hirsutism in 62% of women with PCOS (Table 3). These

findings are due to hyperandrogenism present in PCOS patients. Presence of fasting blood glucose of 110 mg/dl or greater had highest positive predictive value (100%) which is in concordance with the study done by Dey et al[8]. HDL cholesterol less than 50 mg/dl had 95% positive predictive value for the metabolic syndrome which is supported by Dokras et al[9] showing triglyceride/HDL-C ratio; more than 3 has high positive predictive value (85.5%). This correlates well with insulin resistance in severely obese and non diabetic individuals[16]. Similarly, waist circumference of ≥ 88cm had positive predictive value of 77% in our study where as it was 100% according to Dey et al[8]. In the present study waist circumference of 88 cm corresponds to BMI of 25.8 kg/m^2 (Fig1). None of the 20 women with BMI less than 25 kg/m^2 met the criteria of MBS. Ehrmann DA et al[11] found in their study that no women with BMI≤27.0 kg/m^2 met the criteria for MBS. This difference in cut-off value may be due to the accumulation of subcutaneous fat in Indian female population than western women having more or less same BMI. Misra et al[17] in their study showed a low cut-off value of BMI (<23 $kg/m^{2)}$ in Indian women. Fasting insulin (≥ 25µIU/ml) level was noted in 60% (12/20) of cases having MBS with clinical significance in the present study. This has been supported by the study of Dokras et al[9] and Ehrmann et al [11]. In our study prevalence of MBS is 40% in cases and 10% in age matched control (P=0.001) which shows higher(4 fold) prevalence of MBS in PCOS women, but most of the published studies reported 11 fold increased risk of metabolic syndrome in PCOS women when compared to control [9, 14].

V. Conclusion

Women with PCOS undoubtedly are at greater risk of metabolic syndrome than normal women. PCOS presents with overt symptoms of infertility, hirsutism and acne to a large extent. It is noted from our study that the MBS manifests at an early age in women with PCOS. Prevalence of MBS in PCOS women is strongly influenced by increasing age (above 25 years) and elevated BMI with waist circumference of ≥ 88cm. Blood pressure, fasting blood glucose and serum triglyceride levels are powerful predictors of MBS in PCOS women. Hyperinsulinemia also has a critical link between PCOS and metabolic syndrome. So, detection of MBS in PCOS women and early measures for primary prevention of its long term sequel is needed.

Limitations

In our study NCEP ATP III criteria was used for diagnosis of MBS, which is not ethnicity specific. The study was conducted only in the two centres of east zone in India with small sample size for shorter duration of time without follow-up of patients. However, a large prospective multicenter controlled trial has to be designed with study of long term effect of different biochemical abnormalities.

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Table 1. Age stratified prevalence of MBS among PCOS

Age (years)	With MBS (n=20)	without MBS (n=30)
17-25 (n=27)	7(25.93%)	20(74.07%)
26-40(n=23)	13(56.52%)	10(43.48%)
Total (n=50)	20(40%)	30(60%)

Chi square= 4.844; DF=1; P <0.02

Table2. Distribution of individual components of metabolic syndrome in case and control groups

Components of metabolic syndrome	Case (n=50) n (%)	Controls (n=50) n(%)	p-value
Waist circumference (≥88 cm)	26(52)	9(18)	0.001
Hypertension (≥ 130/85 mm of Hg)	20(40)	5(10)	0.001
Fasting blood glucose (≥ 110mg/dl)	8(16)	2(4)	0.046
Triglycerides (≥ 150 mg/dl)	19(38)	5(10)	0.001
HDL-cholesterol (< 50 mg/dl)	21(42)	(14)	0.002
Fasting insulin (≥ 25µIUml)	13(26)	4(8)	0.017
FBS/ fasting insulin (<4.5)	15(30)	4(8)	0.005

Table 3. Clinical features in women with PCOS compared with control

Variables	Case (n=50) n (%)	Control (n=50) n(%)	Total	P value
Oligomenorrhea 46(92)	6(12)	52	0.001	
Polycystic ovaries (USG) 45(90)	3(6)	48	0.001	
Infertility	41(82)	7(14)	48	0.001
Hirsutism	31(62)	2(4)	33	0.001
Acne	21(42)	7(14)	28	0.002
Hyper pigmentation	6(12)	0	6	0.012

Table 4: Positive and negative predictive values of each component of the metabolic syndrome in PCOS women

Components of the MBS	No. of subjects with criteria n=50 n (%)	No. of subjects with criteria and at least three total criterion n=20 n (%)	Percentage of subjects with positive predictive value (%)	No. of subjects without criterion n=50 n (%)	Percentage of subjects without criterion and less than total criterion n=30	with negative predictive value(%)

	n (%)					
Waist Circumference ≥ 88 cm	26(52)	20(100)	76.92	24(48)	24 (80)	100
Hypertension ≥ 130/85 mm of Hg	20(40)	20(100)	100	30(60)	30(100)	100
Fasting blood glucose≥ 110 mg /dl	8(16)	8(40)	100	42(84)	30 (100)	71.43
Triglyceride ≥150 mg/dl	19(38)	14(70)	73.68	31(62)	25 (83.34)	80.65
HDL-C <50 mg/dl	21(42)	20(100)	95.24	29(58)	29 (96.67)	100

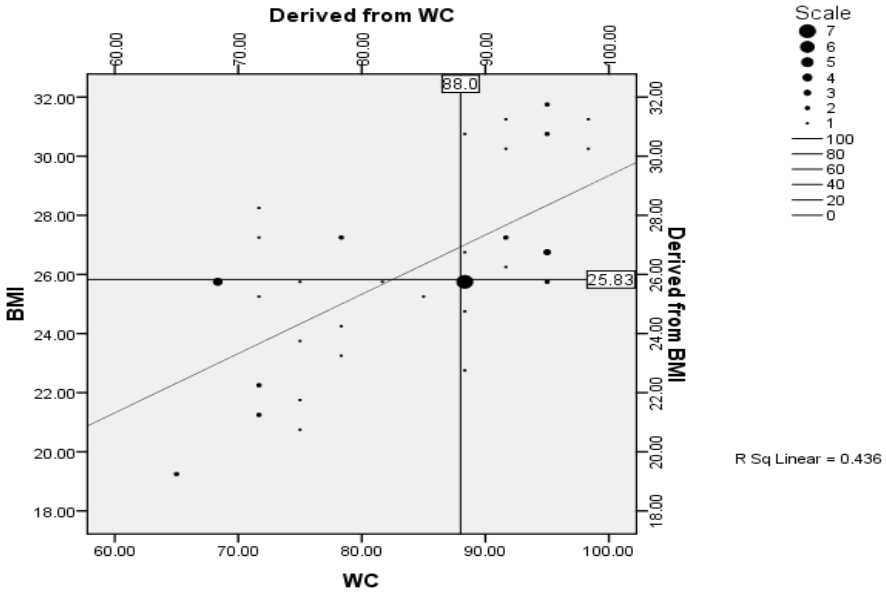

Fig1. Correlation between BMI (kg/m^2) and waist circumference (WC, cm) of studied women with PCOS [n=50, Correlation coefficient(r) =0.67; P=0.000000].Waist circumference (median 88 cm) corresponds to BMI of median 25.83 kg/m^2.

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