

Divergences in Clinical, Anthropometric, Metabolic, and Hormonal Parameters among Different Phenotypes of Polycystic Ovary Syndrome Presenting at Endocrinology Outpatient Departments: A Multicenter Study from Bangladesh

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous androgen-excess disorder. Data comparing the PCOS phenotypes in Bangladesh are scarce. **Objectives:** The objective of this study was to find out the distribution of Rotterdam classified PCOS phenotypes and to compare the phenotypes concerning clinical, anthropometric, metabolic, and hormonal parameters.

Subjects and Methods: In this cross-sectional study, 370 PCOS cases in the age group of 20–45 years diagnosed by the Rotterdam consensus criteria were recruited from the endocrinology outpatient departments of several tertiary hospitals of Bangladesh. Metabolic syndrome (MetS) was diagnosed using the International Diabetes Federation criteria. **Results:** The prevalence of phenotypes A, B, C, and D were 59.2%, 14.1%, 11.9%, and 14.9%, respectively. More than one-third (34.6%) of the women had pre-hypertension (pre-HTN)/hypertension (HTN), 34.1% had abnormal glucose intolerance (AGT), 93.0% had dyslipidemia, and 57.0% had MetS. The hyperandrogenic phenotypes (A, B, and C) had higher prevalence of pre-HTN/HTN, AGT, dyslipidemia, and MetS compared to the normoandrogenic phenotype D, though the differences were statistically insignificant. The clinical and biochemical markers of hyperandrogenism (Ferriman-Gallwey score, hirsutism, acne, and serum testosterone levels) did not differ among the hyperandrogenic phenotypes. The serum prolactin level was highest in phenotype C. No differences were observed in most other clinical, anthropometric, metabolic, and hormonal parameters among the four phenotypes. **Conclusion:** Phenotype A is the most prevalent phenotype of PCOS in our setting. The prevalence of MetS was considerably high. Most of the clinical, anthropometric, and metabolic parameters were similar across the four PCOS phenotypes in this study.

KEYWORDS: Polycystic ovary syndrome, polycystic ovary syndrome phenotypes, metabolic syndrome, dyslipidemia, diabetes mellitus, central obesity

INTRODUCTION

The polycystic ovary syndrome (PCOS) was first reported in 1935, and at present, it is the most common endocrinopathy in the women of reproductive age, affecting almost 6%–10% of

them.^[1] The pathogenesis of PCOS is complex and not precise. Clinically, PCOS is characterized by oligo/

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anovulation manifested as irregular menstruation and hyperandrogenism. Beyond its effect on reproductive health, PCOS has many adverse metabolic and cardiovascular manifestations and thereby is a long-term health concern across the lifespan.^[2] Despite the widespread prevalence of PCOS, the variability of clinical presentations, and the complexity of its etiopathogenesis make PCOS a problematic diagnosis to place in everyday clinical practice.^[3] In the last few decades, many attempts have been made to standardize the diagnosis of PCOS. In 1990, a subset of criteria was suggested by the National Institutes of Health, in which both hyperandrogenism (clinical or biochemical) and chronic anovulation were required for the diagnosis.^[4] Following this, a consensus workshop group, sponsored by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, proposed that for diagnosis of PCOS at least two of the following three criteria are mandatory: (i) chronic ovulatory dysfunction (OD) in the form of oligo/anovulation, ii) clinical and/or biochemical hyperandrogenism (HA), and iii) polycystic ovaries on ultrasound (PCO) in addition to the exclusion of other etiologies such as Cushing's syndrome, congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, and androgen-secreting tumors; this criterion is popularly known as the Rotterdam criteria.^[5] Finally, in 2009, the Androgen Excess and PCOS (AE-PCOS) Society Task Force recommended that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or PCO), and the exclusion of related disorders.^[6]

The Rotterdam criteria are most widely used for the diagnosis of PCOS. Since PCOS tends to present as a spectrum of diseases, the Rotterdam criteria divided the disease into four phenotypes: (i) Phenotype A, also known as frank, full-blown or classic PCOS (OD + HA + PCO), ii) Phenotype B, also known as classic non-polycystic ovary PCOS (OD + HA), iii) Phenotype C, also called nonclassic ovulatory PCOS (HA + PCO), and iv) Phenotype D, also called nonclassic mild or normoandrogenic PCOS (OD + PCO).^[5] The AE-PCOS criteria have excluded the normoandrogenic phenotype in the diagnosis of PCOS.^[6]

To date, it is not clear whether PCOS represents a unique clinical entity or is an aggregate of different disorders with a similar clinical presentation. It is also still unclear if these four phenotypes represent a broad spectrum of the same syndrome, that is, PCOS.^[7] Researchers have observed heightened risks of insulin resistance, diabetes mellitus (DM), cardiovascular disease,

metabolic syndrome (MetS), endometrial dysfunction, and pregnancy complications in hyperandrogenic phenotypes of PCOS compared to the normoandrogenic and ovulatory PCOS.^[5-8] Women with ovulatory PCOS appear to have lower risks of endometrial carcinoma.^[9] Thus, the phenotypic classification of PCOS may guide the clinicians to choose the most appropriate therapeutic strategy for such patients.

There is marked heterogeneity in the prevalence of PCOS phenotypes not only across different countries and races but also the clinical specialties attended by such patients.^[7,8] Not enough work has been done to study the different PCOS phenotypes in our setting. The present study aimed to investigate the percentage occurrence of different phenotypes of PCOS attending endocrinology outpatient departments (OPD) of several tertiary hospitals of Bangladesh and to compare their clinical, anthropometric, metabolic, and hormonal characteristics.

SUBJECTS AND METHODS

This cross-sectional study was conducted from January 2017 to December 2019, in the endocrinology OPD of several tertiary hospitals in Bangladesh. All women in the age group of 20–45 years presenting with menstrual irregularities and/or hirsutism were evaluated for the presence of PCOS. Patients previously diagnosed as DM, thyroid dysfunction, congenital adrenal hyperplasia, Cushing's syndrome, or other endocrinopathies, those with a chronic debilitating illness and those taking oral contraceptive pills or other hormonal methods of contraception, metformin, and any drug treatment for PCOS or hirsutism were excluded. The protocol of the study obtained approval from the institutional review board of Mymensingh Medical College, Bangladesh; written permission was taken from the authorities of the other hospitals before the commencement of the study. Informed written consent was taken from all of the study participants.

Oligo- and anovulation were defined as irregular menstrual cycles (>35 days or <21 days). A semi-structured questionnaire-based interview on a one-to-one basis with the consenting study subjects was conducted to gather detailed information on clinical presentation and family history; anthropometric measurements were done. Hirsutism was assessed by the modified Ferriman-Gallwey (F-G) score; a score ≥ 8 was the cut-point for diagnosis of hirsutism.^[10] Fasting oral glucose tolerance test (OGTT) was done, and fasting lipids were measured in all. Transvaginal ultrasonography (USG) was preferred within the married patients, whereas transabdominal pelvic USG was done in unmarried ones, and the procedure was performed on the day of

presentation. The PCO morphology has been defined by the presence of 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary.^[5] Serum total testosterone (TT), thyroid-stimulating hormone (TSH), and prolactin (PRL) were measured by automated hormone analyzers using either the chemiluminescence immunoassay or radioimmunoassay depending on the availability of the test method at the particular center; the hormone levels were interpreted according to the normal reference ranges of the corresponding laboratories.

The diagnosis of PCOS was made by using the revised Rotterdam criteria, 2003.^[5] Of the total 483 women having an initial diagnosis of PCOS, 113 women having a TSH >10.0 μ IU/mL and/or hyperprolactinemia (e.g., serum PRL >31.0 ng/mL) were further excluded. Hence, finally, 370 women with PCOS were ultimately included in this study for further analysis.

Obesity status was determined by body mass index (BMI) categories applicable to the south Asian population.^[11] Central obesity was defined as waist circumference (WC) \geq 80 cm.^[12] Blood pressure status was defined according to the Joint National Committee VII criteria.^[13] Prediabetes and DM was diagnosed according to criteria described by the American Diabetes Association.^[14] Dyslipidemia was defined according to cut-points described in Adult Treatment Panel III (ATP III).^[15] MetS was diagnosed by using the International Diabetes Federation (IDF) criteria applicable to the South Asian adult women.^[12]

Statistical analysis

Assuming the highest prevalence of PCOS 25% reported in the previous studies, the confidence level of 95%, and 5% margin of error, the estimated sample size was 289. We have investigated 370 PCOS cases; hence, the study has adequate power. Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) for Windows, version 23.0 software (SPSS Inc.; Chicago, IL, USA). The categorical variables were presented as percentages; measurable variables with normal distribution were presented as mean \pm standard deviation, and those not following normal distribution were presented as median. Student's *t*-test, Chi-square test, one-way ANOVA, Mann–Whitney U-test, or Kruskal–Wallis tests were performed as applicable for comparing the variables between different groups. Values of $P \leq 0.05$ were considered to be statistically significant.

RESULTS

Phenotype A was the most common PCOS phenotype observed in this study, which had a prevalence of 59.2%.

The prevalence of phenotypes B, C, and D were 14.1%, 11.9%, and 14.9%, respectively [Figure 1].

Tables 1 and 2 provide the comparison of clinical, metabolic, and hormonal profile among the PCOS phenotypes.

The study participants in the four phenotypes did not differ in age, age at the first onset of PCOS clinical features, BMI, WC, systolic BP, diastolic BP, fasting plasma glucose (FPG), plasma glucose 2-h after OGTT (PG 2H-OGTT), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum TSH levels. The four groups had similar frequencies of subfertility, overweight/obesity, central obesity, acanthosis nigricans, pre-hypertension (HTN)/HTN, glucose intolerance, dyslipidemia, and MetS. Significant differences among the four groups were observed in the frequencies of married women (highest in phenotype D), menstrual irregularity, participants who gained weight during the course of the disease (highest in phenotype C), and serum PRL level (highest in phenotype C). Significant differences among the four groups were also observed in the clinical and biochemical markers of hyperandrogenism, namely F-G score, hirsutism, acne, and serum testosterone levels.

The differences in hyperandrogenic features persisted when the comparison is made between the hyperandrogenic phenotypes as a whole (phenotypes A + B + C) and the normoandrogenic phenotype D. When hyperandrogenic phenotypes (as a whole) were compared to normoandrogenic phenotype, the two groups had similar age, age at the first onset of PCOS clinical features, BMI, WC, systolic BP, FPG, PG 2H-OGTT, TG, TC, LDL-C, HDL-C, serum TSH, and PRL levels. The two groups had similar frequencies of subfertility, subjects who gained weight during

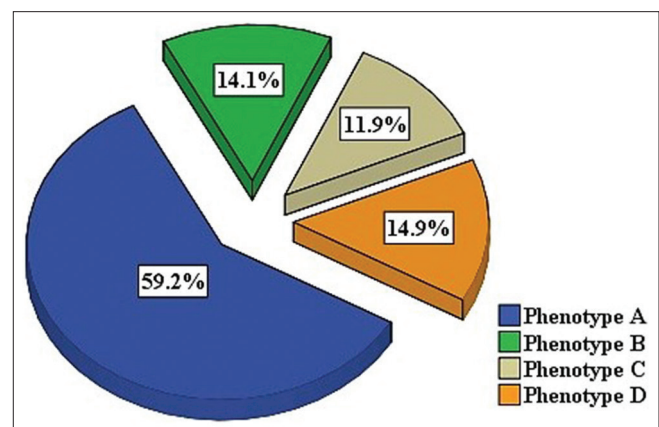


Figure 1: Distribution of various polycystic ovary syndrome phenotypes ($n = 370$)

Table 1: Comparison of demographic, anthropometric and clinical profile of various polycystic ovary syndrome phenotypes (n=370)

Variables	Mean±SD or frequency (%)					P*	P†	P‡	P§
	All (n=370)	Phenotype A (n=219)	Phenotype B (n=52)	Phenotype C (n=44)	Phenotype D (n=55)				
Age (years)	25.16±4.54	25.15±4.36	25.85±5.19	25.57±5.35	24.24±3.83	0.283	0.103	0.578	0.397
Age at disease onset	19.74±5.35	19.29±5.31	20.02±5.34	21.11±5.69	20.16±5.15	0.175	0.523	0.106	0.065
Married	233 (63.0)	137 (62.6)	28 (53.8)	25 (56.8)	43 (78.2)	0.045	0.015	0.451	0.183
Menstrual irregularity	326 (88.1)	219 (100)	52 (100)	0 (0%)	55 (100)	<0.001	0.001	<0.001	<0.001
Modified F-G score	11±5	12±5	13±5	13±4	4±2	<0.001	<0.001	0.365	<0.001
Hirsutism	292 (78.9)	201 (91.8)	49 (94.2)	42 (95.5)	0	<0.001	<0.001	0.623	<0.001
Acne	76 (20.5)	50 (22.8)	11 (21.2)	15 (34.1)	0	<0.001	<0.001	0.242	0.146
Subfertility (in married)	75/233 (32.2)	47/137 (34.3)	6/28 (21.4)	4/25 (16.0)	18/43 (41.9)	0.085	0.150	0.104	1.000
Gained weight	261 (70.5)	157 (71.7)	29 (55.8)	37 (84.1)	38 (69.1)	0.023	0.873	0.009	0.200
Family history of T2DM	113 (30.5)	64 (29.2)	15 (28.8)	16 (36.4)	18 (32.7)	0.783	0.751	0.626	0.373
BMI (kg/m ²)	27.46±4.99	27.76±5.16	26.81±4.60	27.93±4.60	26.52±4.87	0.261	0.129	0.430	0.462
Overweight/obese	312 (84.3)	185 (84.5)	42 (80.8)	39 (88.6)	46 (83.6)	0.768	0.842	0.570	0.747
WC (cm)	91.05±11.65	91.39±11.31	90.37±10.97	92.57±13.02	89.11±12.48	0.451	0.181	0.646	0.689
Central obesity	313 (84.6)	185 (84.5)	45 (86.5)	37 (84.1)	46 (83.6)	0.978	0.840	0.925	0.871
Acanthosis nigricans	304 (82.2)	185 (84.5)	38 (73.1)	39 (88.6)	42 (76.4)	1.000	0.252	0.082	1.000
Systolic BP (mmHg)	118±13	118±13	117±15	120±13	116±12	0.547	0.279	0.626	0.804
Diastolic BP (mmHg)	77±8	77±8	77±10	77±8	74±7	0.113	0.015	0.986	0.102
Pre-HTN/HTN	128 (34.6)	76 (34.7)	17 (32.7)	19 (43.2)	16 (29.1)	0.521	0.443	0.504	0.902

P-values by Student's *t*-test, Chi-square test, one-way ANOVA, Mann-Whitney U-test or Kruskal-Wallis test as applicable. P*: Within all phenotypes; P†: Between hyperandrogenic (A+B + C) and normoandrogenic (D) phenotypes; P‡: Within hyperandrogenic (A, B and C) phenotypes; P§: Between classical (A+B) and nonclassical (C+D) phenotypes. F-G score=Ferriman-Gallwey score, BMI=Body mass index, WC=Waist circumference, BP=Blood pressure, HTN=Hypertension, T2DM=Type 2 diabetes mellitus, SD=Standard deviation

Table 2: Comparison of biochemical and hormonal profile of various polycystic ovary syndrome phenotypes (n=370)

Variables	Mean±SD or frequency (%)					P*	P†	P‡	P§
	All (n=370)	Phenotype A (n=219)	Phenotype B (n=52)	Phenotype C (n=44)	Phenotype D (n=55)				
FPG (mmol/L)	5.27±1.38	5.24±1.38	5.40±1.32	5.24±0.94	5.31±1.73	0.883	0.824	0.714	0.953
PG-2HOGTT (mmol/L)	7.27±2.71	7.19±2.52	7.56±3.40	7.29±2.51	7.26±2.93	0.848	0.999	0.661	0.960
AGT	126 (34.1)	70 (32.0)	23 (44.2)	16 (36.4)	17 (30.9)	0.366	0.646	0.239	0.902
TG (mg/dL)	149.68±50.21	150.69±48.31	151.89±38.46	150.28±68.10	143.13±51.59	0.771	0.295	0.985	0.435
TC (mg/dL)	179.48±30.96	179.96±31.94	181.16±29.49	180.68±26.81	175.07±31.83	0.710	0.252	0.964	0.471
LDL-C (mg/dL)	109.81±27.88	110.10±28.76	110.30±24.19	112.35±27.13	106.17±28.56	0.721	0.295	0.887	0.710
HDL-C (mg/dL)	38.80±6.19	38.90±6.53	39.95±6.06	38.60±5.37	37.57±5.39	0.232	0.092	0.497	0.128
Dyslipidemia	344 (93.0)	205 (93.6)	49 (94.2)	41 (93.2)	49 (89.1)	0.675	0.249	0.977	0.363
Metabolic syndrome	211 (57.0)	124 (56.6)	34 (65.4)	28 (63.6)	25 (45.5)	0.152	0.076	0.411	0.477
Testosterone (ng/mL)	0.85 (median)	0.85 (median)	1.01 (median)	0.95 (median)	0.59 (median)	0.002	0.002	0.108	0.069
Prolactin (ng/mL)	11.25 (median)	10.81 (median)	12.60 (median)	16.35 (median)	11.91 (median)	0.009	0.381	0.017	0.159
TSH (μIU/mL)	1.50 (median)	1.45 (median)	1.23 (median)	2.11 (median)	1.58 (median)	0.055	0.737	0.039	0.052

P-values by Student's *t*-test, Chi-square test, one-way ANOVA, Mann-Whitney U-test or Kruskal-Wallis test as applicable. P*: Within all phenotypes; P†: Between hyperandrogenic (A+B + C) and normoandrogenic (D) phenotypes; P‡: Within hyperandrogenic (A, B and C) phenotypes; P§: Between classical (A+B) and nonclassical (C+D) phenotypes. FPG=Fasting plasma glucose, PG 2H-OGTT=Plasma glucose 2-h after oral glucose tolerance test, AGT=Abnormal glucose tolerance, TC=Total cholesterol, TG=Triglyceride, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TSH=Serum thyroid-stimulating hormone, SD=Standard deviation

the course of the disease, overweight/obesity, central obesity, acanthosis nigricans, pre-HTN/HTN, glucose intolerance, dyslipidemia, and MetS.

When the comparison was made among the three hyperandrogenic phenotypes (phenotypes A, B, and

C), significant differences were observed in the frequencies of menstrual irregularity (100%, 100%, and 0%, respectively), the number of participants who gained weight during the course of the disease (71.7%, 55.8%, and 84.1% respectively), median PRL (10.81,

12.60, and 16.35 ng/mL, respectively), and median TSH levels (1.45, 1.23, and 2.11 μ IU/mL, respectively). Other variables, including blood glucose and lipids, were found to be similar across the hyperandrogenic phenotypes.

The classical (A + B) and nonclassical (C + D) PCOS phenotypes had indifferent clinical, metabolic, and hormonal profiles except for higher frequencies of menstrual irregularity, hirsutism, and higher F-G score in the classical PCOS than nonclassical PCOS.

In binary logistic regression analysis, PCOS Phenotypes A, B, and C had similar risks for MetS to phenotype D. None of the parameters viz-a-viz higher age (>25 years), marital status, hirsutism, acne, acanthosis nigricans, a family member with type 2 DM (T2DM), a history of gaining weight during the course of the disease, subclinical hypothyroidism, and hypertestosteronism were found to be significant predictors of MetS in the study participants [Table 3].

DISCUSSION

In the current study, conducted in several centers throughout the country delivering specialized care for endocrinology, the observed prevalence of PCOS phenotypes A, B, C, and D were 59.2%, 14.1%, 11.9%, and 14.9%, respectively. Except for a higher diastolic BP in hyperandrogenic phenotypes compared to the normoandrogenic phenotype, the metabolic parameters were similar across the four phenotypes of PCOS. A higher PRL level was observed in the phenotype C than other phenotypes. Among the hyperandrogenic phenotypes, phenotype C had a higher TSH. All the PCOS Phenotypes had similar risks for MetS.

Worldwide, there is large heterogeneity in the prevalence of various PCOS phenotypes, as described by previous researchers [Table 4].^[16-23] Except for the Iranian and Chinese studies, phenotype A is the most prevalent phenotype of PCOS worldwide. In the current study, we also had similar observations. Similar to most of the previous researches, the frequency of phenotype C was the lowest in the current study. The clinical presentation of PCOS is varied and determined by many factors, including ethnicity.^[1] The phenotypic differences are also influenced by the clinical specialties attended by the PCOS patients [Table 4]; patients with hirsutism and acne are more likely to attend the dermatology clinics, whereas those having menstrual irregularities may prefer gynecology and endocrinology clinics for initial evaluation. In gynecology clinics, phenotype A had the highest prevalence, and phenotype C had the lowest prevalence.^[16,18,20,22] In the infertility clinics, the prevalence of the PCOS phenotypes greatly varied in the available literature.^[17,19,21] One study conducted in

Table 3: Binary logistic regression for predictors of metabolic syndrome in the study participants (n=370)

Variables	Subgroups	OR (95% CI)	P
PCOS phenotype	Phenotype D	Referent	
	Phenotype A	0.978 (0.227-4.225)	0.977
	Phenotype B	1.666 (0.299-9.270)	0.560
	Phenotype C	1.061 (0.188-5.980)	0.947
Age (years)	<25	Referent	0.493
	\geq 25	0.801 (0.425-1.510)	
Marital status	Unmarried	Referent	0.130
	Married	1.657 (0.862-3.185)	
Hirsutism	Absent	Referent	0.139
	Present	2.506 (0.742-8.463)	
Acne	Absent	Referent	0.725
	Present	1.142 (0.545-2.391)	
Acanthosis nigricans	Absent	Referent	0.366
	Present	1.531 (0.607-3.860)	
Family history of DM	Absent	Referent	0.215
	Present	0.662 (0.345-1.270)	
History of weight gain	Absent	Referent	0.989
	Present	0.995 (0.499-1.985)	
BMI (kg/m ²)	<23	Referent	<0.001
	\geq 23	28.036 (7.502-104.767)	
Pre-HTN or HTN	Absent	Referent	<0.001
	Present	17.036 (7.514-38.624)	
Glycemic status	NGT	Referent	<0.001
	AGT	5.014 (2.529-9.942)	
Dyslipidemia	Absent	Referent	0.006
	Present	7.896 (1.783-34.962)	
Serum testosterone	Normal	Referent	0.335
	Elevated	0.707 (0.349-1.430)	
Serum TSH (μ IU/mL)	\leq 5.0	Referent	0.607
	>5.0	1.328 (0.450-3.917)	

BMI=Body mass index, HTN=Hypertension, NGT=Normal glucose tolerance, AGT=Abnormal glucose tolerance, TSH=Serum thyroid-stimulating hormone, CI=Confidence interval, OR=Odds ratio, PCOS=Polycystic ovary syndrome, DM=Diabetes mellitus

endocrinology OPD of our country had almost similar frequencies of PCOS phenotypes as observed in the current study.^[23]

Overall, 57.0% of the participants in this study had MetS. The prevalence of MetS in PCOS widely varied in the available literature; two Indian studies reported the prevalence of 35.07% and 24.39%, the prevalence was 30.6% in Sri Lanka, 24.9% in Iran, and 18.89% among the Turkish PCOS patients.^[16-20] The differences in the prevalence of MetS in different countries and ethnic groups may result from different genetic factors, dietary habits, adopted lifestyle, and differential body configurations globally. The use of different diagnostic criteria for defining MetS may also influence the prevalence. In this study, MetS was diagnosed by using the IDF criteria applicable to the South Asian

Table 4: Prevalence of polycystic ovary syndrome phenotypes observed by other authors

Authors' name	Country	Clinical specialty	PCOS phenotypes (%)			
			A	B	C	D
Kar ^[16]	India	Gynecology outpatient	65.6	11.2	0.9	22.2
Sachdeva <i>et al.</i> ^[17]	India	Infertility clinic	67.7	11	17.7	3.6
Wijeyaratne <i>et al.</i> ^[18]	Sri Lanka	Endocrine clinic of obstetrics and gynecology unit	54.6	17.5	7.7	20.3
Mehrabian <i>et al.</i> ^[19]	Iran	Infertility clinic	32.1	14.8	6.3	46.8
Yilmaz <i>et al.</i> ^[20]	Turkey	Gynecology polyclinics	44.09	22.84	14.17	18.9
Zhang <i>et al.</i> ^[21]	China	Infertility and endocrine clinics	26.8	7.6	13.4	52.2
Pehlivanov and Orbetzova ^[22]	Bulgaria	Obstetrics and gynecology outpatient clinic	58.6	11.4	10	20
Tania-Sultana <i>et al.</i> ^[23]	Bangladesh	Endocrinology outpatient clinic	57	14	13	16

PCOS=Polycystic ovary syndrome

adult women.^[12] Sachdeva *et al.* and Wijeyaratne *et al.* used the criteria described by the National Cholesterol Education Program's ATP III [NCEP ATP III] report for defining MetS while Kar used the revised version of the NCEP ATP III criteria.^[15-18] In a recent study done in a single center of Bangladesh, the frequency of MetS using the ATP III criteria was 44.0%.^[23] The observed prevalence of MetS in our study is higher than those of other studies done in this area. Another explanation of the varying prevalence of MetS is the varying proportions of PCOS phenotypes in the studies which have an impact on MetS prevalence.

In the current study, the highest prevalence of MetS was observed in the phenotype B (65.4%), followed by phenotype C (63.6%) and phenotype A (56.6%); phenotype D had the lowest prevalence (45.5%) of MetS though the differences in the prevalence of MetS among the phenotypes were not statistically significant. In the regression analysis, PCOS Phenotypes A, B, and C had similar risks for MetS to Phenotype D. Similar prevalence of MetS were also observed in hyperandrogenic (A + B + C) and normoandrogenic (D) PCOS, in classical (A + B) and nonclassical (C + D) PCOS, and among different types of hyperandrogenic phenotypes (A, B, and C). Similar prevalence of MetS in the four phenotypes was also observed by other researchers including Sachdeva *et al.* in India, Wijeyaratne *et al.* in Sri Lanka and Tania-Sultana *et al.* in Bangladesh.^[17,18,23] On the other hand, Kar and Mehrabian *et al.* observed that hyperandrogenic phenotypes have a higher prevalence of MetS compared to the normoandrogenic phenotype D.^[16,19] Yilmaz *et al.* also found a higher prevalence of MetS in phenotype A in comparison to phenotypes B, C, and D.^[20] Zhang *et al.* also observed significant differences in MetS prevalence among various PCOS phenotypes with the highest prevalence in the phenotype A, followed by B, C, and D.^[21] The normoandrogenic phenotype D is found to have the lowest prevalence of MetS and has mildest metabolic profile among all phenotypes in the previous researches.^[16,19-21] Insulin resistance and

compensatory hyperinsulinemia are the key pathogenic factors in PCOS; insulin may act directly or indirectly through the pituitary to stimulate ovarian production.^[24] This explains the relationship of insulin resistance and MetS with HA, but the question still remains unanswered as to what is primary or secondary: MetS or HA. Though it is suggested that testosterone is significantly related to MetS and its components in PCOS women, such role of testosterone is controversial.^[25,26] At this point, it is hard to explain the observed differences in the correlation between HA and MetS in various studies. Moreover, heterogeneity in defining clinical HA, inequity in the form of testosterone (free or total) measured, a lack of definitive cut-points of serum testosterone levels to define biochemical HA in PCOS, and variations in the methods of testosterone measurement may contribute to the varying relationships of HA with MetS and its components.

In this study, all the clinical and biochemical metabolic parameters were also similar among the four phenotypes; the prevalence of abnormal glucose tolerance and dyslipidemia were also similar across the phenotypes. Except for higher diastolic BP in the hyperandrogenic than NA phenotype, all parameters were identical in the two groups. Moreover, none of the metabolic parameters differed among the hyperandrogenic phenotypes and between the classical and non-classical phenotypes of PCOS. Kar observed no differences in BMI, FPG, and HDL-C among the phenotypes though the dispute was found in the WC, which was highest in the phenotype C and lowest in the phenotype D.^[16] Sachdeva *et al.* observed no differences in WC, systolic BP, diastolic BP, FPG, PG-2HOGTT, and TG levels, and in the frequencies of overweight and obesity; however, significant differences were observed in BMI, TC, LDL-C, HDL-C, and the rate of abnormal glucose intolerance with the worst metabolic parameters in the phenotype A.^[17] Wijeyaratne *et al.* found a similar number of participants with pre-HTN/HTN, IFG, and dyslipidemia in their study, though BMI, WC, and abdominal obesity were lowest in

phenotype C.^[16] BMI, WC, FPG, and HDL-C were also different in the study done by Mehrabian *et al.*^[18] BMI was lowest in phenotype D in the research done by Yilmaz *et al.*, they also observed higher TG, TC, and LDL-C, and lower HDL-C in hyperandrogenic than normoandrogenic PCOS.^[20] Lipid parameters were also worse in the hyperandrogenic PCOS phenotypes according to the observation of Zhang *et al.* though FPG was similar to normoandrogenic ones.^[21] There was no difference among the PCOS phenotypes for systolic BP, diastolic BP, BMI, WC, FPG, TG, HDL-C, frequencies of prediabetes and DM in the previous study from Bangladesh by Tania-Sultana *et al.* though the differences in TG and LDL levels among the phenotypes were observed in their study.^[23]

In the current study, none of the higher age (>25 years), marital status, hirsutism, acne, acanthosis nigricans, a family member with T2DM, a history of gaining weight during the course of the disease, subclinical hypothyroidism and hypertestosteronism were found to be significant predictors of MetS in the study participants. BMI ≥ 23 Kg/m², pre-HTN or HTN, and abnormal glucose tolerance were associated with increased risks of MetS. Kar found that BMI >25, WC ≥ 80 cm, acanthosis nigricans, and family history of diabetes were associated with the risk of having MetS.^[16] Age ≥ 25 years, WC ≥ 80 cm, BMI ≥ 25 , and high FG scores were related to chances of having MetS in the study done by Tania-Sultana *et al.*^[23]

This study has several limitations; we did not investigate healthy women of similar age group to compare with the PCOS patients; the biochemical markers of insulin resistance were not investigated also. We only measured serum TT level, bioavailable, or free serum testosterone level, and the free androgen index was not measured in this study due to resource limitations. Clinical assessment was made by multiple investigators, and hence, this is the risk of observer bias. Ultrasonographic assessment by multiple radiologists in multiple instruments also carries the risk of observer bias. Transvaginal USG, which is considered to be the gold-standard for the evaluation of ovarian morphology, was not done in all patients. Moreover, the age-specific cutoffs for ovarian follicle count were not considered for defining PCO. The primary strength of the study is its multicenter design across the country and its large sample size. Nevertheless, this study is the first to characterize phenotypes of PCOS in a large cohort of our country and to show the data on various metabolic components in these phenotypes.

CONCLUSION

Phenotype A is the most prevalent phenotype of PCOS

in the population studied, representing about three-fifth of them. The prevalence of MetS was 57%; phenotype B had the highest prevalence, and phenotype D had the lowest prevalence of MetS though the differences in the prevalence of MetS among the four phenotypes were not statistically different. Most of the clinical, anthropometric, and metabolic parameters were also similar across the four PCOS phenotypes.

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Conflicts of interest

There are no conflicts of interest.

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