Original Article

Comparison of the Different PCOS Phenotypes Based on Clinical Metabolic, and Hormonal Profile, and their Response to Clomiphene

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Abstract

Objective: To compare the different polycystic ovarian syndrome (PCOS) phenotypes based on their clinical, metabolic, hormonal profile, and their differential response to clomiphene. **Design:** Prospective observational study. **Setting:** Infertility clinic, a government hospital. **Sample Size:** 164 women with PCOS-related infertility. **Materials and Methods:** Sample population was divided into four phenotypes based on the NIH (National Institute of Health) consensus panel criteria. The incremental dose of clomiphene from 50 to 150 mg/day over three cycles was given. **Outcome Measures:** Clinical history, metabolic, hormonal profile, and ultrasound features of each phenotype. Also, the response to clomiphene citrate was studied as presence or absence of ovulation. **Results:** The prevalence of phenotypes A, B, C, and D were 67.7%, 11%, 17.7%, and 3.6%, respectively. Phenotype A had significantly higher weight, body mass index, clinical, and biochemical hyperandrogenism, menstrual irregularities, ovarian reserve parameters, fasting insulin, HOMA-IR, and more deranged lipid profile ($P < 0.05$). Clomiphene resistance was significantly more common in phenotype A ($P < 0.05$). No significant differences were noted in the waist circumference, waist-hip ratio, blood pressure and blood sugar values (fasting, 1-hour postprandial, 2-hour postprandial). Also, the Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), LH-FSH ratio, 17-hydroxyprogesterone, and vitamin D levels were not significantly different among various PCOS phenotypes. **Conclusion:** Full-blown PCOS (phenotype A) is at a higher risk of adverse metabolic and cardiovascular outcomes as compared with the others, and phenotype D is the least severe phenotype. Thus, the phenotypic division of patients with PCOS-related infertility can help in prognosticating the patients about the severity of the disease and the fertility outcome.

Keywords: Diabetes mellitus, hyperandrogenism, metabolic syndrome, obesity, polycystic ovaries

Introduction

Polycystic ovarian syndrome (PCOS) is a common syndrome with a prevalence of around 2.5%-11.9%.[1] The diagnosis involves the presence of menstrual irregularities, hyperandrogenism, and polycystic ovaries.[2] It is a common cause of infertility in the reproductive age group. It is a complex disorder involving not only the reproductive system but also is associated with obesity,[3] insulin resistance,[4] type 2 diabetes mellitus,[5] dyslipidemia,[3] and metabolic syndrome.[3]

So far, numerous attempts have been made to classify PCOS. It started with the NIH (National Institute of Heath) criteria,[6] 1990 which classified women with hyperandrogenism and oligo-anovulation to have polycystic ovarian syndrome after excluding other endocrine disorders. The expert committee at Rotterdam's[2] gave the second definition, which included the presence of two out of the three features: clinical or biochemical hyperandrogenism, oligo-anovulation, and polycystic ovaries on ultrasound. Over time, as research continued hyperandrogenism was considered to be the strongest determinant[7] affecting the pathophysiology of PCOS and thus in 2006, came the Androgen Excess and PCOS Society (AE-PCOS) criteria[8] which considered that the diagnosis of PCOS should be based on clinical or biochemical hyperandrogenism in combination with oligoanovulation or polycystic ovaries. Thus, this criterion excluded the

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non-hyperandrogenic phenotype of PCOS. This created a lot of confusion in the diagnostic approach of PCOS. So finally, in 2012, NIH consensus panel[9] proposed the phenotypic approach to classify PCOS. Phenotype A (full-blown syndrome PCOS: HA+OD+PCO) includes hyperandrogenism (HA) (clinical or biochemical), ovulatory dysfunction (OD), and polycystic ovaries (PCO) (HA+OD+PCO). Phenotype B (non-PCO PCOS: HA+OD) includes hyperandrogenism (HA) and ovulatory dysfunction (OD). Phenotype C (ovulatory PCOS: HA+PCO) includes hyperandrogenism (HA) and polycystic ovaries (PCO). Phenotype D (non-hyperandrogenic PCOS: OD+PCO) includes ovulatory dysfunction (OD) and polycystic ovaries (PCO).

It is still unclear if these four phenotypes represent a broad spectrum of the same condition, that is, PCOS. Not enough work has been done to study the different PCOS phenotypes. This study is done with the aim to compare the differences among the clinical, metabolic, and hormonal profile of different PCOS phenotypes and also to study their differential response to clomiphene citrate.

Materials and Methods

This prospective observational study was done over a period of 1 year.

Consecutive sampling method was adopted for this study. Data collection was done for 1 year. In each week, 2 days were fixed for sample collection which was done during OPD time. Each day, first three patients were contacted for the study. Thus, total of 312 patients were contacted in the study. But, 96 patients were excluded after primary evaluation (they fell in the exclusion criteria). Fifty-two patients lost to follow up during the course of the study. So, the final sample size was 164 patients with PCOS-related infertility [Figure 1], who were classified into four PCOS phenotypes based on the NIH consensus panel criteria.[9]

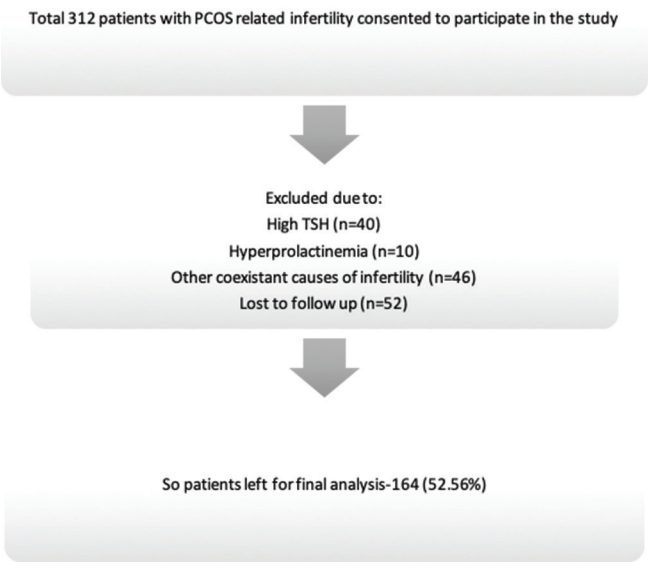

Figure 1: Recruitment of the study population

Inclusion criteria included women with PCOS (based on Rotterdam's criteria[2]) related infertility of age less than 40 years. Women on any insulin-sensitizing agent or lipid-lowering agent or having an endocrine disorder or anorexia nervosa/bulimia nervosa or with hypothalamic or pituitary dysfunction were excluded.

Of the total 312 women recruited, 96 patients were excluded due to endocrine disturbances like hypothyroidism and hyperprolactinemia and 52 patients lost to follow up and thus excluded. [Figure 1]. So, the final sample size included 164 patients, who were classified into four PCOS phenotypes based on the NIH consensus panel criteria.[9]

A written and informed consent was taken from each patient enrolled in the study. Ethical clearance for the study was taken from the institutional ethical committee.

The physical examination of the enrolled patients included their blood pressure, weight (kg) and height (cm). Body mass index (BMI) was recorded with the above measurements. Waist circumference (WC) was measured midway between lower rib margin and the iliac crest in the mid-axillary line at the end of normal expiration.[10] Hip circumference was measured with the measuring tape at the highest prominence of the buttocks and parallel to the floor.[10] Waist and hip circumference were recorded after removing clothing from the area over waist and hip. Thyroid and breast were examined for any abnormalities. Signs of androgen excess were looked for like excessive hair growth, acne, or alopecia. Excessive hair growth was graded by the modified Ferriman and Gallwey[11] (FG) score.

FIGO classification[12] was used to characterize menstrual irregularity. The cycle length of 24-38 days was considered normal, and length >38 days were included in the oligomenorrheic group.

The diagnosis of metabolic syndrome was based on ATPIII criteria.[13] Their presence or absence was compared between the obese and non-obese PCOS group.

All the patients enrolled in the study were called on the day 2-3 of their next cycle for baseline investigations like Follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH), 17-hydroxyprogesterone levels (17-OHP), testosterone, androstenedione, vitamin-D, 75 gm oral glucose tolerance test (OGTT), fasting insulin, fasting triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), and cholesterol levels. The homeostasis model assessment of insulin resistance (HOMA-IR),[14] a surrogate marker of insulin resistance was used in this study. Patients with HOMA-IR >2[15] were defined as having insulin resistance. LH, FSH, AMH, testosterone, vitamin D, and insulin were determined in the fasting plasma samples of the study subjects by electrochemiluminescence immunoassay (ECLIA) (E-2020, Roche Diagnostics, Basel,

Table 1: Distribution of various pcos phenotypes

Pcos phenotypes	Definition	Includes	Distribution (percentage)
A	Full blown PCOS	HA[1] + OD[2] + PCO[3]	111 (67.7%)
B	Non-PCO PCOS	HA[1] + OD[2]	18 (11%)
C	Ovulatory PCOS	HA[1] + PCO[3]	29 (17.7%)
D	Non-hyperandrogenic PCOS	OD[2] + PCO[3]	(3.6%)

[1]HA-Hyperandrogenism, [2]OD-Ovulatory Dysfunction, [3]PCO-Polycystic Ovaries

Table 2: Comparison of clinical, metabolic and hormonal profile of various pcos phenotypes

	Phenotype A HA[1] + OD[2] + PCO[3] (Mean+SD) (*n*=111)	Phenotype B HA[1] + OD[2] (Mean+SD) (*n*=18)	Phenotype C HA[1] + PCO[3] (Mean+SD) (*n*=29)	Phenotype D OD[2] + PCO[3] (Mean+SD) (*n*=6)	*P*
Age (in years)	27.78+3.79	27.33+2.93	29.59+3.41	25.83+4.79	0.041*
Weight (in kg)	64.05+10.72	59.89+10.50	57.65+8.87	58.00+11.61	0.015*
BMI[4] (in kg/m^2)	26.99+4.32	25.61+3.66	23.57+3.41	22.58+3.44	0.000*
Waist circumference (in inches)	34.04+3.30	33.59+4.55	32.22+4.27	33.00+4.82	0.126*
Waist-hip ratio	0.88+0.04	0.87+0.04	0.86+0.05	0.88+0.06	0.198*
SBP[5] in mmHg	118.00+7.45	114.11+7.59	117.66+8.07	112.67+5.61	0.093*
DBP[6] in mmHg	75.18+5.75	72.78+4.60	74.97+5.62	71.67+4.08	0.126*
Ferriman Gallwey Score	14.68+3.41	13.00+3.72	12.72+4.32	6.17+0.41	0.000*
Testosterone (nmol/l)	2.89+1.37	2.60+1.01	2.44+1.02	1.63+0.64	0.028#
Androstenedione (ng/ml)	3.16+1.45	2.72+0.99	2.61+1.14	1.90+0.62	0.008#
Mean Ovarian Volume in cm^3	13.58+2.69	8.42+1.36	11.06+2.77	12.15+0.87	0.000*
Mean AFC[7]	12.86+2.89	8.75+1.87	10.02+2.80	10.16+2.78	0.000*
AMH[8] (ng/ml)	11.34+5.25	8.69+3.39	9.44+4.53	7.76+3.24	0.035*
OGTT1[9] (mg/dl)	91.37+13.13	88.17+14.65	87.52+11.04	86.00+15.88	0.370*
OGTT2[10] (mg/dl)	151.83+35.71	143.00+33.76	137.41+27.35	143.83+56.77	0.224*
OGTT3[11] (mg/dl)	133.09+31.24	129.72+25.78	122.97+23.47	127.67+28.44	0.422*
Fasting Insulin (mIU/L)	13.17+6.95	9.43+5.67	9.19+6.35	8.45+2.99	0.006*
HOMA-IR[12]	3.04+1.87	2.17+1.68	2.02+1.49	1.87+0.97	0.012*
Serum Triglycerides (mg/dl)	137.77+51.93	120.05+46.80	119.49+40.73	151.83+76.34	0.101#
Serum Cholesterol (mg/dl)	179.37+41.78	147.20+39.54	157.59+40.40	155.50+50.22	0.003*
LDL[13] (mg/dl)	114.37+24.91	102.55+20.03	102.47+20.46	102.79+19.01	0.031*
HDL[14] (mg/dl)	45.93+8.59	51.08+8.76	51.71+8.76	51.90+6.50	0.002*
Baseline FSH[15] (IU/l)	5.60+2.24	6.89+3.00	6.25+3.09	5.12+1.47	0.217#
Baseline LH[16] (IU/l)	13.37+6.56	15.20+6.97	13.79+10.39	10.01+4.94	0.507#
LH[16]:FSH[15]	2.86+1.98	2.95+1.95	2.34+1.28	2.11+1.30	0.707*
17 OHP[17] (ng/dl)	1.43+0.79	1.02+0.26	1.49+0.85	0.99+0.21	0.059#
Vitamin D	16.77+10.20	16.72+7.77	16.57+7.75	20.34+11.26	0.664#

#Kruskal-wallis, *ANOVA. [1]HA: Hyperandrogenism, [2]OD: Ovulatory dysfunction, [3]PCO: Polycystic ovaries, [4]BMI: Body mass index, [5]SBP: Systolic blood pressure, [6]DBP: Diastolic blood pressure, [7]AFC: Antral follicle count, [8]AMH: Anti mullerian hormone, [9]OGTT1: Oral glucose tolerance test (Fasting), [10]OGTT2- Oral glucose tolerance test (1 hour postprandial), [11]OGTT1: Oral glucose tolerance test (2 hour postprandial), [12]HOMAIR: Homeostatic model assessment insulin resistance, [13]LDL: Low density glycoprotein, [14]HDL: High density glycoprotein, [15]FSH: Follicle stimulating hormone, [16]LH: Luteinizing hormone, [17]17 OHP: 17-Hydroxyprogesterone

Switzerland), using kits supplied by the same manufacturer. Appropriate controls and calibrators were run in parallel during all the assays.

Baseline transvaginal scan (TVS) was also done on the same visit (day 2) for ovarian volume and antral follicle count (AFC) using a Philips ultrasound machine, model IU22 (probe frequency range 5-7 MHz).

These patients were then treated with clomiphene citrate starting with 50 mg/day on day 2-5 of their cycle for days. In case of failure of ovulation, the dose will be increased by 50 mg in subsequent cycles to a maximum dose of 150 mg over three cycles. Response to clomiphene was assessed by TVS which was done on alternate days, starting from day 10 of the cycle until the follicle size was >18 mm or day 20 of the cycle. Patients were called 2-3 days after the development of dominant follicle to look for rupture of the follicle. Based on the ovulation pattern these patients were divided into two groups: clomiphene citrate-sensitive (if ovulation present) and clomiphene citrate-resistant (no ovulation even with 150 mg clomiphene citrate). The various parameters were compared between the four PCOS phenotypes.

Table 3: Comparison between the pcos phenotypes

		HA[1] + OD[2] + PCO[3] (*n*=111)	HA[1] + OD[2] (*n*=18)	HA[1] + PCO[3] (*n*=29)	OD[2] + PCO[3] (*n*=6)	χ^2	*P*
Clomiphene response	Clomiphene resistant (*n*=88)	72 (64.86%)	7 (38.89%)	8 (27.59%)	1 (16.67%)	18.414	0.000
	Clomiphene sensitive (*n*=76)	39 (35.14%)	11 (61.11%)	21 (72.41%)	5 (83.33%)		
Endometrial hyperplasia	Present (*n*=13)	11 (9.9%)	0 (0%)	1 (3.45%)	1 (16.67%)	3.573	0.311
	Absent (*n*=151)	100 (90.1%)	18 (100%)	28 (96.55%)	5 (83.33%)		
Metabolic syndrome	Present (*n*=40)	31 (27.93%)	2 (11.11%)	5 (17.24%)	2 (33.33%)	3.538	0.316
	Absent (*n*=124)	80 (72.07%)	16 (88.89%)	24 (82.76%)	4 (66.67%)		
Blood Sugar abnormalities	Normal (*n*=87)	51 (45.94%)	12 (66.67%)	20 (68.96%)	4 (66.67%)	9.504	0.147
	Impaired glucose tolerance (*n*=66)	51 (45.94%)	5 (27.78%)	9 (31.03%)	1 (16.67%)		
	Overt Diabetes Mellitus (*n*=11)	9 (8.1%)	1 (5.55%)	0 (0%)	1 (16.67%)		
Body Mass Index in kg/m^2	<18.5 (*n*=3)	1 (0.9%)	0 (0%)	2 (6.90%)	0 (0%)	18.074	0.034
	18.5-23 (*n*=37)	20 (18.02%)	4 (22.22%)	10 (34.48%)	3 (50%)		
	23-27.5 (*n*=69)	44 (39.64%)	9 (50%)	13 (44.83%)	3 (50%)		
	>27.5 (*n*=55)	46 (41.44%)	5 (27.78%)	4 (13.79%)	0 (0%)		
Menstrual irregularities (in days)	24-38 days (*n*=29)	1 (0.9%)	0 (0%)	28 (96.55%)	0 (0%)	157.841	0.000
	38-60 days (*n*=31)	21 (18.92%)	7 (38.89%)	0 (0%)	3 (50%)		
	>60 days (*n*=104)	89 (80.18%)	11 (61.11%)	1 (3.45%)	3 (50%)		

1-HA- Hyperandrogenism, 2- OD- Ovulatory Dysfunction, 3- PCO- Polycystic Ovaries

The various parameters of the patients were recorded as mean ± SD. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality. ANOVA or Kruskal-Wallis tests were used to compare the various parameters among the four PCOS phenotypes. Post hoc test was used to establish the differences between the groups. Proportions were compared using Chi-square or Fisher's exact test, whichever applicable. All statistical tests were two-sided and performed at a significance level of α =0.05. The analysis was conducted using IBM SPSS STATISTICS (version 24.0).

Results

The most common PCOS phenotype in this study was the full-blown PCOS (phenotype A) which includes all three features: hyperandrogenism, irregular cycles and PCOs on ultrasound. It had a prevalence of 67.7% (111 patients). The prevalence of phenotypes B, C, and D were 11% (18 patients), 17.7% (29 patients), and 3.6% (6 patients), respectively [Table 1].

Table 2 provides a comparison between the clinical, metabolic and hormonal profile of the four PCOS phenotypes.

Phenotype A had significantly higher weight and BMI ($P < 0.05$) in comparison to phenotypes C and D. Although phenotype B had higher weight and BMI than phenotypes C and D, but the results were not statistically significant ($P > 0.05$). However, no significant differences were noted in the waist circumference, waist-hip ratio ($P > 0.05$).

Both clinical and biochemical hyperandrogenism (Ferriman-Gallwey score, total testosterone, and androstenedione levels) were significantly more in phenotype A as compared with the phenotype C and D. Although phenotype B had higher Ferriman-Gallwey score, total testosterone, and androstenedione levels than phenotypes C and D but the results were not statistically significant ($P > 0.05$).

Menstrual irregularities (cycle length >60 days) were significantly more common in phenotype A as compared with phenotype D (80.18% vs 50%, $P = 0.000$).

Ovarian reserve (mean AFC, mean ovarian volume, AMH) parameters were significantly higher in phenotype A ($P < 0.05$) as compared to the phenotypes B and D. Although phenotype A had a higher ovarian reserve than phenotypes C also, but the results were not statistically significant ($P > 0.05$).

Fasting insulin and HOMA-IR was significantly more in phenotype A as compared to phenotypes B and D ($P < 0.05$). Phenotype B had higher insulin and HOMA-IR values than phenotypes C and D, but the results were not statistically significant ($P > 0.05$).

Lipid profile was significantly more deranged in phenotype A with higher LDL and total cholesterol and lower HDL values ($P < 0.005$) as compared to phenotype D. Although phenotype B had more deranged lipid profile than phenotypes C and D but the results were not statistically significant ($P > 0.05$).

No significant differences were noted in the waist circumference, waist-hip ratio, blood pressure and blood sugar values (fasting, 1-hour postprandial, 2-hour postprandial). Also, the FSH, LH, LH-FSH ratio, 17-hydroxyprogesterone (17-OHP) and vitamin D levels were not significantly different amongst various PCOS phenotypes ($P > 0.05$).

The prevalence of clomiphene resistance was significantly higher in full-blown PCOS (phenotype A) as compared to phenotype D (64.86% vs. 16.67%, $P = 0.000$). Obesity was also more commonly seen in phenotype A as compared to phenotype D (41.44% vs. 0%, $P = 0.034$) and the results were statistically significant [Table 3].

Although the prevalence of endometrial hyperplasia, impaired glucose tolerance, overt diabetes and metabolic syndrome were higher in phenotype A as compared to the others, but the results were not statistically significant [Table 3].

Discussion

The prevalence of phenotypes A, B, C, and D were 67.7%, 11%, 17.7%, and 3.6%, respectively. Phenotype A had significantly higher weight, BMI, clinical, and biochemical hyperandrogenism, menstrual irregularities, ovarian reserve parameters, fasting insulin, HOMA-IR, and more deranged lipid profile ($P < 0.05$). Clomiphene resistance was significantly more common in phenotype A ($P < 0.05$). No significant differences were noted in the waist circumference, waist-hip ratio, blood pressure and blood sugar values (fasting, 1-hour postprandial, 2-hour postprandial). Also, the FSH, LH, LH-FSH ratio, 17-hydroxyprogesterone, and vitamin D levels were not significantly different among various PCOS phenotypes.

Full-blown PCOS (phenotype A) was the most common phenotype with prevalence of 67.7% followed by phenotype C, B, and D, respectively. These results are supported by the study conducted by Gluszak *et al*.[16] in which the prevalence of phenotype A, B, C, and D were 60.2%, 16.1%, 18.3%, and 5.4%, respectively. Similar results were obtained by the study conducted by Pehlivanov *et al*.[17] Moreover, obesity, hyperandrogenism, insulin resistance, deranged lipid profile, and metabolic syndrome were more common in phenotype A as compared to others suggesting a higher risk of adverse metabolic and cardiovascular outcomes in this phenotypic group as compared to others. This is also supported by other studies.[16,17]

Phenotype D, the non-hyperandrogenic phenotype represents a milder form of PCOS with the lesser prevalence of obesity, hyperandrogenism, insulin resistance, deranges lipid profile, and metabolic syndrome. They are better clomiphene responders. Similar results were obtained by Zhang *et al*.[18] and Gluszak *et al*.[16]

The study by Gluszak *et al*.[16] observed significantly higher 17-OHP, LH, and LH-FSH ratio in phenotype A ($P < 0.03$). Also, the blood sugar values were statistically higher in their study.[16] Contrary to this, no significant differences were noted in these parameters in the present study.

This study suggests that presentation of PCOS is not homogenous, but it depends on the presence or absence of three elements: hyperandrogenism, menstrual irregularity, and PCO which makes up the phenotypic classification. Different phenotypes present differently concerning their clinical, metabolic, hormonal profile which also alters their response to ovulation inducing agents like clomiphene. These differences suggest that each phenotype of PCOS is a variation of a common syndrome. Various hypotheses have been given in the literature to explain this heterogeneity in clinical presentation. It could be an interplay between genetic and environmental factors which affect the pathogenesis of PCOS.[19] Another possible explanation given is the intrauterine exposure to maternal androgens which might be responsible for a particular phenotype.[20] There are reports available to prove that excessive androgen exposure to the foetus affects the hypothalamic-pituitary-ovarian axis resulting in adverse reproductive and metabolic outcomes.[19]

Although the sample size of the present study is small, but it gives a good idea of the distribution and differences in the clinical metabolic and hormonal profile of various PCOS phenotypes. Another limitation of this study is that it provides data of the Indian population. Thus, it does not take into account the ethnic differences.

This study gives a detailed comparison of the four PCOS phenotypes. It also justifies the importance of classifying the patients into the various phenotypes. Phenotypic division of patients with PCOS-related infertility can help in prognosticating the patients about the severity of the disease and the fertility outcome.

Conclusion

The study suggests that phenotypic group A is the most prevalent phenotype of PCOS. Phenotypic group A have a higher prevalence of obesity, hyperandrogenism, insulin resistance, deranged lipid profile, and metabolic syndrome and thus are at a higher risk of adverse metabolic and cardiovascular outcomes as compared to others. Also, this group is more likely to be clomiphene resistant. On the contrary, phenotype D is the least severe or the mildest presentation of PCOS.

Thus, phenotypic division helps in better understanding of the pathophysiology of PCOS and can, therefore, help in predicting adverse metabolic and cardiovascular outcomes and also a poor response to clomiphene. Moreover, identifying various phenotypes will not have diagnostic implications but will also assist in providing appropriate treatment and prognosticating the patients with PCOS-related infertility.

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Conflicts of interest

There are no conflicts of interest.

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