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ORIGINAL ARTICLE

Endocrine and Metabolic Profile of Different Phenotypes of Polycystic Ovarian Syndrome

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Abstract

Background Polycystic ovarian syndrome (PCOS) is a common endocrinopathy associated with wide heterogeneity and serious clinical implications. Prevalence and characteristics of different phenotypes are not well defined. Therefore, this study was planned to determine the prevalence of four phenotypes of PCOS and to evaluate their endocrine and metabolic parameters including insulin resistance and metabolic syndrome with respect to controls.

Methods This observational, case–control study was conducted in the gynecology outpatient department of a tertiary care center where 161 PCOS and 50 non-PCOS women were recruited and investigated.

Results All phenotypes of PCOS had higher BMI with respect to controls ($P < 0.000$). Overweight women were maximum in phenotype H + O followed by phenotype H + P. Significantly higher levels of luteinizing hormone ($P < 0.01$), testosterone ($P < 0.0001$), were observed in all phenotypes of PCOS as compared to controls. Serum cholesterol ($P < 0.026$) and triglycerides ($P < 0.05$) were significantly higher in all PCOS phenotypes compared to controls. Levels of fasting ($P < 0.000$) and post-prandial

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($P < 0.009$) insulin were significantly higher in all phenotypes of PCOS with respect to controls. Mean insulin resistance (IR) was 24.09 % in PCOS and 2 % in controls, prevalence being highest in H + O phenotype followed by H + O + P. Prevalence of metabolic syndrome in women with PCOS was 36.02 %, being highest in H + O + P followed by H + O and that of control was 10 %.

Conclusion All phenotypes of PCOS had deranged endocrine and metabolic profile compared to controls, but prevalence of IR and metabolic syndrome was maximum in hyperandrogenic phenotypes which require a strict surveillance for prospective metabolic disorders as compared to O + P phenotype.

Keywords PCOS · Phenotypes · Insulin resistance · Metabolic syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is a multisystem endocrinopathy of women of reproductive age [1]. It is the heterogeneity of the disease which makes it difficult to diagnose. Rotterdam criteria for diagnosis of PCOS include the presence of any two of the following criteria: clinical or biochemical hyperandrogenism, polycystic ovaries on ultrasonography, anovulation or oligomenorrhea. Using the possible combination of Rotterdam criteria, four different types of combinations have been identified.

Women with PCOS vary in clinical presentations from mild irregularity in menstruation, menorrhagia, acne, acanthosis, hirsutism, balding, obesity, infertility to amenorrhea [2]. The basic pathology lies in deregulation of enzyme cytochrome P-450-17-α which is present in ovaries and adrenals. Polycystic ovaries on ultrasonography are common, but it is not an absolute requirement in all definitions of this disorder. The most common immediate problems are anovulation, excess androgenic hormones and insulin resistance. Anovulation results in menstrual disturbances. Hyperandrogenism generally manifests as acne and hirsutism. Insulin resistance is associated with obesity, type II diabetes and deranged lipid profile. The symptoms and severity of the syndrome vary greatly by factors such as obesity, genetic, racial predisposition, geographic diversity and lifestyle factors [3]. Therefore, the aim of this study was to evaluate the prevalence of different phenotypes of PCOS and analyze their endocrine and metabolic characteristics including insulin resistance and metabolic syndrome compared to non-PCOS controls in women presenting to a tertiary care center of Delhi.

Materials and Methods

This observational, case–control study was performed in women between the age group of 20–38 years presenting to gynecology outpatient department of a tertiary care center where consecutive 161 infertile women with PCOS and 50 non-PCOS infertile women as control were recruited after obtaining clearance from the Ethics Committee of Human Research of the Institute. The diagnosis of PCOS was made according to the ESHRE/ASRM [4] criteria. Subjects having PCOS were divided into four different phenotypes:

- Phenotype A with hyperandrogenism (H) + oligomenorrhea (O) + polycystic ovaries on USG (P)
- Phenotype B with hyperandrogenism (H) + oligomenorrhea (O)
- Phenotype C with hyperandrogenism (H) + polycystic ovaries on USG (P) and
- Phenotype D with oligomenorrhea (O) + polycystic ovaries on USG (P)

Clinical evaluation of each patient comprised of a thorough menstrual, obstetrics, personal, past, family history followed by complete physical examination. Hirsutism was assessed by Ferryman–Galway (FG) scores of ≥8 [5]. Polycystic ovaries on ultrasound were defined as the presence of at least one ovary >10 mL or at least 12 follicles of 2–9 mm in diameter. Height and weight were recorded by the standard methods. BMI (body mass index) was defined as body weight in kilograms divided by height in meters square. Individuals with a BMI ≥ 23 kg/m^2 were considered as overweight [6]. Waist–hip ratio ≥0.88 was considered to having central obesity [7]. Blood pressure ≥130/85 mmHg was considered to be abnormal. Subject with known thyroid disorder, hypothalamic, diabetes, pituitary, adrenal and neoplastic disorders were excluded from the study.

Sample Collection and Estimation

Blood collection was done after a fasting of 8–10 h, and sample was analyzed for fasting lipid profile, OGTT, serum insulin and hormonal profile. Lipid profile was considered to be abnormal if cholesterol >200 mg/dL; triglycerides ≥150 mg/dL; and HDL ≤ 50 mg/dL [8, 9]. Lipid profile was estimated by using enzymatic colorimetric technique, and the criteria adopted were in consonance with NCEP-ATP III guidelines [10]. Blood sugar values were determined during a 75-g oral glucose tolerance test (OGTT) [11] and were assessed according to WHO, 2002. The presence of insulin resistance was defined if fasting insulin was >25 mg/dL or if insulin level post 75 g glucose load

was >55 mg/dL, respectively [12, 13]. Fasting glucose-to-insulin ratio was calculated as a measure of insulin sensitivity [14]. Hormonal profile included FSH, LH, estradiol, total testosterone, prolactin and TSH on day 2 or 3 of menstrual cycle. Hormonal estimation was done by chemiluminescence immunoassay.

Statistical Analysis

The clinical, hormonal and metabolic profile of different phenotypes of PCOS was compared with controls, and data are presented as mean ± SD. If the value followed normal distribution, one-way ANOVA (analysis of variance) was used. If the values did not follow normal distribution, nonparametric Kruskal–Wallis test was used. Bonferroni test was used for multiple intergroup comparisons, and univariate logistic regression was used to compare associations with metabolic syndrome. Comparison of percentages of different groups was calculated using Fisher Chi-square test. Significance was set at $P < 0.05$. For statistical analysis, Strata 12 was used.

Results

One hundred and sixty-one infertile women with PCOS were characterized into four different phenotypes. Prevalence was maximum for phenotype C (H + P; 31.28 %) followed by phenotype A (H + O + P; 20.85 %), phenotype D (O + P; 12.80 %) and least of phenotype B (H + O; 11.37 %). Mean age of the subjects was 27 ± 4.20 (range 20–38 years). Mean age of women of all phenotypes was similar [phenotype A (H + O + P) was 26.93 years, phenotype B (H + O) was 28.04 years, phenotype C (H + P) was 28.11 years, and phenotype D (O + P) was 27.19 years and that of controls was 27.46 years].

Clinical Profile

Clinical profile of all phenotypes of PCOS and controls is given in Table 1. All phenotypes of PCOS had a higher BMI with respect to controls ($P < 0.000$). Overweight women were maximum in phenotype B (H + O; 66.66 %) followed by phenotype C (H + P; 55.55 %), phenotype A (H + O + P; 54.54 %) and phenotype D (O + P; 48.48 %) and were least in controls (22 %, $P < 0.0001$). Waist–hip ratio was significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.02$). Percentage of women with abnormal WHR (≥0.88), were significantly higher in all PCOS phenotypes with respect to controls ($P < 0.030$). Diastolic blood pressure was significantly higher in all phenotypes of PCOS with reference to controls ($P < 0.013$).

Endocrine Profile

Endocrine profile of all phenotypes of PCOS and controls is given in Table 2. Significantly higher prevalence of luteinizing hormone ($P < 0.01$), testosterone ($P < 0.0001$) and ratio of luteinizing to follicular stimulating hormone ($P < 0.05$) was observed in all phenotypes of PCOS as compared to controls. Raised LH was maximum in phenotype B (H + O; 41.66 %) followed by phenotype A (H + O + P; 38.63 %), phenotype D (O + P; 27.27 %) and phenotype C (H + P; 14.81 %) and was least in controls (2 %, $P < 0.000$). High testosterone levels were seen in phenotype B (H + O; 70.83 %) followed by phenotype A (H + O + P; 56.81 %), phenotype C (H + P; 51.85 %) and phenotype D (O + P; 4.54 %) and were least in controls (2 %, $P < 0.000$).

Metabolic Profile

Lipid profile of all phenotypes of PCOS and controls is given in Table 3. Cholesterol was significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.02$). On comparing percentage of women with high cholesterol level (>200 mg/dL), it was highest in phenotype B (H + O; 16.66 %), followed by phenotype A (H + O + P; 11.36 %), phenotype D (O + P; 6.06 %) and phenotype C (H + P; 3.70 %), and nil in controls ($P < 0.023$). Triglyceride level in serum was significantly high in all phenotypes of PCOS with respect to controls ($P < 0.002$). On comparing percentage of women with high

Table 1 Clinical parameters of study population

Parameters	H + O + P ($n = 44$)	H + O ($n = 24$)	H + P ($n = 27$)	O + P ($n = 66$)	Control ($n = 50$)
Age (years)	26.93 ± 4.33	28.04 ± 3.47	28.11 ± 3.89	27.19 ± 4.49	27.46 ± 3.99
Hirsutism	44 (100 %)	24 (100 %)	27 (100 %)	1 (1.51 %)	4 (8 %)
BP systolic (mmHg)	123.5 ± 16.74	131.23 ± 13.74	127.2 ± 18.4	124.4 ± 18.88	117.03 ± 15.28
BP diastolic (mmHg)	74.53 ± 9.41*	77.88 ± 16.36*	79.4 ± 10.98*	72.11 ± 12.17*	69.25 ± 8.63
BMI (kg/m^2)	26.24 ± 5.43**	28.13 ± 6.01**	25.72 ± 5.66**	24.49 ± 5.09**	21.35 ± 2.51
WHR	0.814 ± 0.88*	0.802 ± 0.086*	0.78 ± 0.121*	0.814 ± 0.093*	0.75 ± 0.068

All values are expressed as mean ± SD

* $P < 0.05$, significant; ** $P < 0.001$, highly significant

Table 2 Hormonal parameters of study population

Parameter	H + O + P ($n = 44$)	H + O ($n = 24$)	H + P ($n = 27$)	O + P ($n = 66$)	Control ($n = 50$)
FSH (IU/L)	8.63 ± 5.33	7.20 ± 2.97	8.44 ± 3.86	8.53 ± 3.59	7.42 ± 3.32
LH (IU/L)	9.24 ± 5.35*	9.90 ± 4.90*	8.08 ± 6.32*	9.35 ± 10.23*	6.07 ± 2.49
Testosterone (ng/mL)	33.27 ± 35.75**	35.69 ± 25.55**	22.56 ± 29.11**	2.12 ± 3.65**	0.58 ± 0.49
Estradiol (pg/mL)	36.71 ± 35.56	39.03 ± 51.49	61.68 ± 81.04	10.93 ± 13.76	46.67 ± 24.89
Prolactin (ng/mL)	14.04 ± 6.94	14.35 ± 8.63	17.02 ± 7.08	16.41 ± 15.90	15.24 ± 8.09
TSH (μIU/mL)	2.94 ± 1.62	2.85 ± 1.65	3.50 ± 4.75	3.25 ± 2.02	3.37 ± 2.11
LH/FSH ratio	1.295 ± 0.854*	1.44 ± 0.75*	1.093 ± 0.671*	1.242 ± 1.39*	0.905 ± 0.464

All values are expressed as mean ± SD

* $P < 0.05$, significant; ** $P < 0.001$, highly significant

Table 3 Lipid profile of study population

Parameter	H + O + P ($n = 44$)	H + O ($n = 24$)	H + P ($n = 27$)	O + P ($n = 66$)	Control ($n = 50$)
Cholesterol (mg/dL)	166.06 ± 43.61*	192 ± 68.51*	160.58 ± 34.66*	161.91 ± 31.3*	146.30 ± 22.86
Triglyceride (mg/dL)	116.68 ± 39.51**	144.43 ± 53.1**	112.03 ± 41.63**	98.39 ± 43.16**	90.20 ± 29.48
HDL (mg/dL)	38.36 ± 8.24	33.52 ± 14.54	36.21 ± 10.74	32.82 ± 9.60	41.07 ± 10.37
TG/HDL ratio	3.25 ± 1.13*	6.02 ± 5.30*	3.17 ± 1.16*	4.08 ± 2.85*	2.90 ± 2.02

All values are expressed as mean ± SD

* $P < 0.05$, significant; ** $P < 0.001$, highly significant

triglycerides, it was highest in phenotype B (H + O; 20.83 %) followed by phenotype A (H + O + P; 13.63 %), phenotype C (H + P; 7.40 %) and phenotype D (O + P; 6.06 %) and was least in controls (2 %, $P < 0.030$). Triglycerides-to-high-density lipoprotein ratio was significantly higher in PCOS with respect to controls ($P < 0.05$).

Insulin Resistance

Profile of insulin resistance of all phenotypes of PCOS and controls is given in Table 4. Insulin fasting ($P < 0.000$) and 2 h after 75 g glucose intake ($P < 0.009$) was significantly higher in all phenotypes of PCOS with respect to controls. Prevalence of fasting insulin was highest in phenotype B (H + O) and was least in controls (0 %). Prevalence of post-glucose insulin was similar in phenotypes A (H + O + P), B (H + O) and C (H + P) and was least in controls. Ratio of fasting glucose to fasting insulin was significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.02$) being highest in B (H + O) followed by A (H + O + P), D (O + P) and C (H + P).

Metabolic Syndrome

Prevalence of all parameters of metabolic syndrome in phenotypes of PCOS and controls is given in Table 5. Overall prevalence of metabolic syndrome in the study was 29.86 %. However, prevalence of metabolic syndrome in women with PCOS was 36.02 % and that in controls was 10 %. Proportion of women with higher waist circumference (≥80 cm) and deranged triglycerides, HDL, fasting glucose were significantly higher among different phenotypes of

Table 4 Profile of insulin resistance

Parameters	H + O + P ($n = 44$)	H + O ($n = 24$)	H + P ($n = 27$)	O + P ($n = 66$)	Control ($n = 50$)
Glucose F (mg/dL)	90.65 ± 18.27	70 ± 30.62	99.25 ± 21.95	86.78 ± 22.26	94.39 ± 9.75
Insulin F (μU/mL)	19.08 ± 19.26**	26.82 ± 22.32**	13.47 ± 15.11**	15.81 ± 26.47**	6.27 ± 4.34
Insulin post-glucose (μU/mL)	68.69 ± 43.02**	64.88 ± 47.94**	67.95 ± 45.96**	48.22 ± 35.07**	22.50 ± 19.04
GIR	8.60 ± 7.31*	4.17 ± 3.0*	23.45 ± 26.61*	18.45 ± 17.47*	49.02 ± 86.84

All values are expressed as mean ± SD

* $P < 0.05$, significant; ** $P < 0.001$, highly significant

Table 5 Prevalence of components of metabolic syndrome

Parameters	H + O + P ($n = 44$)	H + O ($n = 24$)	H + P ($n = 27$)	O + P ($n = 66$)	Controls ($n = 50$)
WC ≥ 80 cm	16 (36.36 %)	8 (33.33 %)	4 (14.81 %)	19 (28.78 %)	4 (8 %)
TG ≥ 150 mg/dL	6 (13.63 %)	5 (20.83 %)	2 (7.40 %)	4 (6.06 %)	1 (2 %)
HDL ≤ 50 mg/dL	24 (22.72 %)	7 (8.33 %)	12 (33.33 %)	21 (12.12 %)	9 (18 %)
Glucose F ≥ 100 mg/dL	8 (18.18 %)	0 (0 %)	2 (7.40 %)	5 (7.57 %)	5 (10 %)
BP diastolic ≥ 85 mmHg	3 (6.81 %)	4 (16.66 %)	7 (25.92 %)	6 (9.09 %)	1 (2 %)
BP systolic ≥ 130 mmHg	6 (13.63 %)	10 (41.66 %)	9 (33.33 %)	17 (25.75 %)	3 (6 %)

Table 6 Predictive association of metabolic syndrome parameters

Parameters	Unadjusted OR	*P* value	95 % CI for OR
WC ≥ 80 cm	6.66	0.0001	3.17
TG ≥ 150 mg/dL	4.90	0.005	1.61
HDL ≤ 50 mg/dL	9.21	0.012	1.63
Glucose F ≥ 100 mg/dL	2.80	0.054	0.98
BP diastolic ≥ 85 mmHg	45.40	0.0001	5.87
BP systolic ≥ 130 mmHg	127.46	0.0001	27.69

PCOS in relation to control ($P < 0.000$, $P < 0.00$, $P < 0.01$, $P < 0.05$, respectively). Number of women with high diastolic and systolic blood pressure was significantly higher among different phenotypes of PCOS with respect to control ($P < 0.000$ and $P < 0.000$, respectively).

Univariate logistic regression (Table 6) showing predictive association of metabolic syndrome parameters in different phenotypes of PCOS and controls was significantly high for all deranged parameters (WC ≥ 80 cm, BP ≥ 130/85 mmHg, fasting blood glucose ≥100 mg/dL, TG ≥ 150 mg/dL and HDL ≤ 50 mg/dL) in women with PCOS compared to non-PCOS infertile women.

Discussion

In this observational, case–control study, 211 infertile women were recruited. Out of these 211 infertile women, 50 were non-PCOS (controls) and 161 had PCOS. Prevalence of women with PCOS was maximum for phenotype C (H + P; 31.28 %) followed by phenotype A (H + O + P; 20.85 %), phenotype D (O + P; 12.80 %) and phenotype B (H + O; 11.37 %). In a few previous studies, the phenotypic distribution of PCOS was determined. Chauhan et al. [15] found observed phenotypes A, B, C and D to be 23.3, 13.3, 52.6 and 19.5 %, and Kar et al. [16] found it to be 37.04, 11.2, 22.2 and 0.9 %, respectively. This difference in prevalence of different phenotypes depends on the genetic, racial/ethnic and geographic variations. Phenotype may also vary depending upon the study population from where patients have been recruited that is from infertility, gynecology, dermatology or medicine clinic.

BMI was significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.000$). Obese women (BMI > 30 kg/m^2) among different phenotypes of PCOS and controls were maximum in phenotype B (H + O; 25 %), phenotype A (H + O + P; 18.18 %), phenotype C (H + P; 16.66 %) and phenotype D (O + P; 14.18 %) and none in controls. Overweight women (BMI ≥ 23 kg/m^2) among different phenotypes of PCOS were highest in phenotype B (H + O; 66.66 %), and the prevalence was similar in the other three phenotypes ($P < 0.001$). In a similar study, obesity was found to be 28.2 % in Mumbai population [15]. BMI was also found to be higher in phenotype B in a study conducted by Welt et al. [17]. Prevalence of WHR was also significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.02$).

Levels of FSH, TSH and prolactin were comparable among all groups. LH and testosterone levels were significantly higher in PCOS women as compared to controls ($P < 0.01$ and $P < 0.00$, respectively). Percentage of women with deranged LH and testosterone were maximum in phenotype B and least in controls ($P < 0.000$). In similar study, Zhang et al. [18] observed higher level of testosterone in phenotypes A and B.

Cholesterol level was significantly higher in all phenotypes of PCOS with regard to controls ($P < 0.026$). Percentage of women with hypercholesterolemia were highest in phenotype B (H + O; 16.66 %) followed by phenotype A (H + O + P; 11.36 %), phenotype D (O + P; 6.06 %) and phenotype C (H + P; 3.70 %, $P < 0.023$). Triglyceride levels were significantly higher in all phenotypes of PCOS with regard to controls ($P < 0.003$). A significantly higher prevalence was observed among phenotype B (H + O) with respect to control as well as with phenotype D (O + P) ($P < 0.05$). Percentage of women with hypertriglyceridemia were ten times higher in phenotype B (H + O; 20.83 %) than that of controls (2 %, $P < 0.030$). High-density lipoprotein was comparable in all PCOS groups ($P < 0.157$).

Insulin resistance (IR) is a condition where body cells do not respond to insulin. Triglycerides-to-high-density

lipoprotein ratio is a marker of insulin resistance and was significantly higher in PCOS with respect to controls ($P < 0.05$). Percentage of women with deranged TG/HDL ratio were maximum in phenotype B (H + O; 20.83 %) followed by phenotype C (H + P; 18.51 %), phenotype D (O + P; 16.66 %) and phenotype A (H + O + P; 15.20 %) and were least in controls (4 %). The gold standard method to measure IR is hyperinsulinemic euglycemic clamp. As it is difficult and cumbersome to perform this test in clinical practice, other surrogate indicators used to determine insulin resistance.

Triglycerides-to-high-density lipoprotein ratio is a marker of insulin resistance and was significantly higher in PCOS with respect to controls ($P < 0.05$). Percentage of women with deranged TG/HDL ratio were maximum in phenotype B (H + O; 20.83 %) followed by phenotype C (H + P; 18.51 %), phenotype D (O + P; 16.66 %) and phenotype A (H + O + P; 15.20 %) and were least in controls (4 %). In some studies, phenotype D had similar TG, HDL and TG/HDL ratio compared to control group which again emphasizes its mild nature in terms of metabolic derangements as is evident from this study also.

Levels of fasting and post-prandial insulin were significantly higher in all phenotypes of PCOS with respect to controls ($P < 0.000$ and $P < 0.009$, respectively). Fasting hyperinsulinemia was maximum in phenotype B (H + O; 16.66 %) followed by phenotype A (H + O + P; 6.81 %), phenotype D (O + P; 4.54 %) and phenotype C (H + P; 3.70 %) and none in controls, ($P < 0.18$). Post-prandial hyperinsulinemia was highest in phenotype A (H + O + P; 31.81 %) followed by phenotype C (H + P; 25.92 %), phenotype B (H + O; 25 %) and phenotype D (O + P; 13.63 %) and was least in controls (2 %, $P < 0.12$).

Fasting glucose was comparable in all groups. Glucose-to-insulin ratio (GIR) was significantly lower in all PCOS as compared to controls ($P < 0.02$). Percentage of women with deranged fasting glucose-to-insulin ratio were highest in phenotype B (H + O; 8.33 %) followed by phenotype A (H + O + P; 4.36 %), phenotype C (H + P; 3.70 %) and phenotype D (O + P; 3.03 %) and were least in controls (0 %, $P < 0.172$).

In this study, overall IR was 24.09 % in PCOS and 2 % in controls. Insulin resistance has been reported among PCOS women in other studies and varied from 19.2 to 80 % in different studies. Prevalence of metabolic syndrome was 37.04 % in a study conducted by Kar et al. [16] and 19.2 % in another study by Chauhan et al. [15]. Insulin resistance was higher in phenotype A in the study conducted by Baldani et al. [19], whereas insulin resistance was higher in phenotype B in Welt et al. [16] as well as in the study conducted by Panidis et al. [20].

Prevalence of metabolic syndrome was 36.02 % in PCOS and 10 % in controls. On comparing, proportion of women with metabolic syndrome were similar in phenotype A (H + O + P; 43.11 %) and phenotype B (H + O; 41.67 %), followed by phenotype C (H + P; 33.33 %) and phenotype D (O + P; 30.3 %), and were least in controls (10 %, $P < 0.0001$). The prevalence of metabolic syndrome was 30–40 % in the study conducted by Shroff et al. [20] and 35.07 % in Kar et al. [15]. It is also observed that the prevalence of metabolic syndrome was higher in phenotype A in other studies [15, 17, 21]. Strongest positive association of metabolic syndrome was observed for systolic and diastolic blood pressure followed by waist circumference, triglyceride level, HDL level and lowest with fasting glucose levels.

Conclusion

Appropriate diagnosis of PCOS and accurate identification of phenotype is very important due to its long-term health implications, and it is essential that these women are informed and counseled about their present and long-term risks. This study provides evidence that endocrine and metabolic profile is deranged in all phenotypes of PCOS compared to controls. Prevalence of metabolic syndrome and insulin resistance was highest and most severe in hyperandrogenic phenotypes that is phenotypes B (H + O), A (H + O + P) and C (H + P) followed by phenotype D (O + P). Therefore, these three hyperandrogenic phenotypes require closer surveillance.

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Compliance with Ethical Standards

Conflict of interest Authors have no conflict of interest in the findings of this study.

Ethical Approval This study was initiated after approval from the Ethics Committee of Human Research of the Institute. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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